[18O]Water Target Design for Production of [18F]Fluoride at High Irradiation Currents

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Abstract:
This report contains the complete proceedings of the 13th International Workshop on Targetry and Target Chemistry. The Workshop was held at Risø National Laboratory for Sustainable Energy on July 26-28 2010.

The workshop deals with the development of methods and systems for efficient production of radioactive isotopes with accelerators. The WTTC series of workshops was initiated for the purpose of exchanging information about the problems and solutions associated with the production of radioisotopes for biomedical research and their applications to the diagnosis and treatment of disease. The goal of the WTTC is to advance the science associated with radioisotope production targetry. The Workshops are designed to bring experienced targetry scientists together with newcomers to the field, both from industry and academia, to discuss issues of targetry and target chemistry and approaches to exploring in situ target chemistry and the engineering required to optimize production yields. In the workshop, experience, ideas and information are freely and openly shared; learning and collaborations are fostered, with active participation by all attendees. This participation includes both formal and informal sessions. The present proceedings captures both submitted abstracts and the actual presentations showed during the very successful workshop meeting number 13 in the row, the WTTC13.
The WTTC13 is grateful for the support from the following sponsors without whom the workshop would have been impossible:

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Our Institutions have contributed effort to the benefit of this meeting.
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Abstract 001

Extending a Scintillation Counter’s Dynamic Range

Lewis Carroll
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**Introduction** Our compact, solid-state scintillation probes are widely used as HPLC / GC radiation detectors for quality assurance in PET/nuclear medicine research labs and radio-pharmacies. The detector probes operate in AC-coupled, *pulse-counting mode*, with a threshold discriminator to exclude noise and to minimize baseline fluctuation and drift.

The threshold discriminator is followed by an analog *ratemeter* to produce a voltage signal that is proportional to the time-rate of photon-induced pulses which exceed the pre-set threshold. Using this scheme, the ability to discern and evaluate the smallest radio-chromatography peaks – the minimum detectable signal – is governed by fluctuations in the base-line from ambient radiation background in the lab which, in turn, requires that the detector probe be well shielded so that it ‘sees’ only the radiation emanating from a loop of flow-tubing placed in tight proximity to the probe.

While this scheme is optimum for detection at low-to-moderate levels of radioactivity encountered in a typical quality-assurance radio-assay, pulse-counting detectors generally suffer from saturation effects due to counting system *dead-time* when exposed to high levels of radioactivity. In an effort to broaden the potential application of our scintillation detector products, we are engaged in an ongoing development program to enhance detector system linearity and dynamic range by reducing saturation effects at the ‘high-end’ while preserving system sensitivity at the ‘low end’.

**Stress-Testing at high count-rates** To facilitate our development, we use home-made random pulse generators 1 operating in parallel. Each pulse generator drives its own light-emitting diode to simulate scintillation pulses (pulse width ~ 200 nsec) from a CsI(Tl) scintillator crystal. The fixed-amplitude, random light-pulses are pre-set to match the 511 KeV principal peak in our 1 cm³ crystal, and are directed at a 1 cm² Si PIN diode + charge-integrating preamplifier (to include the effects of electronic noise inherent in a room-temperature semiconductor diode detector) all placed inside a light-tight enclosure to emulate our scintillation detector probe’s ‘front end’. Each generator delivers pulses at Poisson random intervals with an adjustable mean rate covering a range of ~100 pulses per second up to ~125K pulses per second. A pair of generators can produce a mean rate up to ~250K pulses per second, providing a convenient, readily-controllable source of detector system excitation over a wide range of count-rates, without having to handle large quantities of radioactive material. The ‘Poisson-ness’ of our random pulse generators was validated by recording the distribution of inter-pulse waiting times for various mean rates, using a calibrated time-to-amplitude converter plus multi-channel analyzer.

**Extending Dynamic range** In a radiation *counter*, input pulses which exceed a pre-determined threshold generate corresponding output pulses of fixed amplitude which, in turn, are either counted digitally or time-averaged in an analog rate-meter circuit. A different solution, now under development, entails giving up on the notion of pulse ‘counting’, *per se*, and replacing the standard threshold discriminator with a new circuit combining the functions of a threshold discriminator, a *pedestal generator*, and a *linear gate* 2. The sketch below compares the input-output characteristic of a standard discriminator versus our new circuit.

The output of a standard discriminator circuit is zero for input pulses less than the threshold, and steps to a fixed, pre-determined value for input pulses which exceed the threshold. In the new circuit, the output is again zero for input pulses which are less than the threshold; when the input pulse exceeds the threshold, the output steps, then linearly follows the amplitude of the input.

The analog time-averaged (analog rate-meter) output signal from this circuit is proportional to the time-average of energy absorbed (i.e., dose-rate) in the detector probe. The new circuit retains the noise-reducing and drift-reducing advantages of a standard threshold discriminator at low count rates, but with the added advantage that integrated energy/amplitude information contained in


signal pulses which overlap and ‘pile up’ is preserved over a substantially greater range of input excitations. Our useful range now extends well beyond the point where a standard discriminator’s output has ‘flat-lined’.

The plots below compare three different detector outputs versus input count rate excitation. The vertical scales are normalized so that all the curves are tangent at low input count rates. In our present system, ‘busy time’ for a single event is governed by the shaping-amplifier’s pulse-width, which is on the order of ~25 micro-seconds – in our case a necessary but reasonable compromise between low dead-time and low noise floor. A wider system bandwidth (shorter shaping time-constant) would allow a narrower pulse which, in turn, would yield a higher maximum count rate, but that would come at the cost of a higher noise floor, requiring a correspondingly higher threshold setting, potentially compromising performance for lower-energy photon-emitters.

As shown below, the digital output count-rate peaks at ~17 kHz for 50 kHz input, then gradually declines due to a ‘paralyzing dead-time’ component and finally plateaus at ~13 kHz. However, the analog-rate-meter – or analog average – of that same time-over-threshold discriminator signal has a significantly greater dynamic range, since the discriminator’s output pulses vary in duration, staying ‘high’ when responding to multiple, overlapping input pulses as long as they are of sufficient amplitude to exceed the pre-set threshold. Of course the time-over-threshold analog-rate-meter’s output eventually saturates as well, but with a gradual and asymptotic, ‘non-paralyzing’ characteristic.

**New Circuit**

Our new discriminator circuit significantly extends the useable range of the detector. With this circuit, saturation effects begin to set in at ~150 kHz input count-rate, but the analog output is monotonic – still increasing – up to the present limit of our test apparatus.

The simplest, most common means to achieve detector system DC baseline stability – absolutely vital at low count-rates – is to employ capacitive AC coupling with base-line restoration at the input to the discriminator. That, however, combined with the shaping amplifier’s constrained bandwidth, leads to a loss of ‘DC-average’ information, ultimately causing the apparent signal drop-off at high count rates.

We are currently revisiting many of our prior circuit design assumptions. At the time of this submission, we are seeing preliminary, albeit intriguing and very encouraging test-bench results suggesting there is reason to expect significant improvement over the results posted here.

---

Our solid-state radiation detector products are categorized according to two distinct modes of Signal Processing:

1) Pulse mode
   - Pulse mode entails processing each detected photon event pulse by pulse.
   - This permits the use of a threshold discriminator to eliminate noise and to minimize base-line fluctuation and drift.

2) DC-current mode
   - DC-current mode categorizes dynamic range.
Pulse mode is preferred for low to moderate levels of activity (e.g., analytic HPLC).

Hence this mode is more subject to baseline fluctuation and drift. There is no threshold discriminator in DC mode.

DC Current mode is therefore preferred for use with higher activities (e.g., prep HPLC).

But since there is no processing of individual pulses, there is no inherent saturation effect.

DC current mode integrates or averages the radiation-induced photo-current produced in the semiconductor diode.
For low to moderate activity levels, we are committed to pulse mode for detection and quantitation of the smallest chromatography signal peaks.
What happens at much higher levels of activity?

Any pulse counting system is subject to count-rate saturation.

Effects at high activity levels.
The 'raw' signal pulses are quite noisy and must be 'shaped' (smoothed and stretched) to ~25 μsec width, and to optimize signal-to-noise ratio.

It is possible to exploit the noise-rejecting properties of pulse-mode for low-to-moderate activity, and the inherent linearity of DC current and the linear dependence of DC current on the crystal volume.

Suppose we give up the notion of 'pulse-counting, per se, and simply measure the mean value of the detector's analog wave-form to read radiation intensity.

The true count rate is \( \frac{1}{t} \) and the non-pulsating, dead time is \( \frac{1}{t} \exp(-t/\tau) \), where \( \tau \) is the pulse duration. The graph shows the observed count rate vs. time.
Introduce a new type of threshold circuit to facilitate our bench tests. We employ an ensemble of Poisson random pulse generators driving LED’s to stimulate our scintillation detector at high count-rates. The saturating trend still evident results from loss of DC-level due to capacitive interstage coupling. The new discriminator circuit’s performance was evaluated by measuring the mean output counts versus input counts for both the new discriminator and the standard discriminator. Both circuits show similar performance, but the new circuit has a lower threshold, which is desirable for high count-rate applications.
With a factory for moderate count rates, capacitive coupling combined with our shaping amplifier’s constrained bandwidth, is not well-suited for conditions of extreme count-rate overload.

Introduce DC interstage coupling.

Time for a major circuit revision!
Observe the signal at the output of the shaping amplifier.

- 400 KHz
- 600 KHz
- 100 KHz
Our new discriminator circuit accepts this as a valid signal.

As the signal base-line exceeds the discriminator threshold, the discriminator's output is a linear replica of the input yielding a proper measure of the signal's mean value.

Under conditions of extreme pulse-rate overload, the entire signal envelope observed at the output of the shaping amplifier appears to 'levitate' relative to the fixed base-line reference.
As if we are operating in... DC current mode*! A "stabilized base-line" and "DC current mode" are mutually exclusive. A "stabilized base-line" in conjunction with a threshold discriminator, is essential for noise-free detection at low excitations but it is not compatible with true DC current mode operation. Recapturing a threshold, including a threshold detector signal output, is preferred at very low excitations due to cleaner base-line and better detectability for weak signal peaks. Doesn't saturate and is therefore preferred for very high excitations. As if we are operating in...
Our new scheme combines the best features of both modes of operation. We have demonstrated a scintillation detector operating in sensitive pulse-mode at low excitation, having a linear dynamic range from a few tens of pulses per second to more than 500K per second! *USA Patent Pending

CONCLUSION: We have

1. QC systems shall be validated
2. Good, effective, SOP must be implemented
Development of a target system at the baby cyclotron BC1710 for irradiation of solids and gases and the adaptation of existing target systems to the external beamline at the injector of COSY

B. Scholten, S. Spellerberg, W. Bolten, H. H. Coenen

Institute of Neurosciences and Medicine, INM-5: Nuclear Chemistry, Forschungszentrum Jülich GmbH, 52425 Jülich, Germany

In former years most of our radionuclide development studies were done at the compact cyclotron CV 28 of the Forschungszentrum Jülich. Several dedicated target systems were constructed to irradiate solid and gaseous targets, either for cross section measurements or for production of radionuclides \(^{1-16}\).

Due to the decommissioning of the compact cyclotron CV 28 in 2006 new target systems had to be developed at our baby cyclotron BC1710. This cyclotron is used to produce the light PET isotopes \(^{18}\text{F}, ^{11}\text{C}, ^{13}\text{N}\) in special gas chambers and in water targets. These specialized target systems are arranged in a target changing system with six positions. There was no target system at our BC1710 for the irradiation of solid targets and gas cells. So a beam line extension at the lowest position of the target changing system was constructed with a water cooled beam collimator and electrical insulation of the targets for beam current measurement. The front plate allows inserting different target holders close to the main end of the beam line. Target holders were constructed for the irradiation of foils and pellets in the stacked foil technique, which also allows irradiating powders in aluminum capsules. Furthermore, it is also possible to insert a slanting target for the production of radionuclides (i.e. \(^{124}\text{I}, ^{120}\text{Te}, ^{48}\text{V}\)) at higher currents. All target systems are water cooled. A special front plate was constructed for the external irradiation of gas cells. During the development of the target system several optimizations had to be done to collimate the beam and to increase the beam efficiency on the target.

Fig. 1: Drawing of the beamtube extension at the BC 1710 with inserted stack foil holder.
Fig. 2: Picture of the component parts of the BC1710 beamline extension before assembling.

At the injector of COSY an internal target system exists for the irradiation of targets in the stacked-foil mode using the just extracted beam of the cyclotron\(^{[17]}\). At this position there is a geometrical limitation for the target system and special care has to be taken that no contamination of the internal part of the cyclotron can happen. Intense water cooling of the targets is not possible there. Therefore an adaptation system at the end of an external beamline of the injector of COSY was developed which allows using all former target holder systems and dedicated targets developed earlier for the CV 28. In the adapter four adjustable water cooled sector absorbers are built in to collimate the beam. The beam windows are cooled by a helium gas stream. Manual remote control of the system is possible from outside the cyclotron vault and a PC based remote system is projected.

References:

Development of a target system at the baby cyclotron BC1710 for irradiation of solids and gases

No research targets existed for solid and gas samples so far.

Vertical target changer unit with 6 target positions:

- $^{16}$O(p,α)$^{13}$N (water target)
- $^{18}$O(p,γ)$^{18}$F (water target)
- $^{1}$H(p,α)$^{4}$He (gas target)

Dedicated to the production of short-lived PET radioisotopes:

- $^{14}$N(p,α$^{11}$C (gas target)
- $^{18}$O(p,n)$^{18}$F (water target)
- $^{16}$O(p,α)$^{13}$N (water target)

Accelerators at FZ Jülich:

- BC1710: 17 MeV p, 10 MeV d
- BCT170: 17 MeV p, 10 MeV d
Beam Line Extension at BC 1710

- A beamline extension was constructed for the lowest target changer position.
- Water cooled collimators, insulators from peek or plexiglas.
- Target vacuum separate from cyclotron vacuum.
- Long target rod for solid target systems with water cooling.
- Remote control from outside the cyclotron vault required.
- Remote to external beamline.
- Existing sophisticated target systems for CV28 should be adapted to external beamline.
- External beamline was used by other groups so far.
- Internal radiation possible.
- 1990/91 converted as COSY injector (76 MeV H²⁺).
- Ions up to 45 MeV/nucleon.
- Isochronous cyclotron JULIC commissioned in 1968.

Target Systems at BC 1710

- Stacked-foil target holder.
- Gas cell target.
- Slanted targets.
- Long target rod for solid target systems with water cooling.
- Remote controlled by hand, remote controlled via computer.
- Long target rod for lowest target changer position.
- Electrical beam current measurement.
- Target vacuum separate from cyclotron vacuum.
- Water cooled collimators, insulators from peek or plexiglas.
- A beamline extension was constructed for lowest target changer position.
IBA C30a

R1 t of CV28 d BC 1710

Rep1
t of CV28

and BC 1710

Pt 3 0 15

M V 1 350 A

Protions:

30 - 15 MeV, 1 - 350 µA

• Deuterons: 15 - 7 MeV, 50 µA

• Alpha particles: fixed 30 MeV, > 50 µA

Dual beam mode for protons and deuterons

New Institute building (2014)

New building with cyclotron vault and GMP PET laboratory (2011)

Two external beamlines in separate vault

New building with cyclotron vault and GMP PET laboratory (2011)

Dual beam mode for protons and deuterons

• Protions: 30 - 15 MeV, 1 - 350 µA

Replacement for CV28 and BC 1710

IBA C30a

WTTC XII – Presentation Discussions
Search for the ideal cyclotron stripper foil

John O. Stoner, Jr.

ACF-Metals, The Arizona Carbon Foil Co., Inc.
2239 E. Kleindale Road
Tucson, Arizona 85719-2440 U.S.A.
<metalfoil@cox.net>

Although carbon stripper foils can now be obtained in any thickness desired by the cyclotron user, it is still necessary to replace foils occasionally because of their finite lifetimes. Limits on lifetime occur because of poor mounting, vacuum disasters, mechanical shock, nuclear collisions (causing violent atomic displacements), thickening, nuclear and electronic heating with resulting evaporation and diffusion, erosion by residual gas, and many other effects. Beam currents are increasing steadily; this trend is expected to continue. Most problems are accentuated at higher beam currents. ACF-Metals is searching through foil compositions, allotropes and mounting methods to identify promising routes to obtaining longer-lasting foils.
Carbon Foils:

- Thickness <1 nm to >20 µm
- Amorphous, graphitic, or pyrolytic
- Low Z, high strength
- Withstand high temperature

Research:

- Example: Fiber-mounted foils for SNS and other accelerators
- Better mountings for longer lifetimes
- Quantitative production of standard foils
- Flexible production of unusual types
- High-quality foils: experienced

Why ACF-Metals?

- Operation in extreme conditions
- Foil longevity
- Materials & frames
- Continuing research to improve:
  - Quantitative production of standard foils
  - Flexible production of unusual types
  - Personnel
  - High-quality foils: experienced

Accelelator Cost: approx. 1B ($)

One carbon stripper foil cost: approx. $300
Stripper foil: ~1 cm x 5 cm

ACF-Metals:

2239 E. Kleindale Road
Tucson, AZ 85719

$300 for one carbon stripper foil.
Carbon foil, 1/2 micron thick, on cyclotron fork.

Research:

The frontier: Foils to withstand the highest beam currents, the largest beam currents, in corrosive environments, for the longest times.

The Frontier: Foils to withstand the highest temperatures, the largest beam currents, in corrosive environments, for the longest times.

The Frontier: Foils to withstand the highest temperatures, the largest beam currents, in corrosive environments, for the longest times.

One-piece aluminum foil, 10 µg/cm² (40 nm thick) on supporting mesh, ready for shipment. 910 mm

Hotspot™ ACF foil withstood 3500 K! The other foil didn't.

3-micron C foils on tungsten frames.
Carbon Foils:

- Thickness <1 nm to >20 µm
- Amorphous, graphitic, or pyrolytic
- Low Z, high strength
- Withstand high temperature

ACF-Metals

2239 E. Kleindale Road
Tucson, AZ 85719

<metalfoil@cox.net>

1. Foil maintenance
   - Ramp up beam slowly
   - Storage: Desiccators/refrigerators not needed

WTTC XIII – Presentation Discussions
New Gaseous Xenon Target for $^{123}$I Production

Jožef J. Čomor¹, Đuro Jovanović¹, Jean-Michel Geets², Bernard Lambert³

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²IBA Molecular, Chemin du Cyclotron 3, 1348 Louvain-la-Neuve, Belgium
³IBA Molecular Europe, Le christ de Saclay B.P. 32, 91192 Gif-Sur-Yvette, France

$^{123}$I is one of the best suited radionuclides for SPECT (Single Photon Emission Computed Tomography) due to its short half life (13.2 h) and low absorbed dose in patients for its low energy gamma emission (154 keV), which is ideal for detection by common scintillation detectors. It is most commonly produced in gaseous Xe targets irradiating highly enriched $^{124}$Xe by 30 MeV protons and exploiting the indirect production path via $^{123}$Xe. This technology is well established and performed in several cyclotron centers; however radiation safety aspects and the danger of losing the expensive target material are always a concern. Thus, every effort is needed to ensure that the target remains tight during irradiation, while the service and maintenance should be quick and reliable in order to reduce the dose received by the personnel.

The most critical part of every gaseous target is the double window system, there are two possible approaches in handling this issue: hard bolting the windows via flanges and metal seals to the target body, or using window packages, which can be remotely replaced prior failure of elastomer seals. The first approach allows for long periods between scheduled replacements of the target assembly (approx. once in 12 months); however the radiation dose received by the operator during this maintenance is substantial. Moreover, one needs at least two complete targets for uninterrupted production (one in operation while the other is cooling down for maintenance). The second approach requires more frequent replacement of the window package (approx. once in 3 months) without any radiation hazard for the operators.

It is obvious that this second approach is more favorable, thus the new target station has been developed following this concept, with the aim to provide more reliable operation than what the existing target stations can provide. To this end a new mechanism for window foil package replacement has been designed. Unlike the previous target stations, it has no robotic arm. Moreover, there are no sliding seal based connections for compressed air and helium, thus the reliability of the window package replacement mechanism is greatly increased and in the same time the possibility of losing the target material from the helium cooling loop in case of window burst is negligible.

In addition, the target locking mechanism has been also improved: previous designs relied on uninterrupted compressed air supply, thus in case of accidental burst of supply tubing during the irradiation the enriched target material would be lost and the vault would be heavily contaminated. The new locking mechanism keeps the target chamber normally locked. Compressed air is needed only for unlocking the target chamber for window package replacement, i.e. the safety of the target station does not depend on external factors.

The target is patent pending and detailed design will be presented later on (at time of conference).
Irradiation of gaseous $^{124}\text{Xe}$ is the most cost-effective way for large-scale $^{123}\text{I}$ production.

There are two common approaches to the target design:

- **The good:**
  - Very high current acceptance and yield
  - Infrequent (annual) target maintenance

- **The bad:**
  - At least two target sets are needed for normal operation
  - Very high dose delivered to the operators during maintenance
  - Very high dose delivered to the operators during maintenance
  - Remote target maintenance — minimum dose to the operators during maintenance

**Nordion/Triumf/ACSI approach**

- **The good:**
  - Very high current acceptance and yield
  - Remote target maintenance
  - Affordable replacement window packages

- **The bad:**
  - At least two target sets are needed for normal operation
  - Very high dose delivered to the operators during maintenance

**KIPROS approach**

- **The good:**
  - High current acceptance and yield
  - Affordable replacement window packages

- **The bad:**
  - The sliding seals used in the robotic arm might fail unexpectedly due to radiation damage
  - The sliding seals used in the robotic arm might fail unexpectedly due to radiation damage
  - Remote target maintenance – minimum dose to the operators during maintenance
What if a new system is to be designed?

The remote exchange of window packages is a great advantage (ALARA principle).

Therefore, follow this principle and in addition:

- Simplify the window package replacement mechanism.
- Design a fool-proof insertion principle (the orientation of the double window insert is crucial).
- Design a fool-proof target locking mechanism.

The basic idea

... was in fact in the backyard:

The Nirta Solid Compact target system for solid target irradiation can be pre-loaded with three target disks, which are then irradiated one by one.

The concept

Window package guiding mechanism

Target body

Spare window

Collimator

Locking mechanism

Principle of operation (1/2)

Working window package

Target locked

Spare window package

Target unlocked

Working window package

Target body

Spare window

Collimator

Locking mechanism

The concept

Window package guiding mechanism

Target body

Spare window

Collimator

Locking mechanism

Principle of operation (1/2)

Working window package

Target locked

Spare window package

Target unlocked

Working window package

Target body

Spare window

Collimator

Locking mechanism

The basic idea

... was in fact in the backyard:

The Nirta Solid Compact target system for solid target irradiation can be pre-loaded with three target disks, which are then irradiated one by one.
The complete scheme of operation

- Windows changed every 3rd month
- "Kyros" material to handle temperature
- Diagnostic system for window holes
- Why not use 18F experience?

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Mass Production of $^{64}$Cu with $^{64}$Ni(p,n)$^{64}$Cu Nuclear Reaction

Kwon Soo Chun*, Hyun Park, Jaehong Kim

Korea Institute of Radiological and Medical Sciences, Seoul, Korea

* Corresponding author: kschun@kcch.re.kr

Introduction

$^{64}$Cu ($T_{1/2} = 12.7$ h, $\beta^-$ decay: 40%, $\beta^+$ decay: 19%, E.C. decay: 41%) is one of the most useful radioisotope in nuclear medicine due to its multiple decay mode and the intermediate half-life. Several nuclear reactions, i.e., $^{64}$Ni(p,n)$^{64}$Ni, $^{68}$Zn(p,αn)$^{64}$Cu and $^{64}$Ni(d,2n)$^{64}$Cu have been investigated for $^{64}$Cu production[1,2]. The highest production yield could be obtained with proton irradiation on the enriched $^{64}$Ni target. Therefore for mass and routine production, the $^{64}$Ni target fabrication by using electroplating[3], the reliable chemical separation of $^{64}$Cu from the irradiated $^{64}$Ni target and the effective recovery process for the recycling of very expensive enriched material ($^{64}$Ni enrichment : 96%, $20,000$/g) and so on are absolutely necessary to be established. In this work, we report our mass production method of $^{64}$Cu with enriched $^{64}$Ni and Cyclone-30 accelerator.

Methods

$^{64}$Cu was produced with high current cyclotron via $^{64}$Ni(p,n)$^{64}$Cu nuclear reaction at 200$\mu$A, 18MeV proton beam. Nickel target was prepared by electro-plating of enriched $^{64}$Ni (25% of enrichment) on Au coated Cu cooling plate. After proton beam irradiation, Ni target was dissolved with circulation of 50ml of 5N HCl on the dissolving device (home made) and 90$^\circ$C heating. Water was added to $^{64}$Ni solution to dilute the normality of hydrochloric acid to 0.5N. Radiochemical separation of $^{64}$Cu from Ni target solution was performed with 0.01% dithizone in CCl$_4$ solvent extraction and back extraction with 7N HCl[4]. Purification of back extracted $^{64}$Cu solution was carried out with AG1-x8 (Bio-Rad) anion exchange resin. For $^{64}$Ni recycling, $^{64}$Ni from the aqueous phase of solvent extraction and the electrolyte of electroplating was recovered by using AG1-x8 anion and AG50w-x8 (Bio-Rad) cation resin[5].

Results

With the electroplating cell designed by ourselves and the electrolyte, consisting of 1.5g $^{64}$Ni(25% enrichment), 1.0g boric acid and 2.0g NaCl in 90ml distilled water, the smooth and uniformed Ni target (thickness : > 50mg/cm$^2$, area: 1 x 10cm$^2$) was obtained with applying 200mA of constant current on the cathode for 5hrs. The cathode current efficiency was about 50%. There was no damage on Ni surface during more than 200$\mu$A proton beam irradiation. The chemical separation yield of $^{64}$Cu with solvent extraction and anion exchange resin was more than 90% and the radionuclidic purity was more than 99% 1 day after bombardment. The $^{64}$Ni recovery yield was quantitative and measured with $^{57}$Ni activity produced with $^{58}$Ni(p,2p)$^{57}$Ni nuclear reaction and AA spectroscopy.

Conclusion
$^{64}$Cu production yield was about 9mCi/μAh corrected on 96% enrichment at EOB with $^{64}$Ni(p,n)$^{64}$Cu nuclear reaction and Cyclone-30. The chemical separation yield and the radionuclidic purity of the final $^{64}$Cu solution was more than 90% and 99%, respectively. The $^{64}$Ni recovery yield performed with ion exchange resin was more than 98%.

References


64Cu production method

<table>
<thead>
<tr>
<th>Target material</th>
<th>Production route</th>
<th>Expected Yield per batch (mCi)</th>
<th>Yield (mCi/µAh)</th>
<th>Energy (MeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>64Ni(p,n)64Cu</td>
<td>64 Ni(d,2n)64Cu</td>
<td>800-4,000</td>
<td>2-10</td>
<td>15.5</td>
</tr>
<tr>
<td>&gt;95%</td>
<td>$20,000/g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64Ni(p,n)64Cu</td>
<td>64Ni(γ)64Cu</td>
<td>800-4,000</td>
<td>2-10</td>
<td>15.5</td>
</tr>
<tr>
<td>$3,000/g</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>66Zn68Zn(d,α)64Cu</td>
<td>68Zn(p,α)64Cu</td>
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<td>2-10</td>
<td>15.5</td>
</tr>
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<td>&gt;95%</td>
<td>$3,000/g</td>
<td></td>
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</tr>
</tbody>
</table>

64Cu physical properties

- **Therapy**: 64Cu as a therapeutic radionuclide with monoclonal antibody.
- **PET**: 64Cu as a PET radionuclide.

64Cu radionuclide and PET radionuclide

64Cu : Therapeutic RI with monoclonal antibody

Physical properties and potential application of Cu radioisotopes

<table>
<thead>
<tr>
<th>64Cu nuclidic properties (from NNDC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decay mode: E.C.(43.9%), 64Cu(p,n)64Cu</td>
</tr>
<tr>
<td>Half-life: 12.701h</td>
</tr>
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<tr>
<td>PET: 64Cu(p,n)64Cu</td>
</tr>
</tbody>
</table>

2010.7.26

Kwon Soo Chun, Hyun Park, Jaehong Kim

KIRAMS, Seoul, Korea

Korea Institute of Radiological and Medical Sciences

Nuclear Reaction

Mass Production of 64Cu with 64Ni(p,n)64Cu
Excitation functions of 64Cu production

1000 100

100

b

(\text{barn})

Ni-64(\text{p},n)Cu-64, Szelecsenyi (1993)

Ni-64(d,2n)Cu-64, Zweit (1991)

Zn-68(p,\alpha)Cu-64, Qaim (2003)

Zn-66(d,\alpha)Cu-64, Qaim (2003)

Fig. Excitation functions of 64Ni(p,n)64Cu and 64Ni(d,2n)64Cu, 68Zn(p,\alpha)64Cu, 66Zn(d,\alpha)64Cu. From Szelecsenyi, Zweit, Qaim

Schematic procedure for 64Cu mass production

64NiCl₂ recovery yield: >98%

64Ni target fabrication with electroplating:

1) Au pre-plating on Cu plate

2) 64Ni plating on Au coated Cu plate

Proton beam irradiation: 18MeV, 200 μA

64Cu/64Ni chemical separation with solvent extraction

64Cu purification with chromatography

64CuCl₂ production yield: 8.9 mCi/36 kCi

Proton energy (MeV)

Fig. Range of protons in the Ni target tilted 6° compared to the proton beam line.

Ni isotope composition

nuclide

abundance

nat Ni 96.1% 26.4%

58Ni 6.08 26.22

58Ni 6.08 26.22

60Ni 1.95 1.31

68Ni 50.41 9.6

61Ni 0.92 2.8

62Ni 26.4

64Ni

power Watt = \Delta E \times I (18 MeV \times 200 μA = 3.6 kWt)

Target area: 1x10 cm²

Power supply and rotor controller

64Ni target (Au, 64Ni) electroplating system

1) Au plating: 0.3 g KAu(CN)₂/3 g EDTA/2 g phosphate buffer in 500 mL H₂O

2) 64Ni plating: 15 g 64Ni/1 g boric acid/2 g NaCl in 90 mL H₂O

- constant current: 200 mA,
- stirrer: 650 rpm

- 64Ni cathode current efficiency: >30%: 60 μm/target area: 10 cm²

- recovery: cation and anion resin

64Ni electro-plating device

- 64Ni target

- PE motor

- PE Cu cooling plate, 0.5 mm

- 64Ni target thickness: ~8 mg/cm²

- Flow rate: 40 L/min
Solvent extraction of 64Cu with dithizone

Solvent extraction of 64Cu with dithizone

Flow chart of chemical processing for 64Cu production

64Ni recovery yield: >98%

64Ni electrolyte: 200mg Ni, 1.0g boric acid, 2g NaCl in 90ml H2O

64Ni electroplating for target fabrication:
- Electrolyte: 300mg KAu(CN)2, 3g EDTA, 2g KH2PO4 in 500ml H2O
- Thickness control with MCA: 57Ni counting (1377keV)

Target dissolving:
- 50ml hot 5N HCl
- 450ml H2O addition

Solvent extraction:
- 4-0.5N HCl
- 0.1N HCl

Distribution ratio of HCl molarity

<table>
<thead>
<tr>
<th>Distribution ratio of HCl molarity</th>
<th>%</th>
<th>%</th>
<th>%</th>
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<td>0.0%</td>
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<td>5.0%</td>
<td>5.5%</td>
<td>6.0%</td>
</tr>
</tbody>
</table>

Table: Radionuclides in the proton beam irradiated 64Ni target

- Distribution of 64Cu, 57Ni, 55, 57Co
- Irradiation time: 2hr
- Current: 0.2mA
- Particle Energy: p, 18MeV
- Cyclotron: IBA Cyclone-30
- Coolant: water 40L/min
- Target carrier

DCu = [64Cu]org./[64Cu]aq.
Chemical separation system for 64Cu production

- Peristaltic pump
- Heater & TC
- pneumatic cylinder

64Ni target dissolution system

- Target Ni
- Dissolution system
- Cation Column for Ni recovery

- Rotatry heater
- Power supply
- Temp. controller
- Thermocouple
- Cu cooling plate
- Enriched Ni-64 target

Solvent washing

- Organic solvent
- Transparent plastic peristaltic pump
- Rotatry pneumatic cylinder

- Chemical processing device
- Solvent extraction column

- Ni target dissolution with 50 ml of 5N hydrochloric acid (flow rate: 1ml/min, temp.: 90°C)

Quality control of 64Cu

- 24% 64Ni: is it worth?
- 400mCi/batch
- 9mCi/uA (= 90% theoretical value)

- Absence of front cooling

- No problems found

- Why not radiochromatography separation?

Conclusions

- Target material: 26% 64Ni
- 64Cu production yield: 8.9mCi/µAh (96% enrichment, at EOB)
- Proton energy and current: 18MeV, 200µA
- Separation method:
  - solvent extraction: 0.1% dithizone in CCl4-HCl
  - ion chromatography: AG1x-8
  - Separation yield of 64Cu: >90%
  - Radionuclidic purity: >99%

64Ni recovery method:

- Cation, anion resin
- Recovery yield: >98%
- Radionuclidic purity: >99%
- Separation yield of 64Cu: >90%

- Quality control of 64Cu (γ-ray, metal impurity)
Activity Delivery System

D.B. Mackay¹, C. Lucatelli¹, R. van Ham², M. Willemsen², P. Thoonen², B. Kummeling², J.C. Clark¹

¹CRIC, University of Edinburgh, ²Von Gahlen, Nederland B.V

The CRIC radio-chemistry facility requires that radio-nuclides produced on a GE PETtrace 8 cyclotron are delivered to 4 hot cells in a GMP production lab and to 3 hot cells in a R&D lab. CRIC is working closely with Von Gahlen to develop a comprehensive radionuclide delivery system. The ADS is capable of supplying radioactive gases and liquids safely and reliably from the cyclotron to all of the points of use. The switching valves also have the possibility of directing the radio-nuclides to waste.

The route possibilities are shown in figure 1.

Figure 1: Delivery system routes.
The switching valves and isolation valves have all been selected for their proven reliability and adequate performance characteristics. The system will be controlled by a plc. Software will be validated to GAMP 5. The operator can control the delivery from one of three touch screen panels. The system has been designed with a high level of safety both for the operators and the environment. The whole system is enclosed in a stainless steel box. The box has separate compartments for the valves and the control equipment. The valves and filters are housed in an airtight lead-shielded compartment (75mm) which is ventilated. The extract air is filtered with HEPA/charcoal filters. Access inside the shielded compartment is not possible while delivery is in progress or when the radiation level is above a pre-set threshold. This is achieved by interlocking the door lock to an internally mounted radiation detector. Delivery along the chosen route can only occur when safe pre-conditions have been met (e.g. hot cell doors closed). The lines to the hot cells are run in floor trenches under the hot cells. The trenches are shielded with 75mm of lead and provided with hatches to facilitate replacement of lines.

Views of the box are shown below.

Figure 2: Activity delivery system shielded box
The CRIC Facility, Edinburgh

**The GMP hot cell lab**
- 4 Production hot cells (2x Von Gahlen SB2S)
- GMP lab with 4 hot cells
- GMP lab with 4 hot cells
- GE PETtrace 8 cyclotron in a vault
- Facilities for dispensing and sterilising either by autoclave or aseptic filtration
- Separate R&D lab with 3 hot cells
- PET/CT, CT and 3T MRI scanners
- HPLC cabinet
- The GMP hot cell lab
- Integrated filter integrity test
- Aseptic dispensing facility (Von Gahlen DPB)
- GE Fastlab dispenser/sterilizer
- GE Fastlab dispenser/sterilizer
- MX, 1x FXC Pro, 1x FXFN
- Products from all 4 hot cells can be transferred to either dispensing cell
- HPLC cabinet
- The CRIC Facility, Edinburgh

**System Delivery Activity**

D.B. Mackay
Risoe, 27 July 2010
The R&D hot cell lab

- 3 Von Gahlen hot cells (1x SB2S and 1xHC(R))
- Cells equipped with GE synthesisers (1x FXC Pro, 1x FXFN)
- All 3 hot cells are interconnected

HPLC cabinet

The Activity Delivery System Schematic

The HPLC support cabinet
The Activity Delivery System Hardware

**Safety**
- FMEA analysis conducted
- All lines run in 75mm lead-shielded floor trenches
- Door interlocks
- Door lock
- Radiation monitor built-in
- Exhaust air HEP/Charcoal filtered
- Box vented (negative pressure)
- Inlet air HEP filtered
- Rotary valve position feedback
- Valves separate from actuation
- Seal dried compartment
- 75mm lead shielding
- Log in with user levels and password control.

**Control**
- Plc control Modicon M340 Type 2020
- Touch screen with user log in and access levels
- Delivery only possible if cyclotron status door interlocks and radiation levels ok.
- Software to GAMP 5
- Pic control Modicon M340 Type 2020

**Values**
- Low dead volume for liquids
- Wetted path materials checked
- Helium specified for noble rising clean, high-performance valves
- Cleanliness for C-1 - labory
- Safety valves default to closed
- Separate analog valves (clean)
- High pressure specs
- Different valves for gases and liquids

**11 11**
- Software to GAMP 5
- Delivery only possible if cyclotron status door interlocks and radiation levels ok.
- Touch screen with user log in and access levels
- Pic control Modicon M340 Type 2020
Conclusion

- Flexible
- Expandable
- Safe
- Reliable
- Affordable

Authors and acknowledgements

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Integrated GMP PET Radiotracer Production and Dispensing Facility

C. Lucatelli¹, D. B. Mackay¹, G. Mokosa², C. Arth², R.C. van Ham, M.A.B. Willemsen³, J. C. Clark¹

¹University of Edinburgh, CRIC, ²Millipore France, ³Von Gahlen Nederland B.V

Dispensing of PET radiopharmaceuticals can be done either by final thermal sterilization or by sterile filtration. If thermal sterilization is the recommended method, it is very often impractical (short half-life, tracer thermo-sensitive) and many PET radiotracers are therefore dispensed by sterile filtration.

Among all the Quality Control tests required, prior to batch release, by Good Manufacturing Practice and European Pharmacopeia standards, the integrity of the membrane filter used during the final dispensing is to be checked. This activity is relatively time consuming and is the main source of analyst finger radiation doses.

To overcome this problem, we decided that this test should be automated and “in line” to avoid manual handling of this highly active filter, and to allow other activities to be performed as the filter is being tested.

The University of Edinburgh is currently setting up a brand new PET radiotracer production facility, as part of its new Clinical Research Imaging Centre (CRIC) and wants to achieve a state of the art uncluttered integrated facility.

![Figure 1: GMP production lab hot cells assembly.](image1)
From left to right: ventilated HPLC cabinet; GE FASTLab dispenser and sterilizer; 2 VG SB2S hot cells; 2 VG SB2S hot cells; VG Grade A DPB-LF dispenser.

![Figure 2: Millipore Integritest® 4](image2)

This facility will operate a GE PETtrace 8 cyclotron equipped with 5 targets: 2 Niobium for $^{18}$F production, 1 $^{11}$C-CO$_2$, 1 $^{11}$C-CH$_4$ and 1 $^{15}$O-target. The 4 first targets will be connected to 2 independent labs, a GMP production housing 4 hot cells and a R&D lab housing 3 hot cells. The target will be routed to the right destination using a specially designed Activity Delivery System. A specially designed ventilated HPLC cabinet, integrated within the row of hot cells will house 2 GE
synthesiser module electronic racks, 2 semi-preparative HPLC pumps and a computer controlling the cyclotron.

In addition to the 4 production hot cells, the GMP production lab will be equipped with 2 dispenser hot cells, a GE FASTLab dispenser and autoclave for thermal sterilisation and a Grade A Von Gahlen DPB-LF hot cell for the aseptic dispensing of radiotracers sensitive to heat or with a short half-life. Each of the production hot cells will be connected via shielded ducts to both dispensers.

As part of the design of the lab, we investigated the possibility of integrating a filter integrity test facility into our aseptic dispensing hot cell.

We decided to use the “off the shelf” Millipore Integritest 4 (Networked version) as a basis for this system, due to its modular design. We worked jointly with Millipore and Von Gahlen to achieve a solution which would allow the filter to be directly and automatically tested as part of the dispensing process.

The challenge was to integrate this tabletop system into the hot cell without compromising the Grade A laminar flow and the radioprotection. To achieve this integration, the commercial system needed to be disassembled. The touch screen computer panel is located on the front face of the hot cell. The part connected to the filter (External Valve Array) is fitted into the shielded environment and the remaining parts are located in a shielded enclosure on the top of the hot cell. A solenoid valve protects the Millipore External Valve Array during the filtration of the product. The filter is connected to product transfer line and to the Millipore Integritest® 4 by a sterile single use Vygon tubing assembly equipped with a check valve.

Figure 3: Integration of the Millipore Integritest® 4 into the Von Gahlen DPB-LF hot cell.
Introduction

Dispensing and sterilisation of PET radiotracers can be done either by terminal sterilisation or by aseptic sterile filtration. Although the recommended method is very clean, it is impractical (short half-life, thermal-sensitive tracers) and many PET radiotracers are therefore dispensed by aseptic sterile filtration.

As part of the design of our new lab, we investigated the possibility of integrating an integrity test facility into our aseptic dispensing hot cell. By Good Manufacturing Practice and European Pharmacopoeia standards, the integrity of the terminal sterilisation membrane filter used during the terminal sterilisation and dispensing must be checked. This activity can be cumbersome and is the main source of analyst finger radiation doses. A test to overcome this problem, we decided that this test should be automated and "in line" to avoid manual handling of this highly active filter, and to allow other activities to be performed as the filter is being tested.

Among the Quality Control tests required, prior to batch release by Good Manufacturing Practice and European Pharmacopoeia standards, the integrity of the membrane filter used during the terminal sterilisation and dispensing must be checked. This activity can be cumbersome and is the main source of analyst finger radiation doses.

To overcome this problem, we decided that this test should be automated and "in line" to avoid manual handling of this highly active filter, and to allow other activities to be performed as the filter is being tested.
The University of Edinburgh is currently setting up a brand new PET radiotracer production facility, as part of its new Clinical Research Imaging Centre (CRIC) aiming to achieve a state of the art integrated uncluttered GMP facility.

As part of the design of the lab, we investigated the possibility of integrating a filter integrity test into our aseptic dispensing hot cell. We decided to use the "off the shelf" Millipore Integritest 4 (Networked version) as a basis for this system due to its modular design.

We have worked jointly with Millipore and Von Gahlen to achieve a solution which would allow the filter to be directly and automatically tested as part of the dispensing process. A solenoid valve protects the Millipore External Valve Array during the filtration of the product. The filter is connected to product transfer line and to the Millipore Integritest® 4 by a sterile single use Vygon tubing assembly "Octopus". The part connected to product transfer line and to the Millipore Integritest® 4 by a sterile Valve Array is fitted into the shielded environment hot cell. The part connected to the filter (External Valve Array) is located on the front face of the complete panel, to be dismantled. The touch screen and the operator manual for this system needed to be dismantled. The touch screen and the operator manual needed to be dismantled.

To achieve this integration, the commercial system was to integrate this tabletop system into the hot cell without compromising the Grade A environment. To achieve this integration, the commercial system was to integrate this tabletop system into the hot cell without compromising the Grade A environment.

Integration

The challenge was to integrate the tabletop system into the hot cell without compromising the Grade A environment. To achieve this integration, the commercial system needed to be disassembled. The touch screen and the operator manual needed to be dismantled. The touch screen and the operator manual needed to be dismantled. The touch screen and the operator manual needed to be dismantled.
A solenoid valve protects the Millipore External Valve, ensuring product integrity. The filter is connected to the product transfer line and the Millipore filter by a sterile Vygon tubing assembly equipped with a check valve.

The facility remains to be validated, but we are quite confident that all will be well. Our thanks go to Millipore and Von Gahlen for their willingness to engage with a user to arrive at a solution to a common problem. It is an example of the willingness of commercial partners to collaborate in this way.

The facility remains to be validated, but we are quite confident that all will be well. Our thanks go to Millipore and Von Gahlen for their willingness to engage with a user to arrive at a solution to a common problem. It is an example of the willingness of commercial partners to collaborate in this way.
Synthesis of 4-[18F]Fluorobenzaldehyde in a CPCU for Peptide Labeling

V.M. Lara-Camacho, J.C. Manrique-Arias, E. Zamora-Romo, A. Zarate-Morales, A. Flores-Moreno, M.A. Avila-Rodriguez

Unidad PET/CT-Ciclotrón, Facultad de Medicina, Universidad Nacional Autónoma de México, México, D.F., México

Objectives: Implement the synthesis of 4-[18F]fluorobenzaldehyde ([18F]FB-CHO) in a CTI/Siemens Chemistry Process Control Unit (CPCU) for peptide labeling.

Methods: No-carrier-added [18F]FB-CHO was prepared by radiofluoridation of 4-formyl-N,N,N-trimethylanilinium triflate precursor in two reaction vessels. Reagents used in the synthesis are summarized in the table below. After elution of 18F from QMA cartridge and azeotropic distillation at 110°C in reaction vessel #1, precursor was added, bubbled for a few seconds, and transferred to reaction vessel #2. Fluorination reaction was performed at 60°C for 10 min [Speranza et al., Appl. Radiat. Isot. 67 (2009) 1664] and the residue mixture was diluted with 3 mL of H2O. The product was trapped in a Sep-Pak C18 cartridge and washed with 10 mL of H2O. [18F]FB-CHO was eluted with 0.5 mL of EtOH. For peptide labeling HYNIC-peptide conjugates were incubated with [18F]FB-CHO at 50°C, 25 min, pH 4.5. Purification was performed by gradient-HPLC in a semi-prep C18 reverse phase column with EtOH/H2O 10-80% in 20 min [Lee et al., Nucl. Med. Biol. 33 (2006) 667]

<table>
<thead>
<tr>
<th>Vial #</th>
<th>Reagents Vessel #1</th>
<th>Reagents Vessel #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K222/K2CO3</td>
<td>Vial empty</td>
</tr>
<tr>
<td>2</td>
<td>2 mL CH3CN</td>
<td>Vial empty</td>
</tr>
<tr>
<td>3</td>
<td>5 mg precursor in 1 mL DMSO</td>
<td>Vial empty</td>
</tr>
<tr>
<td>4</td>
<td>Vial empty</td>
<td>3 mL H2O</td>
</tr>
<tr>
<td>5</td>
<td>Vial empty</td>
<td>10 mL H2O</td>
</tr>
</tbody>
</table>

Results: [18F]FB-CHO was obtained in a decay corrected RCY of 30% within 50 min with a RCP>95%. The peptides Try2-Octreotide (TOC) and c-RGDyK (RGD) were labeled with 60-90 efficiencies with RCP>99% after HPLC purification, independently of the peptide used. MicroPET studies were performed with [18F]FB-CH=N-NYNIC-RGD using C6 glioma xenografts in nude mice.

Conclusions: After the CPCU was replaced with a modern FDG-maker in our institution, to this chemistry module was given a second chance for the synthesis of other tracers taking advantage of its simplicity and versatility. In this work, [18F]FB-CHO was successfully prepared and used for peptide labeling with a RCY highly enough for clinical applications.
**Materials and Methods**

**Steps of [18F]FB-CHO**

1. **Arrangement**
   - CPCU Arrangement
   - Vessel Reagents

<table>
<thead>
<tr>
<th>#</th>
<th>Vial</th>
<th>Reagents</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>1.5 mL K-222/K CO3</td>
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</tr>
<tr>
<td>2</td>
<td>5.0 mL precursor</td>
<td>20 mL CH3CN</td>
</tr>
<tr>
<td>3</td>
<td>1.5 mL K-222/K CO3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>93.0 mL H2O</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>10 mL H2O</td>
<td></td>
</tr>
</tbody>
</table>

2. **Synthesis**
   - 4-Formyl-N,N-trimethylaminium triflate precursor

   ![Synthesis Diagram]

3. **Steps**
   - Reaction Vessel # 1
     - Reaction
     - Purification
   - Reaction Vessel # 2
     - Azeotropic distillation
     - Nucleophilic Reaction

4. **Objective**
   - To implement the synthesis of [18F]FB-CHO in a CPCU for peptide labeling.

**Unidad PET, Facultad de Medicina-UNAM, Mexico D.F.**


For peptide labeling:

[18F]Fluorobenzaldehyde in a CPCU
**Results**

**Receptors Blocking Method**

- **Control**
  - 200 µCi (18F-FB-CH=N-HYNIC-RGD)
  - 1 h

- **Blocked**
  - 200 µCi (18F-FB-CH=N-HYNIC-RGD)
  - 1 h

**Peptide-radiolabeling**

- After elution from C18 with 0.5 ml of EtOH, the [18F]FB-CHO was incubated with peptide conjugated.

**Gradient-HPLC** in a semi-prep C18 reverse phase column with EtOH/H2O, 10-80% in 20 min [Lee et al. 2006].

**MicroPET Focus 120**

- Axial
- Coronal
- Sagittal

**Targeting Tumor Expression of αvβ3 Integrin with [18F]FB-CH=N-HYNIC-RGD**

G6 glioma xenograft in nude mice

**Peptide-radiolabeling**

- [18F]FB-CHO HYNIC-R

<table>
<thead>
<tr>
<th>R</th>
<th>RCP</th>
<th>RCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>RGD, Octreotide, Bombesine</td>
<td>&gt;95%</td>
<td>~60-90%</td>
</tr>
<tr>
<td>[18F]FB-CHO HYNIC-R</td>
<td>&gt;99%</td>
<td>t = 1 h</td>
</tr>
</tbody>
</table>

**RCY ~ 30%**

- Na(t) = 50 min
- Na(t) = 1 h

**Peptide-radiolabeling**

- [18F]FB-CHO HYNIC-R

**MicroPET Focus 120**

- Axial
- Coronal
- Sagittal

**Receptors Blocking Method**

- Control
  - 200 µCi (18F-FB-CH=N-HYNIC-RGD)
  - 1 h

- Blocked
  - 200 µCi (18F-FB-CH=N-HYNIC-RGD)
  - 1 h

**Results**

- **RCI ~ 30%**
- **RCP > 95%**
- **t = 1 h**

**MicroPET Focus 120**

- Axial
- Coronal
- Sagittal
Conclusions

- The synthesis of $^{18}$FFB-CHO was successfully achieved in the CPCU.
- $^{18}$FFB-CHO was used for peptide labeling.
- The synthesis of $^{18}$FFB-CHO represents a second chance for the CPCU module in the preparation of other tracers.
- $^{18}$FFluorothymidine is another tracer synthesized in the CPCU with a RCY $>$ 30%, with 10 mg of BOC-precursor.
A comparison of Nb, Pt, Ta, Ti, Zr, and ZrO$_2$-sputtered Havar foils for the high-power cyclotron production of reactive $[^{18}\text{F}]\text{F}^-$

K. Gagnon, J.S. Wilson, and S.A. McQuarrie

Edmonton PET Centre, Cross Cancer Institute, University of Alberta, Edmonton, AB, CANADA

Introduction: Previous studies performed at the Edmonton PET Centre (EPC) have demonstrated that the use of Nb-sputtered Havar foils during $[^{18}\text{F}]\text{F}^-$ production via proton irradiation of $[^{18}\text{O}]\text{H}_2\text{O}$ decreases the radionuclidic and chemical impurities within the irradiated water$^1$. Given the improved $[^{18}\text{F}]\text{F}^-$ reactivity, increased $[^{18}\text{F}]\text{FDG}$ yield consistency, and decreased need for target rebuilding noted for Nb-sputtered Havar, these sputtered foils were adopted as the standard practice for $[^{18}\text{F}]\text{F}^-$ production at our facility in mid-2006. Following prolonged use of the Nb-sputtered foils however, degradation of the niobium film has been noted, with Havar impurities, FDG yield consistency and $[^{18}\text{F}]\text{F}^-$ reactivity returning over time to levels comparable with that of non-sputtered Havar.

Aim: The goal of this current work was to find a film that demonstrates increased longevity with regards to $[^{18}\text{F}]\text{F}^-$ reactivity when compared with niobium.

Methods: All film sputtering (Nb, Pt, Ta, Ti, Zr, and ZrO$_2$) was performed on 30 µm Havar at the University of Alberta’s NanoFab micro and nanofabrication research facility (Edmonton, AB). Film thicknesses were verified through profilometer measurements and SEM micrographs.

To test the Havar impurity reducing properties of the sputtered foils (thicknesses = 250–450 nm), test irradiations were performed using 2.8–3.0 mL Barnstead 18MΩ-cm $\text{natH}_2\text{O}$. Multiple (N = 9–15) test irradiations (of 1,000 µAmin and 5,000 µAmin) were performed on all foils at 17.5 MeV using the EPC’s TR 19/9 cyclotron to achieve total integrated currents of approximately 20,000–30,000 µAmin (weighted average currents of 69–81 µA). To ensure consistent irradiation conditions and complete sample transfer, both the $^{13}\text{N}$ saturated yield and the recovered $\text{natH}_2\text{O}$ mass were measured following all irradiations. Following $^{13}\text{N}$ decay, all water samples were assayed for radionuclidic impurities using an HPGe detector (dead time < 5%). Chemical analysis for extractable metals was also performed for a subset of the water samples via inductively coupled plasma mass spectroscopy (ICP-MS) at the Exova Lab (Edmonton, AB).

As tantalum was the only film which demonstrated Havar impurity-reducing properties comparable to niobium, the foil above was further irradiated to a total integrated current of 80,000 µAmin. Given the excellent continued performance noted via radionuclidic contaminant analysis, our next step was to install a new Ta-sputtered foil on our main production target for the purpose of testing both the $[^{18}\text{F}]\text{F}^-$ reactivity and evaluating the tantalum film’s longevity performance. Prior to installation of the Ta-sputtered Havar on our production target, a series of five 1,000 µAmin (65 µA) $\text{natH}_2\text{O}$ test irradiations were performed on the existing (previously irradiated to ~980,000 µAmin) 400 nm Nb-sputtered Havar foil to establish a baseline to which the tantalum results could be compared. A new 900 nm Ta-sputtered Havar foil was installed and the produced $[^{18}\text{F}]\text{F}^-$ used for routine production of $[^{18}\text{F}]\text{FDG}$, $[^{18}\text{F}]\text{FAZA}$, and $[^{18}\text{F}]\text{FLT}$. Periodically (every 75,000–100,000 µAmin), a series of four test irradiations (1 @ 5,000 µAmin followed by 3 @ 1,000 µAmin) were carried out at 65 µA on $\text{natH}_2\text{O}$. All test irradiations were assayed for radionuclidic impurities.

Results: The following figure summarizes the Havar-associated radionuclidic impurities measured for the initial (approx. 20,000–30,000 µAmin) test irradiations, and the Ta-sputtered sputtered foil to 80,000 µAmin ("Ta (80k)"). With a clear dependence noted on the integrated current, the reported values are given as the average and standard deviation of the end-of-bombardment (EOB) radioactivity normalized to the integrated current for each irradiation. It is important to note that since the radionuclidic impurities showed a marked decrease for the first few irradiations on all new foils before reaching a relatively constant value, the first three 1,000 µAmin irradiations were omitted when producing the figure below. Evaluation of this figure reveals that tantalum is the only film which demonstrates radionuclidic impurity reducing characteristics similar to that of niobium. Based on strong correlations observed between the radionuclidic and ICP-MS measurements, we have concluded that trends noted in the radionuclidic impurities are reflective of trends in the ionic impurities.

Table 1 summarizes the radionuclidic impurities (in units of mBq/µAmin at EOB) measured for the previously employed Nb-sputtered foil and the Ta-sputtered foil used on the production target. All values are reported as the average and standard deviation of the normalized activities. The integrated current (C) is reported as the total current on target prior to the test irradiations.

Table 2 summarizes the [18F]FDG decay-corrected (DC) yields and end-of-synthesis (EOS) activities (A) obtained on the EPC’s GE TracerLab MX synthesis unit for all syntheses performed up to the reported integrated current. A comparison of the average [18F]FDG DC yield (for comparable total integrated currents) demonstrates a 6.4 percent improvement (one-tailed t-test, p = 0.0025) with the Ta-sputtered foil when compared with the previously employed Nb-sputtered foil.

Conclusions: Compared with our current Nb-sputtered Havar standard, the Ta-sputtered Havar demonstrates a significant reduction in the Havar-associated impurities following prolonged use up to ~1,000,000 µAmin. In addition to decreased Havar-associated impurities, we have also noted an improvement in the [18F]FDG yields and yield consistency. Studies are currently underway to further evaluate this Ta-sputtered foil to a total integrated current of ~1,500,000 µAmin.

Acknowledgements: This project was supported by the University of Alberta’s MicroSystems Technology Research Initiative (MSTRI). The authors would like to thank Dr. Chris Backhouse and Ms. Eva Sant for their helpful discussions in film selection, and for performing the film sputtering.
Background

- Ionic contaminants in irradiated \( [^{18}O]H_2O \) have been attributed to decreases in the reactivity of \( [^{18}F]F \).
- Nb-sputtered Havar reduced the radionuclidic impurities and improved the \[^{18}F\]FDG yields and yield consistency.
- Early 2006, Nb-sputtered Havar foils were first introduced at the Edmonton PET Centre.
- TracerLab MX

Irradiations performed:

- \( [^{18}O]H_2O \) irradiations to:
  - Assess \[^{18}F\]FDG yield using TracerLab MX.
  - Perform ICP-MS (small sample subset).
  - Measure conductivity of irradiated water.
  - Assess radionuclidic impurities (both Havar and \( [^{18}O]H_2O \) irradiations).

Challenge:

- \( \text{Goal: Investigate alternative sputtering materials} \)
- \( \text{Over time following prolonged irradiation, the Nb film oxidizes} \)

A comparison of Nb, Pt, Ta, Ti, Zr, and ZrO_2
Initial test irradiations on nat\(H_2O\)

<table>
<thead>
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<tbody>
<tr>
<td>1219 ± 39</td>
<td>0</td>
<td>0</td>
<td>29000</td>
<td>13</td>
<td>15</td>
<td>375</td>
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<td>375</td>
</tr>
<tr>
<td>1237 ± 32</td>
<td>7</td>
<td>1</td>
<td>1000</td>
<td>15</td>
<td>375</td>
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<td>1190 ± 30</td>
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<td>17047</td>
<td>6</td>
<td>250</td>
<td>1255 ± 36</td>
<td>12</td>
<td>1255 ± 36</td>
</tr>
<tr>
<td>1216 ± 42</td>
<td>7</td>
<td>8</td>
<td>32053</td>
<td>13</td>
<td>250</td>
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<td>1237 ± 36</td>
<td>1</td>
<td>12</td>
<td>2800</td>
<td>12</td>
<td>250</td>
<td>815 ± 9</td>
<td>12</td>
<td>815 ± 9</td>
</tr>
</tbody>
</table>

Tantalum – a promising candidate?

Results of initial irradiations

Information from thin radioactive contaminants was also useful.

Care taken to ensure consistent sample handling.
Trends for Ta-Havar

Summary

<table>
<thead>
<tr>
<th>Nb vs. Ta Impurities [mbg/μAmin]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niobium</td>
</tr>
<tr>
<td>936.892</td>
</tr>
</tbody>
</table>

Min EOS Activity [GBq]

Max EOS Activity [GBq]

Mean EOS activity [GBq]

Mean decay corrected yield [%]

35

38

45

54

9248 ± 1476

42 ± 6

62 ± 14

72 ± 14

Co-57

94 ± 18

2038 ± 2038

Co-52

92 ± 13

206 ± 206

Co-56

94 ± 13

204 ± 204

Note: Nb @ ~1,000,000 μAmin.
A simple calibration-independent method for measuring the beam energy of a cyclotron

K. Gagnon1, M. Jensen2, H. Thisgaard2+, J. Publicover3++, S. Lapi3+++ S.A. McQuarrie1 and T.J. Ruth3

1Edmonton PET Centre, Cross Cancer Institute, University of Alberta, Edmonton, AB, CANADA
2Hevesy Laboratory, Risoe-DTU, Technical University of Denmark, Roskilde, DENMARK
3TRIUMF, Vancouver, BC, CANADA
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Introduction: When used for medical radionuclide production, both new and old cyclotrons need to have their beam energy checked periodically. This is not only part of good manufacturing practice and quality assurance but is also necessary for optimising target yields and minimising the radiation dose overhead of radionuclide production. As the production targets for most medical cyclotron configurations sit more or less straight on the vacuum tank with no room for beam diagnostics, an off-line approach for evaluating the beam energy of a medical cyclotron is required. Although beam monitor reactions have been extensively published, evaluated, and used for many years, the reliable use of these methods, at present, requires access to and knowledge of a well calibrated (typically HPGe) detector system.

Aim: Develop a simple method for evaluating the beam energy of a cyclotron to an accuracy of a few tenths of an MeV without using complex data analysis methods or sophisticated equipment.

Theory: To overcome the need for gamma spectroscopy and high quality efficiency calibrations, this study suggests the irradiation of two thin monitor foils of the same material interspaced by a thick energy degrader. By carefully selecting both the monitor foil material and degrader thickness, the differential activation of the two monitor foils may be used to determine the beam energy. The primary advantage to this technique is that by examining the ratio of two identical isotopes produced in the two monitor foils (e.g. $^{63}\text{Zn} / ^{63}\text{Zn}$) as opposed to, for example, the $^{62}\text{Zn} / ^{63}\text{Zn}$ ratio resulting from proton irradiation of a single copper monitor foil, all detector efficiency calibration requirements are eliminated. The energy can thus be monitored by experimentally measuring the activity ratio and comparing this value with activity ratios predicted using published cross section data ($\sigma$) as given by:

$$\frac{A_{\text{Foil1}}}{A_{\text{Foil2}}} = \frac{\sigma_{\text{Foil1}}}{\sigma_{\text{Foil2}}}. $$

A sample plot of the predicted $^{63}\text{Zn}$ activity ratio is given [right] for a 350 µm aluminum degrader, 25 µm copper monitor foils, and a 25 µm aluminum vacuum foil.

Methods: The proposed strategy was evaluated using 25 µm natCu monitor foils, a 25 µm aluminum window, and an aluminum energy degrader for protons in the 11–19 MeV range on the Edmonton PET Centre’s (EPC) TR 19/9 cyclotron and the tandem Van de Graaff at Brookhaven National Lab (BNL). As the sensitivity of this technique depends upon the degrader thickness employed, this technique assumes prior knowledge of the beam energy (within ~ 1 MeV).
degrader thicknesses employed in this study are given in the table [top right]. For the blind BNL measurements, the energy range was specified so that an appropriate degrader thickness could be selected.

Prior to irradiation, the predicted activity ratios were determined using the IAEA recommended $^{nat}$Cu(p,x)$^{63}$Zn cross sections (www-nds.ipen.br/medical/) and simulations performed in the TRIM module of SRIM (www.srim.org), v.2008.04. From these predicted ratios, we present in the above table the coefficients (A, B, and C) necessary for determining the proton energy incident on the aluminium vacuum window, $E$(MeV) = Ar$^2$ + Br + C, where r is the experimental $^{63}$Zn activity ratio measured between the front and back copper foil. In obtaining these coefficients we have assumed the presence of a 25 µm Al vacuum window, the Al degrader, and two 25 µm Cu monitor foils.

Following irradiation, the $^{63}$Zn activity ratios were measured using Capintec™ CRC-15PET (EPC) and CRC-15W (BNL) dose calibrators set to an arbitrary calibration setting of 100. As $^{62}$Cu and $^{62}$Zn production is also possible during irradiation of $^{nat}$Cu, activity measurements were made at: (i) a single time-point roughly 1-hour post-EOB to ensure minimal $^{62}$Cu contribution, and (ii) multiple time-points from 20 minutes to 3 hours post-EOB where the $^{63}$Zn activity reading contribution was determined through exponential curve fitting to account for both the $^{62}$Cu and $^{62}$Zn contributions.

Results: The table [bottom right] summarizes the incident energies evaluated using the $^{63}$Zn activity ratio measured using either the single 1-hour post-EOB time-point or exponential stripping of the $^{63}$Zn activity contribution via curve-fitting. All energies are reported as the energy incident on the vacuum foil and were calculated using the coefficients provided above. The excellent agreement noted with the nominal energy for the 1-hr measurements up to 17 MeV suggests that half-life discrimination is not necessary below this energy.

Conclusions: The new, simple, calibration-independent method proposed for measuring the beam energy of a cyclotron was found to provide an accurate determination of proton energies in the 11–19 MeV range without the need for sophisticated equipment. To facilitate the adoption of this technique into routine evaluation of the cyclotron beam energy, we have included a look-up table of recommended aluminum degrader thicknesses as well as a list of the corresponding curve fit data for evaluation of the proton energy using the measured $^{63}$Zn activity ratio.

Acknowledgements: The authors would like to thank Drs. Chuck Carlson, Michael Schueller, and David Schlyer for helpful discussions and organizing the experiments at BNL. This work was supported through a grant from NSERC.
Proposed Method:

Irradiate two monitor foils interspaced by an energy degrader.

Compare the activation of the same isotope for both foils.

Proposed Method:

\[
\frac{A_{\nu}^{(63)Zn}}{A_{\nu}^{(63)Zn}} > 1
\]

\[
\frac{A_{\nu}^{(63)Zn}}{A_{\nu}^{(63)Zn}} < 1
\]

*Not to scale*
Proposed Method:

Example given for 875 μm Al degrader and two 25 μm Cu foils.

Predicting the ratio:

\[
\frac{\delta \rho}{\delta \phi} = \frac{\delta \gamma}{\gamma}
\]

Efficiency calibration independent!

Implementation

- Efficiency calibration independent!
- Since we are examining the ratio of the same isotope, detector efficiency calibration factors will cancel!
- We are examining the ratio of the same isotope.

Benefits:

- Ratio depends only on the shape of the cross section curve.
- Ratio is independent of irradiation length.
- Ratio is independent of irradiation time post-EOB.
- Ratio is independent of energy.
- Error in magnitude will not impact the results.

\[
\frac{(\gamma) \frac{d\rho}{d\phi}}{(\gamma) \frac{d\rho}{d\phi}} = \frac{(\gamma) \frac{d\rho}{d\phi}}{(\gamma) \frac{d\rho}{d\phi}} = \frac{(\gamma) \frac{d\rho}{d\phi}}{(\gamma) \frac{d\rho}{d\phi}} = \frac{(\gamma) \frac{d\rho}{d\phi}}{(\gamma) \frac{d\rho}{d\phi}} = \frac{(\gamma) \frac{d\rho}{d\phi}}{(\gamma) \frac{d\rho}{d\phi}}
\]

Step 1 - Before experiment:

- Produce graph of energy vs. 63Zn activity ratio.
- Note: One degrader isn’t optimal for all energies.
- Example above: Al = 350 μm, Cu = 25 μm Al in vacuum.

Step 2 - After experiment:

- Measure the activity ratio.
- Use the plot to determine the irradiation energy.
- Produces graph of energy vs. activity ratio.
- Efficiency calibration independent!
### Results EPC:

<table>
<thead>
<tr>
<th>Incident energy (MeV)</th>
<th>Measured energy (MeV)</th>
<th>Max. from nominal</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.1</td>
<td>11.2</td>
<td>0.1</td>
</tr>
<tr>
<td>11.6</td>
<td>11.6</td>
<td>0.1</td>
</tr>
<tr>
<td>13.8</td>
<td>13.8</td>
<td>0.1</td>
</tr>
<tr>
<td>15.4</td>
<td>15.4</td>
<td>0.1</td>
</tr>
<tr>
<td>16.0</td>
<td>16.2</td>
<td>0.2</td>
</tr>
<tr>
<td>17.0</td>
<td>17.0</td>
<td>0.1</td>
</tr>
</tbody>
</table>

### Reproducibility at EPC:

<table>
<thead>
<tr>
<th>Reproducibility at EPC</th>
<th>Tandem Van de Graaff at BNL:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Competing Reactions?

- Said that:
  - Only true if Zn is the only contribution to the reading
- Said that:
  - Only true if Zn is the only contribution to the reading

\[
\frac{R_{op}}{R_{op}} = \frac{1}{V}
\]
Evaluated a new method for measuring $E_p$

Method is independent of detector calibration and shows good reproducibility and agreement with the nominal energies.

Method is insensitive to small variations in nominal foil thickness error.

Future work: Other energy ranges? Detectors?
Thermal modelling of a solid cyclotron target using finite element analysis: An experimental validation

K. Gagnon, J.S. Wilson, and S.A. McQuarrie

Edmonton PET Centre, Cross Cancer Institute, University of Alberta, Edmonton, AB, CANADA

Introduction: Although radioisotope production yields may be increased by elevating the irradiation current, the maximum allowable irradiation current is often dictated by the thermal performance of a target. This limitation is commonly observed for solid targets as these materials often demonstrate poor thermal conductivities and low melting points. As we are interested in improving the power rating of solid targets by optimizing the shape and location of the cooling channels, we have investigated the use of finite element analysis to model both heat transfer and turbulent flow. Before cooling optimization can be performed however, we needed to first validate our initial model. Such an experimental validation is the focus of this work.

Methods: For the purpose of validating the finite element model, we have designed a target plate with a simplistic geometry. In order to perform on-line real-time temperature measurements, this target plate is equipped with a thermocouple that extends to the centre of the plate [upper right]. Target plates of both copper and zirconium were constructed. These materials were selected for their markedly different thermal properties: copper is an excellent thermal conductor with a thermal conductivity, $k$, of 401 Wm$^{-1}$K$^{-1}$ (@ 300 K), while zirconium is a relatively poor thermal conductor with $k$ equal to 22.6 Wm$^{-1}$K$^{-1}$ (@ 300 K). The target plate and thermocouple were mounted into the water/helium cooled target assembly [lower right]. Irradiations were performed with proton currents up to 80 µA (17.5 MeV) for the copper plate and 50 µA (15.5 MeV) for zirconium. Both the beam tuning$^1$ and target positioning were optimized to maximize the temperature readout. In calculating the power on the target plate, we have assumed a 10 percent beam loss to the target nosepiece/helium cooling chamber. Several low current measurements were also obtained without helium cooling as this source of cooling is not yet incorporated into the finite element model.

The 3D heat transfer and turbulent flow of the cooling water were modelled using the COMSOL Multiphysics® v. 3.5a. steady-state general heat transfer and k-$\varepsilon$ turbulence models, respectively. Experimental input parameters to the model include the cooling water temperature, cooling water flow rate, target plate/cooling water channel geometry, and a sample proton beam profile obtained using radiochromic film$^2$. The temperature dependent material properties (i.e. thermal conductivity, density, heat capacity, etc.) were defined using COMSOL’s built-in material library.

One of the primary challenges in developing the model was to accurately define the convective heat transfer at the water/plate boundary. Although COMSOL has built-in heat transfer coefficients for various geometrical configurations, at present these coefficients are limited exclusively to air cooling applications. To this end, three user-defined strategies were employed for evaluating the convective heat transfer coefficient at the water/plate interface.

---

$^1$ See WTTC13 abstract: J.S. Wilson et al., A Simple Target Modification to Allow for 3-D Beam Tuning

The cooling geometry under consideration consists of a single central-inlet water-cooling channel and two water-outlets, all of which are perpendicular to the target plate [upper right]. Although the Dittus-Boelter and Sieder-Tate heat transfer formalisms are used to describe turbulent forced convection within long straight pipes (which is not representative of our geometric configuration), these two strategies were nevertheless investigated as both formalisms have been previously implemented and recommended for targetry applications\textsuperscript{3,4,5}. The third model employed for evaluating the heat transfer coefficient (selected for its geometric similarity to our configuration) was a method characterized by Chang et al. for turbulent submerged liquid jets\textsuperscript{6}. In all three strategies the Reynolds number was calculated from the temperature dependent water properties, the hydraulic diameter of the inlet water-cooling channel and the inlet water velocity, while the Prandtl number was calculated from the temperature dependent water properties. COMSOL’s non-linear, direct (UMFPACK) parametric segregated solver was employed to evaluate beam powers ranging from 50–1300 W.

**Results:** Three models were employed for characterizing the heat transfer at the water/plate boundary. Although all three strategies give rise to heat transfer coefficients whose magnitude increases as the cooling-water flow rate increases, when comparing the model predictions with experimental data [graphs, right], the results of this work suggest that the heat transfer in our geometric configuration is best described by the method proposed by Chang et al\textsuperscript{6}. The poor performance of the Dittus-Boelter and Sieder-Tate correlations has been attributed to the underlying geometric assumptions of these models.

**Conclusion:** The experimental measurements performed in this study have allowed us to select a convective heat transfer model which is capable of accurately predicting the target plate temperature for materials with widely varying thermal properties. Future finite element investigations will include the introduction of helium cooling and the optimization of the cooling channel geometry for the purpose of improving the solid target power rating.

**Acknowledgements:** The authors would like to thank Dr. Avila-Rodriguez for early development of the 3D target model. This project has been made possible through a grant from the Alberta Health Services and the Alberta Cancer Foundation.

\textsuperscript{3} Pavan et al., J. Radioanal. Nucl. Chem., 2003, 257: 203
\textsuperscript{5} IAEA Technical Reports Series no. 465, Vienna, 2008
\textsuperscript{6} Chang et al., Int. J. Heat Mass Transfer, 1995, 38: 833
Motivation

Motivation: Although increased beam currents are desired, production is often limited by the thermal performance of the target. Finite element analyses are employed to model heat transfer and impingement flow within the target. Target materials and geometry (plate/coating) are important parameters to model include.

Desire to use models to improve target thermal performance.

Goal of this work: Experimentally validate a finite element analysis based heat transfer/turbulent flow model.

Heat transfer coefficient

Difficulty: How to define the convective heat transfer coefficient?

3

Heat transfer coefficient

$\frac{\alpha}{\eta} = \frac{1}{\mathbf{Re}_t} \left( \frac{\eta}{\mathbf{Re}_t} \right)^{0.4}$

$\mathbf{Re}_t = \frac{\eta D}{k}$

$\eta = \frac{\mu}{\mu_b}$

$D = \text{hydraulic diameter}$

$k = \text{thermal conductivity}$

$\mu = \text{kinematic viscosity}$

$\mu_b = \text{bulk kinematic viscosity}$

Impact of plate spacing ($z_p$)

4

Thermal modelling of a solid cylinder target using COMSOL Multiphysics (finite element analysis).

- Proton current
- Convective heat transfer coefficient
- Cooling flow/temperature
- Target materials
- Geometry (plate/coating)

Experimental beam profile and scaling as a function of depth to account for non-uniform dE/dx.
Experimental validation

Compared experimental measurements with the three strategies for defining the heat transfer coefficient at the water/plate interface.

Examined Cu and Zr defining the heat transfer coefficient at the water/plate interface.

Compared experimental measurements with the three strategies for materials.

Mo on Cu vs. Mo on Ta @ 217 μA

Material | m.p. (°C) | I = 217 μA
---|---|---
Zirconium | 2128 | 22.6
Platinum | 2780 | 53.7
Rhodium | 3290 | 77.5
Molybdenum | 2896 | 14.6
Nickel | 1728 | 22
Tantalum | 3290 | 22.6
Niobium | 2750 | 53.7
Copper | 1357 | 40.1
Areas for optimization?

- Target plate material
- Water flow rate
- Input water temperature
- Cooling channel geometry
- Helium cooling geometry

Summary

- The experimental measurements have led to the selection of the heat transfer coefficient described by Chan et al.
- Model allows us to explore methods for improving the thermal performance of the target.

Beam profile & scaling with depth
Abstract 012

RDS-111 to Eclipse HP Upgrading with Improvement in $^{18}$F Production

A. Zarate-Morales, A. Flores-Moreno, J.C. Manrique-Arias, E. Zamora-Romo, M.A. Avila-Rodriguez

Unidad PET/CT-Ciclotrón, Facultad de Medicina, Universidad Nacional Autónoma de México, México, D.F., México

The first PET Center in Mexico was inaugurated in 2001 at the School of Medicine of the National Autonomous University of Mexico (UNAM). In that time a self-shielded CTI RDS-111 cyclotron with targetry for the production of the main sequence CNOF radionuclides was installed. Nowadays, there are 3 compact cyclotrons in the country and 11 PET/CT cameras in different hospitals. UNAM’s cyclotron produces FDG for 6 of the 8 PET scanners located in hospitals and clinics of Mexico City, and more hospitals are planning to install more PET/CTs. To satisfy this increased demand of FDG, one of the beam lines of our RDS-111 cyclotron was recently upgraded to an Eclipse HP configuration. In this way, now we have a hybrid cyclotron with BL1 as Eclipse HP and BL2 as RDS-111.

The main features of the upgrade include a new ion source that increased the beam current from 40 to 60 $\mu$A, a new four-position target carrousel capable to handle 60 $\mu$A, high power gridded-targets designed to be operated under high pressure conditions (>1000 psi), target body of refractory material (Ta) for the production of $^{18}$F, and installation of high vacuum butterfly valves to the diffusion pumps. In addition, the Eclipse HP beam line has no vacuum window, and therefore no helium recirculation cooling system. With this upgrade we practically double the yield of $^{18}$F with the same time of bombardment. Table 1 shows the yield of the different radionuclides in both versions while Table 2 summarizes our experience regarding $^{18}$F production.

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>RDS-111 (40 $\mu$A)</th>
<th>Eclipse HP (60 $\mu$A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{18}$F</td>
<td>1187 mCi (1h, 1200 $\mu$L H$_2^{18}$O)</td>
<td>2300 mCi (1h, 2400 $\mu$L H$_2^{18}$O)</td>
</tr>
<tr>
<td>$^{13}$N</td>
<td>146 mCi (10 min)</td>
<td>213 mCi (10 min)</td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>1547 mCi (40 min)</td>
<td>1902 mCi (40 min)</td>
</tr>
</tbody>
</table>

Table 1. Comparison of yields (EOB) obtained in RDS-111 vs. Eclipse HP targets.

<table>
<thead>
<tr>
<th>Bombardment time</th>
<th>$A_{EOB}$ of $^{18}$F</th>
<th>$A_{EOB}$ of FDG</th>
<th>Production runs</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDS-111</td>
<td>747.2 h</td>
<td>536.4 Ci</td>
<td>271 Ci</td>
</tr>
<tr>
<td>Eclipse HP</td>
<td>393.3 h</td>
<td>839.2 Ci</td>
<td>455 Ci</td>
</tr>
<tr>
<td>HP/RDS</td>
<td>0.53</td>
<td>1.56</td>
<td>1.68</td>
</tr>
</tbody>
</table>

The benefits of the upgraded BL were immediate for the production of $^{18}$F. The high volume Ta target produces more activity of highly reactive n.c.a. $[^{18}F]$fluoride compared with the traditional Ag target of the RDS-111 configuration. We are still producing $^{18}$F in both targets using the Ta target for the heavy morning-production run, and the Ag target for the second and less heavy production run at midday. Other benefits of the upgrade include a faster (0.5 h vs. 4 h) recovery of the vacuum in case of the rupture of a window, and lengthened the maintenance intervals of the $^{18}$F target decreasing the radiation exposition to the cyclotron staff. Our plans for this year are to upgrade the second BL to the Eclipse HP configuration with the option for the irradiation of solid targets.
The first PET Center in Mexico was inaugurated in 2001 at the School of Medicine of the National Autonomous University of Mexico (UNAM). In that time a self-shielded CTI RDS-111 cyclotron with Targetry for the production of the main sequence CNOF radionuclides was installed.

Nowadays, there are 3 compact cyclotrons in the country and one TRACE (GE) and 11 PET/CT cameras in different hospitals. UNAM's cyclotron produces FDG for 6 of the 8 PET scanners located in hospitals and clinics of Mexico City, and more hospitals are planning to install more PET/CTs.

To satisfy this increased demand of FDG, one of the beam lines of our RDS-111 cyclotron was recently upgraded to Eclipse HP. In this way, now we have two compact cyclotrons with BL1 as Eclipse HP and BL2 as RDS-111. In 2005, our facility provided 10 unidoses per day, today we produce 35 unidoses per day on average. In 2006, we increased the unidoses and had to make more than two or three runs per day.

Some reasons for upgrading the RDS were:

a) Trouble with carousel system
   The target position was non-reproducible when the carousel moved to F-15 and F-18.

b) RF and magnet are not stable.

c) When the window target was broken, the recovery of the accelerator consumed four hours.

Improvement in RP-111 To Eclipse HP Upgrading with RDS-111...
With this upgrade we practically double the yield of F-18 with the same time of bombardment. Table 1 shows the yield of the different radionuclide in both version.

Table 1. Comparison of yields (EOB) obtained in RDS-111 vs. Eclipse HP targets.

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>RDS-111 (40 μA)</th>
<th>Eclipse HP (60 μA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18F</td>
<td>1187 Ci (1h) 1200 L</td>
<td>2300 Ci (1h) 2400 L</td>
</tr>
<tr>
<td>18F-1187mCi</td>
<td>1200 μL</td>
<td>2400 μL</td>
</tr>
<tr>
<td>18F-1187mCi</td>
<td>1200 μL</td>
<td>2400 μL</td>
</tr>
<tr>
<td>13N-146mCi</td>
<td>10 min</td>
<td>10 min</td>
</tr>
<tr>
<td>13C-1547mCi</td>
<td>40 min</td>
<td>40 min</td>
</tr>
<tr>
<td>13C-1902mCi</td>
<td>40 min</td>
<td>40 min</td>
</tr>
</tbody>
</table>

RESULTS

F-18 Production and Time of Bombardment

<table>
<thead>
<tr>
<th>RDS-111</th>
<th>Eclipse HP</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Activity (Ci)</td>
<td>Time of Bombardment (h)</td>
</tr>
<tr>
<td>0-12 Apr</td>
<td>0-12 May</td>
</tr>
<tr>
<td>747.2 h</td>
<td>536.4 Ci</td>
</tr>
<tr>
<td>393.3 h</td>
<td>839.2 Ci</td>
</tr>
<tr>
<td>0.53</td>
<td>1.56</td>
</tr>
</tbody>
</table>

Comparison of F-18 production runs in RDS-111 vs. Eclipse HP targets. Bombardment time AEOB of F-18 and FDG.
**Conclusion:**

**Benefits of the RDS Eclipse**  

The benefits of the upgraded BL1 were immediate for the production of FDG-18:

- The high volume Ta target produces more activity of highly reactive n.c.a. [F18]fluoride compared with the traditional Ag target of the RDS-111 configuration.

- We are still producing F-18 using both targets for the heavy morning production run, and the Ag target for the second and less heavy production run at midday.

- Other benefits of the upgrade include a faster (0.5 h vs. 4 h) recovery of the vacuum in case of the rupture of a window and lengthened the maintenance intervals of the F-18 target decreasing the radiation exposition to the cyclotron staff.

- The RDS Eclipse upgrade allows the routine production of 40 unidoses of FDG with a high degree of success added of production of (N-13) Ammonia and (C-11) Acetate and (F-18) FLT.

---

**Upgrade of 2nd Beam Line in 2011**

With solid target irradation option

**Upgrade of 2nd Beam Line in 2011**

With solid target irradation option

**Conclusion:**

Benefits of the RDS Eclipse
Title: CYCLOTECH – A method for Direct Production of $^{99m}$Tc using Low Energy Medical Cyclotrons

Authors: Johnson RR$^1$, Wm. Gelbart$^2$, Benedict M$^3$, Cunha L$^4$, Metello LF$^4$

1 – Best Cyclotrons Systems Inc (BSCI - Team BEST), Ottawa, Canada and University of British Columbia, Vancouver, Canada;
2 – Advanced Systems Design (ASD), Garden Bay, Canada;
3 - Molecular Diagnostics and Therapeutics Inc. (MDTI), Longmont, Colorado, USA;
4 – Isótopos para Diagnóstico e Terapêutica SA (IsoPor SA), Porto, Portugal and Nuclear Medicine Department of the High Institute for Allied Health Technologies of Porto, Polytechnic Institute of Porto (ESTSP.IPP), Porto, Portugal.

Introduction:

This paper presents work in progress, to develop an efficient and economical way to directly produce Technetium $^{99m}$Tc using low-energy – so-called “medical” – cyclotrons. Its importance is well established and directly relates to the increased global trouble in delivering $^{99m}$Tc to Nuclear Medicine Departments relying on this radioisotope. Since the present delivery strategy has clearly demonstrated its intrinsic limits, our group decided to follow a distinct approach that uses the broad distribution of the low energy cyclotrons and the accessibility of Molybdenum 100 ($^{100}$Mo) as the Target material. This is indeed an important issue to consider, since the system here presented it is not based on the use of HEU (or even LEU) 235 Uranium, so entirely complying with the actual international trends and directives concerning the use of this potentially critical material.

The production technique is based on the nuclear reaction $^{100}$Mo $(p,2n)$ $^{99m}$Tc whose production yields have already been documented.

The object of the system is to present $^{99m}$Tc to Nuclear Medicine radiopharmacists in a routine, reliable and efficient manner that, remaining always flexible, entirely blends with established protocols.

Material and Methods:

We have developed a Target Station that can be installed on most of the existing PET cyclotrons and that will tolerate up to 400 μA of beam by allowing the beam to strike the Target material at an adequately oblique angle. The Target Station permits the remote and automatic loading and discharge of the Targets from a carriage of 10 Target bodies.
Fig 1. The remotely controlled Target Changer ejects the irradiated Target (to a Transfer System that transports it to a Processing Unit –inserted in a dedicated Hot Cell) and loads a new one. Up to 10 Targets can be pre-loaded in the Target Changer.

Several methods of Target material deposition and Target substrates are presented. The object was to create a cost effective means of depositing and intermediate the target material thickness (25 - 100μm) with a minimum of loss on a substrate that is able to easily transport the heat associated with high beam currents.

The separation techniques presented are a combination of both physical and column chemistry. The object was to extract and deliver $^{99m}$Tc in the identical form now in use in radiopharmacies worldwide. In addition, the Target material is recovered and can be recycled.
The 13th International Workshop on Targetry and Target Chemistry
July 26 – 28th 2010
Nuclear Medicine… is a Medical Speciality in which low doses of radioactive materials are used for therapy in many disease processes. (WHO, 1960)

Technetium-99m is used in over 85% of NM Procedures for therapy in many disease processes.

Demand for Nuclear Medicine Procedures and 99mTc Generators 2010
Minimal Annual Growth Rate: 6% (average: 12.3%)

Reference: Committee on Medical Isotope Production Without Highly Enriched Uranium, National Research Council (2009).

Radioactive Waste!
99Mo/99mTc Generator Waste!

Medical - Cyclotrons
99Mo using low energy cyclotrons for direct production of medical - cyclotrons

for Direct Production of
Cyclotron - a Method

NRU OSIRIS HFR BR2 SAFARI
MDS NORDION CIS BIO COVIDIEN LANTHEUS GE HEALTHCARE

Cascade of Technetium-99m Production
The Industry Profile

**July 26 – 28th 2010**

**Cascade of Technetium-99m Production 2010**

**NRU N. America**

- Market = 75%
- > 50,000 patient procedures affected!
- 1957 USA 50% 60%
- 40%
- (Perkins et al., 2008)

**MDS Nordion (Canada)**

- One month outage
- 1961 Market = 75%
- 1966 MHFR 84% facilities affected!
- (SNM, 2008)

**COVIDIEN (The Netherlands)**

- Market = 75%
- 1961 BR2 84% facilities affected!
- (SNM, 2008)

**Osiris (Belgium)**

- Market = 75%
- 1961 1966 40% operating (Belgium)
- 84% facilities affected!
- (SNM, 2008)

**NTP (S. Africa)**

- Market = 75%
- 1965 Safari 1961 1966 84% facilities affected!
- (SNM, 2008)

---

**The Problem**

Definitely… Nuclear Medicine Community needs a reliable and regular source of 99mTc!!

---

**The Solution**

Value System of the 99mTc Production (following CYCLOTECH)

- PRODUCTION LICENSE Ready to use Target
- Ready-to-use Target Purification Modules
- Maintenance
- Consulting & Education

Addressable Market: ≈ 350 Cyclotron Based Centers

---

**Advantages**

- Cyclotron value chain for the Cyclotron Owners
- For NM Departments
  - o Ceramic value chain optimization (actual occupation rate: only 15%);
  - o Reliable and daily - based delivery;
  - o Additional service;
  - o Workflow optimization;
  - o Increase in number of procedures;
  - o Small facility investment;
  - o Less storage of radioactive material on site;
  - o Higher predictability of product delivery;

- For the Environment
  - o Unlike NR production, Cyclotron based 99mTc production process is safer, cleaner and easier to spread worldwide in a short term

---

**The Problem**

Definitely… Nuclear Medicine Community needs a reliable and regular source of 99mTc!!

---

**The Solution**

Value System of the 99mTc Production (following CYCLOTECH)
Babcock & Wilcox Technical Services Group (B&W TSG) has been awarded $9 million from the National Nuclear Security Administration (NNSA) for further development of reactor technology for medical isotope production using low-enriched uranium.

Production cross section for the reaction $^{100}$Mo(p,2n)$^{99m}$Tc

The inner workings of a High Current Isotope Production Target

Target Material comparisons for distinct bombarding energies

<table>
<thead>
<tr>
<th>Proton Beam (º)</th>
<th>Cyclotron Energy (MeV)</th>
<th>Target coating</th>
<th>Target defining collimators</th>
<th>Target Defining Collimators</th>
</tr>
</thead>
<tbody>
<tr>
<td>15º</td>
<td>96 MeV</td>
<td>8.0 um</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16º</td>
<td>254 MeV</td>
<td>5.3 um</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19º</td>
<td>383 MeV</td>
<td>10.0 um</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24º</td>
<td>673 MeV</td>
<td>17.4 um</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25º</td>
<td>74 MeV</td>
<td>0.1 um</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: That 96º angle appears as a contaminant in the target material

Production yields for various cyclotrons

<table>
<thead>
<tr>
<th>Proton Energy (MeV)</th>
<th>Activity Ratio</th>
<th>Target Coating</th>
<th>Cyclotron Energy (MeV)</th>
<th>Target Defining Collimators</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>25000</td>
<td>15.0 um</td>
<td>96 MeV</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>400000</td>
<td>10.0 um</td>
<td>254 MeV</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>670000</td>
<td>17.4 um</td>
<td>383 MeV</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>1600000</td>
<td>17.4 um</td>
<td>673 MeV</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>2000000</td>
<td>0.1 um</td>
<td>74 MeV</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>1500000</td>
<td>0.1 um</td>
<td>74 MeV</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>2000000</td>
<td>0.1 um</td>
<td>74 MeV</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>2500000</td>
<td>0.1 um</td>
<td>74 MeV</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>3000000</td>
<td>0.1 um</td>
<td>74 MeV</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>3500000</td>
<td>0.1 um</td>
<td>74 MeV</td>
<td></td>
</tr>
</tbody>
</table>

The thick target yield for the reaction (100)Mo(p,2n)$^{99m}$Tc has been presented by B. Schloten et al. in Applied Radiation and Isotopes 51 (1999) 69.
The preferred Target material would be 100Mo metal, though most processes now use MoO₃. The Oxide is not preferred, because the extra Oxygen atoms reduce the yield of the Technetium and contribute with an additional radioactive contaminant background of 13N.

The Target Material will be a metal sheet converted from a metal powder. Solid metal foils must be laid down on the Target Body. The thicknesses of 100 Mo foil differ according to accelerator energy. (Note that the Target is inclined at 15° so that the actual Target coating is thinner.)

As the Target coating becomes thicker, the Molybdenum becomes brittle and has a tendency to flake. Thinner foils are much more malleable. (The metallic foil development is underway, after studying the various options to produce foils in the 25 to 100 um range.)

One key starting point is that separated Molybdenum is supplied as a powder and the foil must be prepared from that.

Molybdenum Deposition

A Molybdenum is first pressed (A). Then, it is melted using an arc or electron gun into a pellet (B). Molybdenum is first pressed (A).

Finally, it is pressed or rolled into a foil (C). The electro plating creates needle-like structures. (From: Kim et al. J. Applied Electrochemistry 18 (1988) 823)

D Molybdenum foil is bonded by a surface brazing technique that joins the copper base substrate to the target foil (D). The presence of oxides results in the formation of metallic and layered oxide film. The process leaves the bonding materials with the base substrate.

Molybdenum Plating on Carbon substrate

The effect of heating the electroplated molybdenum is applied as a power source to produce foils in the 25 to 100 um range. The metallic foil development is currently being studied for various applications. The power source is converted to a metal sheet of 100Mo metal foil, followed by a further conversion to accelerator energy. The resulting thickness of 100Mo metal foil must be less than the target dose. The target material will be a metal sheet converted from a metal powder. Solid metal foils must be laid down on the carbon substrate.
One Key Feature: the distribution of the Proton Beam over the surface of the Target

The back of the Target (top picture) incorporates water cooling channels. The irradiated material is deposited on the front face. An O-ring acts as the vacuum seal.

TARGET IRRADIATION SYSTEM CROSS-SECTION

FEM analysis of the temperature distribution of the Molybdenum Target for a 4.3 kW beam striking the Target face. 20% of the total Beam is deposited on the collimator. The beam is Gaussian and the hot spot at the centre is about 250 degrees Celsius.

TARGET IRRADIATION SYSTEM

Model of High Current Target used on CYCLOTECH
**Sequence of Loading**

**July 26 – 28th, 2010**

**Loading**
- Closed
- Ejecting
- Loading

**Ready to Load:**
- June 13th

**Closed and Ready to Irradiate:**
- July 26th

**Target tilted at 7 to 15 degrees to beam**

**13th International Workshop on Targetry and Target Chemistry – DTU - Risø (Denmark)**
TARGET ASSEMBLY

Ejecting:

2010

Ejecting:

13th International Workshop on Targetry and Target Chemistry – DTU - Risoe (Denmark)

TARGET ASSEMBLY

COLD TEST APPARATUS

HEATER OVEN

DISTILLATION COLUMN

CARRIER GASES

Processing Module Scheme

July 26 – 28th
2010

Processing Module Scheme

July 26 – 28th
2010

First Processing Stage development:

Mo is oxidized in an O₂ environment and then eluted with 10% H₂O₂.

Target Processing:

16. Target
62. Carrier gas
66. heaters
99mTcO₄ elute

All Target Substrate contaminants are left behind and one has pure Mo₂C for subsequent processing.

All Target Substrate contaminants are left behind and one has pure Mo₄C for subsequent processing.

Mo is oxidized in an O₂ environment and then eluted with 10% H₂O₂.

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Mo is oxidized in an O₂ environment and then eluted with 10% H₂O₂.

All Target Substrate contaminants are left behind and one has pure Mo₂C for subsequent processing.
The MoO₃ is deposited in a band corresponding to about 400°C. Since condensation temperatures of molybdenum and technetium oxides are very different, a form of fraction distillation in such a column can be incorporated into the process. (Physical and wet chemistry under study)

**Target Processing System**

- 1. Transfer tube
- 2. Chemicals
- 3. Hotcell
- 4. Lead glass window
- 5. Processing unit
- 6. PLC control

**Status and Summary**

<table>
<thead>
<tr>
<th>1</th>
<th>Technical Feasibility</th>
<th>Cross Section, Process</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Economics</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>3</td>
<td>Development</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

- Target Assembly under construction
- Separation process tested
- Entire system integration
- Prototyping
- Yet to come.

**Cold Test Apparatus**

- 1. Processing unit in a hot cell
- 2. PLC Control
1. MoO$_3$ to Mo reduction

• In H$_2$ environment

2. Production of 99 Mo?

• More energy and high currents needed

3. Target deposition techniques

• Sputtering only good for too thin... 25um needed!

• Plasma deposition does not work

4. Financing

• 99Tc from cyclotron: 3 or 4 x more expensive than today

• Actual chemistry and imaging equipment can be used directly
Effects of the Tantalum and Silver Targets on the Yield of FDG Production in the Explora and CPCU Chemistry Modules

J.C. Manrique-Arias, E. Zamora-Romo, A. Zarate-Morales, A. Flores-Moreno, M.A. Avila-Rodriguez

Unidad PET/CT-Ciclotrón, Facultad de Medicina, Universidad Nacional Autónoma de México, México, D.F., México

Ionic contaminants in water have generally been considered to influence the reactivity of n.c.a. $[^{18}\text{F}]$fluoride decreasing the yield in the synthesis of radiopharmaceuticals by nucleophilic fluorination. Until a few years ago the most widely used material for target chamber in $^{18}\text{F}$-production was silver. However, more recently, the use of refractory materials such as tantalum and niobium has been shown to provide highly reactive fluoride.

The PET Center at the National Autonomous University of Mexico (UNAM) produces $[^{18}\text{F}]$fluoride ion for FDG synthesis in two different targets: a high volume (2.4 mL) gridded tantalum-target and a low volume (1.2 mL) double-foil silver-target capable to withstand 660 and 440W of beam power at 11 MeV, respectively. Chemistry modules for FDG production at this facility include an Explora recently acquired to replace a CPCU in use since 2001. The Explora module is used primarily for the routine production of FDG while the CPCU serves as a backup for the Explora and for the production of other non-FDG tracers. Figure below shows the yields of FDG in six-consecutive months using a tantalum and a silver target for fluoride production. The FDG yields when using the silver target range from 60 to 70% compared to 70 to 80% when using the tantalum target, clearly showing the superiority of tantalum vs. silver to produce highly reactive fluoride.

![Figure 1. Six-month FDG yields in the Explora module using $^{18}\text{F}$ from two different targets.](image-url)

Regarding the use of the Explora and CPCU modules, we found no significant difference in their FDG yields, independently of the target used for fluoride production, and their synthesis time is practically the same (~45 min). However, the Explora features a single closed reaction vessel with heating/cooling by forced convection including temperature, pressure and radiation sensing. Performs up to four sequential runs of FDG without intervention. On the other hand, the CPCU features two open reaction vessels heated by two independent oil baths that can be used for back-to-back synthesis, but it lacks of any kind of sensors to monitor the performance of the synthesis.
Effects of the Tantalum and Silver Targets on the Yield of FDG Production in the Explota and CPCU Chemistry Modules.

J.C. Manrique-Arias, E. Zamora-Romo, A. Zarate-Morales, M. Flores-Moreno, M. Avila-Rodriguez

Unidad PET Facultad de Medicina Universidad Nacional Autónoma de México MÉXICO

PET in Mexico (2001-2010)

Production of FDG at UNAM’s PET Center

Produces FDG from Monday to Saturday

Produces FDG for 9 of the 11 PET Centers in Mexico City

Two production runs per day

More than 8,000 unidoses/year

Other tracers:

-[18F]FLT
-[18F]NaF
-[11C]Acetate
-[13N]Ammonia

2 Cyclotrons

4 Cyclotrons

2 Cyclotrons

4 Cyclotrons

Cyclotrons in Mexico
### Targetry and Target Chemistry - WTTC13

<table>
<thead>
<tr>
<th>Target Body</th>
<th>Volume</th>
<th>Target Type</th>
<th>Heating/cooling</th>
<th>Syntheses Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tantalum</td>
<td>2 mL</td>
<td>HP</td>
<td>Convection</td>
<td>~45 min</td>
</tr>
<tr>
<td>Silver</td>
<td>4 mL</td>
<td>RD</td>
<td>Conduction (oil)</td>
<td>~45 min</td>
</tr>
</tbody>
</table>

### Chemistry Module Explora FDC4

<table>
<thead>
<tr>
<th>Characteristics of the Modules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy of maintenance</td>
</tr>
<tr>
<td>Temperature, pressure and</td>
</tr>
<tr>
<td>From reservoirs</td>
</tr>
<tr>
<td>Precise addition of reagents</td>
</tr>
<tr>
<td>Heating/cooling by forced</td>
</tr>
<tr>
<td>Syntheses time ~45 min</td>
</tr>
<tr>
<td>Two production runs/day</td>
</tr>
<tr>
<td>Two-open reaction vessels</td>
</tr>
</tbody>
</table>

### Water Targets

- **HP Target:**
  - Volume: 2 mL (60 μL)
  - Target Body: Laminated
  - Type: Crimped
- **RD Target:**
  - Volume: 2 mL (60 μL)
  - Target Body: Silver
  - Type: Double foil
- **Window:**
  - Heater Volume: 1.2 mL (4 μL)
RESULTS

No difference in the FDG yield was noticed when using the CPCU or Explora Modules when comparing target yield. However, the Explora Module consistently produced more FDG yields than the CPCU Module.

- The FDG yields when using the Explora Module are significantly higher than those obtained with the CPCU Module.
- The difference in FDG yields between the two target types (silver vs. tantalum) is clearly shown, with silver targets producing a 10-20% higher yield compared to tantalum targets.

Targets

FDG Module Using 18F from Two Different Targets in the Explora Module, with FDG Yields in the Explora Module from July 2010 to December 2010.
FULLY AUTOMATED SYSTEM FOR THE PRODUCTION OF $^{123}$I AND $^{124}$I-IODINE LABELLED PEPTIDES AND ANTIBODIES.

P. Bedeschi$^a$, S. Bosi$^a$, M. Montroni$^a$, G. Brini$^b$, S. Caria$^b$, M. Fulvi$^b$, G. Calisesi$^b$

*a Comecer, Castel Bolognese (RA), Italy

*a Nuclear Specialists Associated, Ardea (Roma), Italy.

Radiolabelled amino acids, peptides and monoclonal antibodies are certainly a useful non-invasive diagnostic tools to detect malignant tumours, infectious and inflammatory lesions$^{1,2}$. In combination with the potential of Positron Emission Tomography (PET), the aim of the present study was to develop a fully automated system for the radiolabelling of these new tracers, that avoids any direct manipulation by operators from target production and recovery, to synthesis and purification of the final product.

Nowadays radionuclides used for PET-imaging are generally short-lived isotopes, such as $^{18}$F-fluorine ($t_{1/2} = 110$ min), but recently the growing need for alternative positron emitters focuses the attention on the long-lived radiohalogen $^{124}$I-iodine ($t_{1/2} = 4.17$ d). $^{124}$I-Iodine, is a suitable radionuclide for both diagnostic, such as Positron Emission Tomography and therapeutic applications, it decays by positron emission (23.3%) and electron capture (76.7%). Its long half-life permits this isotope to be imaged for more than 4 days, which makes it possible to study the labeled molecule over a longer time period. Furthermore the promising clinical aspect of $^{124}$I-iodine leads research institution and commercial company seeking to produce multi-millicurie quantities for distribution purposes$^3$, that means a wider geographical area.

A variety of radioiodination methods is supported by a large amount of literature$^{4,5}$, preferentially a radiodine atom is incorporated in a vinylic or aromatic moiety, due to the high strength of the carbon-iodine bond. Therefore, the radioiodination is often implemented by nucleophilic or electrophilic substitution and is more or less predicted by the structural feature of the molecule$^6$. Obviously this kind of chemistry is applicable to any iodine isotopes, therefore in addition to $^{124}$I-iodine, our attention is focused on $^{123}$I-iodine too.

$^{123}$I-Iodine has a half-life of 13.2 h, decays by electron capture and its medium energy ($E_{\gamma} = 159$ keV) is ideal for planar imaging and for Single Photo Emission Computed Tomography (SPECT), a lower cost diagnostic tool compared to PET.

The production of both $^{123}$I and $^{124}$I-iodine radionuclides is based on a low-energy (p, n) reaction at a small-sized (14 MeV) cyclotron, using TeO$_2$-target technology and dry distillation.
method of radioiodine separation\textsuperscript{7-9,10}. The collected radioiodide is then delivered to a fully-automated module for the product labeling. The module is built with the concepts of the “disposable cassette”, so all the components that get in contact with the product are disposable; this structure avoids the module contamination. Finally the labeled compounds are allowed to pass through an HPLC purification system connected at the end of the synthesis module. The figure 1 below shows a schematic illustration of the fully automated process.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Schematic illustration of the fully automated system}
\end{figure}

In conclusion we develop a fully automated system for the high activity production of iodo-labelled peptides and monoclonal antibodies, high-lived pharmaceuticals for PET and SPECT imaging. Due to the automated process applied from the radio-isotopes production and separation to the synthesis and purification of the final products, the operators are completely shielded from radiation. The use of $^{123}\text{I}$ and $^{124}\text{I}$-iodine, medium and high-lived radionuclides permits longer term studies and a wider geographically distribution.

\textsuperscript{7} Applied Radiation and Isotopes, 2003, 58, 69-78
\textsuperscript{8} Radiochim. Acta, 2000, 88, 169-173
\textsuperscript{9} Applied Radiation and Isotopes, 2007, 65, 407-412
\textsuperscript{10} Journal of Radioanalytical & Nuclear Chemistry, 1996, 213, 2, 135-142
The purposes of an automated system are:

- To establish a background for a future GMP production
- To assure a good product quality in terms of chemical and isotopic purity
- To obtain high production yields for small cyclotrons and to assure the process reproducibility
- To increase radioiodine production standards of the operator during the process
- To produce radioiodine production of labelled peptides and antibodies

Fully Automated System for the production of $^{123}$I and $^{124}$I Iodine

The study has considered:

- Development of a specific irradiation module for the automated target positioning and the dry distillation module between the cyclotron and the dry distillation module
- Development of a bi-directional pneumatic transfer system between the cyclotron and the dry distillation module
- Development of a specific irradiation module for the automated target positioning with a high efficiency water and helium cooling system
- Application of an industrial HF heating system on the dry distillation device
- Application of an industrial HF heating system on the dry distillation device

AIMS

CombiTech

NSA Nuclear Specialists Associated, Inc.
Solid Tar target

Alumina and enriched TeO$_2$ powders loading quickly drives the melting phase of target.

Target automatic transfer from/to the cyclotron.

Iodine harvesting module

Platinum body + Platinum crucible

TeO$_2$ solid Target

ALCEO PTS module (irradiation unit)

TADDEO synthesis module

Connected to:

Connected to:

ALCEO – target processing module

ALCEO - irradiation unit

Radio Frequency heater

500 mg of green glassy TeO$_2$ quickly drives the melting phase of target.

Haynes body + Platinum crucible

Exagonal supporting grid

Aluminium and enriched TeO$_2$.

Water flow: 3 l/min, 850 W

Helium flow: 15 kg/min, 100 W

Dry distillation and plating of target with TeO$_2$.

Connected to:

Iodine harvesting and radioiodine

Automatic transfer from/to the cyclotron.
Prepare enriched Te powders melting at 780°C for 15 min (500 mg of TeO$_2$, 5% Alumina).

4 hours at 12 uA

Beam energy: 12 MeV, Applet current 12-20 mA

Target transfer speed: 2 m/s

Typical beam duration: from 4 to 6 hours

Typical production yield with 500 mg of TeX$_2$, 99.5% enriched: 40/50 mcg 124I-TEB

Production yield: 0.5 mcg/h

Target can be irradiated multiple times (5 to 10).

Automated Radioiodination

Multifunction research module equipped with...
And of course…

Radiopharmaceutical is finally ready to be injected.

Conclusions

• We developed a fully automated system for iodine target handling.
• We developed a fully automated system to label a peptide with iodine-123.
• We applied this system to a biodistribution study with micro-PET.
• Future developments will involve iodine-123 and GMP production.

WTTC XIII - Presentation Discussions

1. System characteristics and running experience
   • TeO2 target material
   • Very low loss of iodine during transport, temperature not high
   • Very low I125 contaminant
   • TeO2 target material
   • System demonstrated and running experience

NSA Rome
Giorgia Brini, Saverio Caria, Marcello Fulvi, Gianni Callesen
Prof. Jacek Koziorowski
Herlev University, Denmark
Prof. Robert J Nickles and his cyclotron gang
Comecer SpA
Stefano Bosi, Paolo Bedeschi

Special thanks to...

[Image of a tumor PET image courtesy of NSA, Rome. PET image 48 hours after injection of 124I-peptide.]
Accepted for ORAL presentation during 13th WTTC 2010 in RISOE/Denmark

Routine Automated Production of $^{18}$F-Labelled Radiopharmaceuticals on IBA Synthera® Multi-Purpose Platform

Bernard Lambert; Jean-Jacques Cavelier, Guillaume Gauron, Christophe Sauvage, Cécile Kech, Tim Neal, M. Kiselev, David Caron, Anat Shirvan, Ilan Ziv

$^1$BP 32 91192 Gif sur Yvette Cedex France. $^2$IBA RI SA, rue de l’Esperance, 1 6220 Fleurus Belgium. $^3$IBA Molecular, 100 Executive Dr. Sterling VA USA; $^4$Aposense Ltd, 5-7 Odem St., P.O Box 7119, Petach-Tikva 49170, Israel  e-mail: christophe.sauvage@iba-group.com.

Although FDG provides most of the clinical PET imaging today its low specificity limits its use. In molecular imaging technology, highly specific probes for clinical applications are crucial justifying the development of non-FDG radiopharmaceuticals such as: $[^{18}F]^{-}\text{NaF}$, for bone metastasis detection; $[^{18}F]^{-}\text{F-Choline (FCH=methylcholine)}$ for diagnosis/staging of prostate cancer; $[^{18}F]^{-}\text{FLT}$, for cell proliferation imaging, and $[^{18}F]^{-}\text{ML-10 (α-methyl 18F-alkyl-dicarboxylic acid)}$, for apoptosis imaging. This work will present automated and optimized processes developed on IBA Synthera® platform for the routine production of $[^{18}F]^{-}\text{NaF}$, $[^{18}F]^{-}\text{FCH}$, $[^{18}F]^{-}\text{FLT}$, $[^{18}F]^{-}\text{ML-10}$.

The synthesis of each radiotracer takes place on single-use IFP™ system (integrated fluidic processor) which comprises appropriate pre-defined synthesis hardware and plumbing. $[^{18}F]^{-}\text{NaF}$ manufacturing is straightforward and employs IFP™ Chromatography. For the $[^{18}F]^{-}\text{FCH}$, two synthesizers as well as two interconnected IFP™ (IFP™ Distillation & IFP™ Alkylation) are necessary for the two-step synthesis (fig. 1). In synthesis of $[^{18}F]^{-}\text{FLT}$ and $[^{18}F]^{-}\text{ML-10}$ IFP™ Nucleophilic is used. The product obtained is purified in Synthera® HPLC unit. In none of the applications hardware changes are required compatible with a multipurpose platform.

Fig 1-Synthera® graphical user interface screen-shots for $[^{18}F]^{-}\text{FCH}$ highlighting main features.

The synthesis of $[^{18}F]^{-}\text{NaF}$ is obtained by washing trapped $[^{18}F]$ with water followed by elution with saline solution. $[^{18}F]^{-}\text{FCH}$ is produced in two steps according to published method$^1$. The first step, performed in IFP™ Distillation, includes the fluorination of dibromomethane (DBM) and purification of fluorinated volatile by distillation through silica cartridges. Next, in the IFP™ Alkylation, fluoromethylation of N,N-dimethylaminoethanol takes place resulting in $[^{18}F]^{-}\text{FCH}$ which is purified through a cation exchange cartridge. $[^{18}F]^{-}\text{FLT}$ is produced according to adapted methodology$^2$. 

The synthesis is realized within IFP™ Nucleophilic. \([^{18}\text{F}]\)-fluorination of 3-N-Boc-5'-O-dimethoxytrityl-3'-O-nosyl-thymidine (Boc-FLT-Precursor) as well as subsequent acid hydrolysis with diluted HCl are carried out at 100°C. These steps take 10 min. and 5 min., respectively. Crude product is buffered and loaded into reversed-phase HPLC column in Synthera® HPLC for final purification. Ethanol/water is used as mobile phase. Synthesis of \([^{18}\text{F}]\)-ML-10 also employs IFP™ Nucleophilic. Both fluorination of the tosylated precursor and consecutive hydrolysis with aqueous HCl were performed at 110°C for 10 min. Buffered reaction mixture was then purified in Synthera® HPLC by reversed-phase HPLC with phosphate buffer/ethanol as mobile phase.

\([^{18}\text{F}]\)-NaF is obtained in less than 10 minutes with RCY (radiochemical yield) > 90% EOS. Analytical data show it complies with European Pharmacopoeia. Average RCY for \([^{18}\text{F}]\)-FCH >20% EOS. The total synthesis time is < 50 minutes. Final product shows high radiochemical purity (99%) and chemical purity (>95 %). \([^{18}\text{F}]\)-FLT total synthesis time is 45 minutes (including HPLC purification) with average RCY>20%. Final product presents high radiochemical purity (>95%) and high chemical purity (>95 %). \([^{18}\text{F}]\)-ML-10 RCY > 40 % after 60 min of total synthesis time including HPLC purification. Final product presents high radiochemical and chemical purity (> 99%) (fig 2).

![Typical chromatogram of \([^{18}\text{F}]\)-ML10 after HPLC purification](image)

The automated platform has proven to be robust and reliable when it comes to routine production of promising radiopharmaceuticals such as \([^{18}\text{F}]\)-NaF, \([^{18}\text{F}]\)-FCH, \([^{18}\text{F}]\)-FLT and \([^{18}\text{F}]\)-ML-10 for clinical applications. The radiochemical yields obtained are reproducible and final products show high radiochemical and chemical purity. All of the radiopharmaceutical syntheses are carried out within dedicated IFP™ systems (Chromatography, Distillation, Alkylation and Nucleophilic) in one single platform set up with open software for customized applications. The IFP™ is a disposable, preventing cross-contamination, which is line with GMP. The modules are fully interchangeable underpinning the platform multipurpose capability (do-all-in-one platform) and flexibility.

References:

Example of proprietary compound
Parallel with FDG

$\text{OAc}$

$\text{AcO}$

$\text{AcO}$

$\text{AcO}$

$\text{OTf}$

$\text{OAc}$

$\text{HCl}$

$\text{CH}_3\text{CN}$

$\text{NaOH}$

$\text{18F, K}_{222}$

$\text{18F}$

$\text{OTs}$

$\text{18F}$

$\text{HPLC}$

$\text{OtBu}$

$\text{OtBu}$

$\text{OtBu}$

$\text{OtBu}$

$\text{OH}$

$\text{OH}$

$\text{ML10 precursor}$

$\text{BOC}$

$\text{HCl 1M acetate buffer}$

$\text{© 2006}$

$\text{18F-ML10 Quality Control}$

- Fully validated process
- Analytical methods validated according to ICH
- RCP and chemical purity > 99 %
- Residual solvents below ICH limits

$\text{18F-FLT Quality Control}$

- Fully validated process
- Analytical methods validated according to ICH
- RCP and chemical purity > 99 %
- Residual solvents below ICH limits

Specifications

- $18F$-ML10
  - Radiochemical yield: $(40 \pm 5) \%$ EOS
  - Radiochemical purity: $(20 \pm 5) \%$ EOS
  - Chemical purity: $> 95 \%$
  - Ts-OH < 0.25 ppm
  - ML-10-OH < 5 ppm

- $18F$-FLT
  - Radiochemical yield: $(40 \pm 5) \%$ EOS
  - Radiochemical purity: $> 95 \%$
  - Chemical purity: $> 95 \%$
  - [19F]-FLT < 0.2 ppm
  - K222 & Residual solvents: USP & Eur. Ph. Compliant
Specifications

- **18F-NaF**
  - Radiochemical yield: 95% EOS
  - Radionuclidic purity > 99%
- **Radiochemical purity: Eur. Ph. Compliant**
  - [18F]-fluoride > 98.5 % of total activity
- **Chemical purity: Eur. Ph. Compliant**
  - [19F]-NaF < 4.5 mg/V

Example of the synthesis of [18F]methylcholine

- **18F-FCH Quality Control**
  - Fully validated process
  - Analytical methods validated according to ICH
  - Residual solvents below ICH limits
  - RCP and chemical purity > 95%
  - Analytical methods validated according to ICH

18F-FCH Platform

Example of the synthesis of [18F]methiodide

- Radiochemical yield: 99.9 % of total activity
- Radionuclidic purity: Eur. Ph. Compliant
- [19F]-NaF < 25 ppm
- Bromocholine < 25 ppm

18F-NaF Platform

Example of the synthesis of [18F]methylcholine

- Radiochemical yield: 95% EOS
- Radionuclidic purity: 99.9 % of total activity
- Residual solvents below ICH limits
- Analytical methods validated according to ICH
- RCP and chemical purity > 95%
- Residual solvents below ICH limits
- Analytical methods validated according to ICH

18F-NaF Platform
Specifications

- Radiochemical yield: (20 ± 2) % EOS
- Radiochemical purity: > 95%
- Chemical purity:
  - DBM < 0.1 ppm
  - [19F]-FCH < 4 ppm
  - DMAE < 1500 ppm
  - Choline < 20 ppm
  - Bromocholine < 0.1 ppm
  - K222 & Residual solvents: USP & Eur. Ph. Compliant

Extend your capabilities

SyntheRA® Multi-tracers Platform

- IFP™ Reformulation
- IFP™ Chromatography
- IFP™ Alkylation
- IFP™ Distillation
- IFP™ Nucleophilic
- FBM, click-chemistry precursor
- FCH
- FDG, FLT, FMISO, FES, ML10...

IFP™ Nucleophilic

- K222 & Residual solvents: USP & Eur. Ph. Compliant
- Bromocholine < 0.1 ppm
- Choline < 20 ppm
- DMAE < 1500 ppm
- [19F]-FCH < 4 ppm
- DBM < 0.1 ppm
- Chemical purity: > 95%
- Radiochemical purity: (20 ± 2) % EOS
- Radiochemical yield: 18F-FCH
Routine Production of Cu-61 and Cu-64 at the University of Wisconsin

Jonathan W Engle, Todd E Barnhart, and Robert J Nickles

University of Wisconsin, Madison, USA

The application of copper isotopes in PET research has undergone a dramatic rise, driven by their versatile chelation chemistry, favourable decay characteristics, and national distribution potential. The (p,n) reaction has long been used to produce $^{61}\text{Cu}$ and $^{64}\text{Cu}$ from $^{61}\text{Ni}$ and $^{64}\text{Ni}$ with reported yields of $21.4 \pm 2.2 \text{ mCi/uA/hr}$ and $8.7 \pm 0.4 \text{ mCi/uA/hr}$ at 11 MeV, respectively.\(^1\) The $^{64}\text{Ni}(p,n)^{64}\text{Cu}$ reaction in particular necessitates careful consideration of incident particle energy. Electrodeposition of enriched $^{61}\text{Ni}$ and $^{64}\text{Ni}$ target material onto high purity gold or silver blanks has been described previously and appears to be limited to approximately 80-120 mg/cm\(^2\), by time and cost concerns.

Using the pooled cross section data $\sigma(E)$ for the $^{64}\text{Ni}(p,n)^{64}\text{Cu}$ reaction,\(^2\) the end of saturated (EoSB) yield of $^{64}\text{Cu}$ can be predicted as a function of $^{64}\text{Ni}$ thickness and incident beam energy, shown below. This family of yield curves strongly suggests that very thick targets ($\approx \frac{1}{2}$ gram/cm\(^2\); $\approx$10,000 in $^{64}\text{Ni}$ inventory) are needed to take advantage of proton energies above 11 MeV, being prohibitive both in cost and plating time. We have degraded the 16 MeV incident proton energy of the PETtrace to approximately 12 MeV with a 0.23 mm tantalum foil to improve the efficiency of our production runs. However, it is apparent that our legacy CTI RDS 112 is still far better suited for the weekly production of $^{64}\text{Cu}$ at the 0.5 Ci level for our own needs, as well as national distribution of the excess.

Copper-61 offers several advantages over $^{64}\text{Cu}$ for PET imaging, namely 61\% vs 20\% $\beta^+$ branching and a 3.4 hr vs 12.7 hr half-life, which combine to result in a three-fold greater useful $\beta^+$ flux to absorbed radiation dose ratio for trapped agents. Three reactions present themselves for cyclotron facilities without alpha beams: $^{61}\text{Ni}(p,n)^{61}\text{Cu}$, $^{60}\text{Ni}(d,n)^{61}\text{Cu}$, and $^{64}\text{Zn}(p,\alpha)^{61}\text{Cu}$. With the
recent three-fold price increase of enriched $^{61}$Ni, we have reverted to the $^{60}$Ni(d,n)$^{61}$Cu reaction for protocols needing Cu-ATSM for hypoxia imaging in human and veterinary patients. Human studies use enriched $^{60}$Ni plated on gold discs. Animal studies, with more relaxed specific activity requirements (>300 mCi/µmole), can utilize the deuteron irradiation of $^{nat}$Ni targets, obviating the need for recycling of enriched target stock. The HPGe spectrum below testifies to the radionuclidic purity of the $^{61}$Cu. Electroplated and foil targets are dissolved in HCl at 100°C, accelerated with $\text{H}_2\text{O}_2$. Alternatively, biasing the Ni foil (10 volts, 1 amp) in unheated concentrated HCl removes approximately 40 mg of the foil and >90% of the activity in 3 minutes. The dissolution apparatus is identical to the electroplating setup. These platers have been recently improved, adding flow, temperature control, pulsed voltage and current regulation under LabView control.

As more subtle targeting strategies develop, the chelation of copper radionuclides to molecular imaging candidates will permit PET to determine the best lead compound, significantly shortening the time to achieve diagnostic utility. Any improvements in the supply of $^{61}$Cu and $^{64}$Cu will greatly serve that end.

---

1 Avila-Rodriguez M A (2007). Low energy cyclotron production of multivalent transition metals for PET imaging and therapy. Ph.D. Dissertation University of Wisconsin Press, Madison, WI.


Routine production of $^{61}$Cu and $^{64}$Cu at Wisconsin

A cottage industry

A sweatshop

Range: $\frac{1}{2} \tau \ln (A_{0}/A_{\text{dead}})$

$Zr_{89}$ = international

$Cu_{61}$ = hundreds km

$Cu_{64}$ = thousands km

$Cu_{64}$ DECAY

$^{64}$Ni $\beta^{+}$ max = 0.656 MeV

$^{64}$Ni $\gamma^{0}$ = 0.283 MeV

$^{64}$Ni $\beta^{+}$ = 0.656 MeV

$^{64}$Ni $\gamma^{0} = 1.346 MeV$

$^{64}$Zn $\beta^{+}$ (19.3%)

$^{64}$Zn EC (40.5%)

$^{64}$Zn $\gamma^{0}$ = 1.346 MeV

$^{64}$Zn $\beta^{+}$ (19.3%)

$^{64}$Zn EC (40.5%)

$^{64}$Zn $\gamma^{0}$ = 1.346 MeV

$^{64}$Zn $\beta^{+}$ (19.3%)

$^{64}$Zn EC (40.5%)

$^{64}$Zn $\gamma^{0}$ = 1.346 MeV

Range = $\{t/2^i \ln (2)^i \text{ velocity} \times (\text{A}_{i}^{\text{A}_{\text{needed}}})$
The production of high specific activity 64Cu for clinical applications requires at least 15 k$ of startup investment.

Materials Needed for the Production of High Specific Activity 64Cu

- Ultra high-purity solvents (ppt Cu)
- High-purity Au disks (>99.99%)
- Natural abundance of 64Ni = 0.9%
- Enriched (>95%) 64Ni ($20/mg)

Optimum scaling

Cost/shipment

Number of shipments/irradiation

0 4 6 8 10 12 14

400 mC/mg²

100 mC/mg²

60 mC/mg²

20 mC/mg²

Mev

0 2 4 6 8 10 12 14

64Cu yield at 635B (mCi/µA)
Radiochemical Separation of Ni and Cu

Key reactions (6 MeV)

- $^{61}\text{Cu}(d,n)^{64}\text{Ni}$
- $^{64}\text{Ni}(d,p)^{65}\text{Ni}$

Half-lives:
- $^{61}\text{Cu}$: 3.4 h
- $^{65}\text{Ni}$: 2.3 h

Target and Proton Beam Profile

500 mg of $^{64}\text{Ni}$ was used in the reaction and recrystallized. More than 130 production runs using and recycling Ni-Cu.

The Challenge

Recovery Efficiency $\geq 96.9\%$ ± 1.8%%

Radiochemical Separation of Ni and Cu

Target dissolved in 0.1N HCl and 6N HCl.

Anion Exchange

AG5-X8 resin

Beam profile FWHM ~ 8 mm

X-ray co-registration

Quartz NE102

Targets: Windowless water cooled mounting

Imaging Apparatus:
- Asahi Pentax K-1000
- 1:2:8 macro lens (Sigma X)
- Micro-meter stage mount

Film chromic

1$^{97}\text{Au}(p,n)^{197}\text{Hg}$

Pre-shot Post-shot (30 $\mu$A x 7.5 h)

~1 Ci ~1 Ci

$^{64}\text{Cu}$

$^{64}\text{Ni}$

Target Holder and Proton Beam Profile

Beam profile FWHM ~ 8 mm

X-ray co-registration

Quartz NE102

Targets: Windowless water cooled mounting

Imaging Apparatus:
- Asahi Pentax K-1000
- 1:2:8 macro lens (Sigma X)
- Micro-meter stage mount

Film chromic

1$^{97}\text{Au}(p,n)^{197}\text{Hg}$

Pre-shot Post-shot (30 $\mu$A x 7.5 h)

~1 Ci ~1 Ci

$^{64}\text{Cu}$

$^{64}\text{Ni}$
CuCl$_2$ for 30 min at 37 $^{\circ}$C

\[ \text{NH}_4\text{OAc} \]

TETA titration

Carrier–free $\Rightarrow$ 245 Ci/µM

64 ppb $\Rightarrow$ 1 nM/µl $\Rightarrow$ 245 Ci/ml CF

61Co (1/2 = 3.4 h, $\beta^{+}$=62%, $E_{\beta^{+}}^{\text{max}}$ = 1.22 MeV)

Yield at EOB (mCi/µAh)

| Reaction | Target $\Rightarrow$Recycle | mCi/µh
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu(p, n)Ni</td>
<td>$\Rightarrow$Cu(76)</td>
<td>65</td>
</tr>
<tr>
<td>Cu(p, n)Ni</td>
<td>$\Rightarrow$Cu(65)</td>
<td>54</td>
</tr>
<tr>
<td>Cu(d, n)Ni</td>
<td>$\Rightarrow$Cu(54)</td>
<td>27</td>
</tr>
<tr>
<td>Cu(p, $\alpha$)Ni</td>
<td>$\Rightarrow$Cu(64)</td>
<td>40</td>
</tr>
</tbody>
</table>

In thick target yield for 100% enrichment with 11.4 MeV protons:

<table>
<thead>
<tr>
<th>Energy (keV)</th>
<th>656</th>
<th>1332</th>
<th>609</th>
</tr>
</thead>
<tbody>
<tr>
<td>2h after EOB</td>
<td>21.4 $\pm$ 2.2 mCi/µAh</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Production Pathways

One copper does NOT fit all
PET Imaging Performance of Copper Radionuclides

- $\beta^+ + \gamma$
- Log N

- $\beta$ spectra

- F-18 ($E_{\beta^{max}} = 0.635$ MeV) Cu-60 ($E_{\beta^{max}} = 2.00$ MeV)

- $\gamma$

- Cu-59 Slow, but free from recycling
- Cu-62
- Cu-61
- Cu-64

In vivo Quantification of Hypoxia (Cu-ATSM)

- Because its low redox potential Cu-(II)-ATSM is retained only in oxygen-depleted tissues
- Cu-(II)-dithiolactone (N4-thiolic acid)

Radioactivity (64Cu-ATSM)

- 100 s
- 200 s
- 300 s
- Radiochemical Purity > 98%

Adapted from Fujibayashi et al. (1997)

Hypoxic head and neck tumor in a human subject

UW-Madison Hospital and Clinics

PET Molecular Imaging of Hypoxia (Cu-ATSM)

Now routinely used at UW-Madison Hospital and Clinics

PET Molecular Imaging of Hypoxia (Cu-ATSM)

Now routinely used at UW-Madison Hospital and Clinics

PET Molecular Imaging of Hypoxia (Cu-ATSM)

Now routinely used at UW-Madison Hospital and Clinics

PET Imaging Performance of Copper Radionuclides
1. Cu production setup implementation
   - Avoid premature automation
   - Specific activity electrode to measure specific activity

2. Production/distribution in the USA
   - Saturation not achieved yet
   - Industry not yet interested in distribution

3. Cobalt contamination
   - Ni purity is important!
   - Co trapped in ion exchanger
   - Co trapped in ion exchanger

WTTC XIII - Presentation Discussions
Sustainable PET tracer production at Wisconsin

Todd E Barnhart1, Jonathan W Engle1, Peter Larsen2, Bradley T Christian3, Dhanabalan Murali1, Dustin Wooten1, Onofre T DeJesus1, Ansel Hillmer1, and Robert J Nickles1

1University of Wisconsin, Madison, USA
2Scansys, Copenhagen, Denmark
3Waisman Institute for Brain Imaging and Research, Madison, USA

Introduction

The University of Wisconsin PET tracer production facility has evolved over four decades, progressing from an EN tandem (1971), the first CTI RDS 112 (1985), an NEC pelletron (1998) and now, a GE PETtrace, bunkered in a new facility. Balancing a mixed assignment of graduate training, basic and clinical research, our emphasis has centered on achieving a sustainable campus-wide resource, free from unrealistic expectations or crippling service contracts. The foundation of this self-support is inherent in the state-audited charge-back account within the autonomy of the Medical Physics Department, where users cover the fair share for the development and production of the tracers that they request.

Targetry

We have continued the Wisconsin tradition of making our own cyclotron targets on the new GE PETtrace. Helium cooling has been cast aside in favour of single, gridded entrance windows. The \([^{18}\text{F}]\)-fluoride target’s niobium body houses a 1.1 mL target volume behind a havar window with a water-cooled grid support described previously.\(^1\) The \([^{13}\text{N}]\text{NH}_3\) target is a 304 stainless steel volume of 2.5 mL also behind a havar foil and grid. A 3 mL/min flow of 5 mM EtOH provides a steady state production of \([^{13}\text{N}]\text{NH}_3\) trapped on an Alltech IC-Na Plus cartridge. \([^{11}\text{C}]\text{CO}_2\) and \([^{11}\text{C}]\text{CH}_4\) targets are electropolished 304 stainless steel tubes (25 cm x 1.6 cm dia.), TIG welded inside the water-jacket. These targets are also sealed to the vacuum by the same havar foil/grid system. All grids are approximately 2.5 cm deep with hexagonal holes (2.5 mm across the flats, 0.3 mm septa) electric discharge-machined into aluminum.

Automated chemistry

\([^{18}\text{F}]\)-fluoride, \([^{13}\text{N}]\text{NH}_3\), \([^{11}\text{C}]\text{CO}_2\), and \([^{11}\text{C}]\text{CH}_4\) are transported to shielded radiochemistry equipment in the lab adjacent to the vault through narrow bore lines. Aqueous fluoride and C-11 carbon dioxide or methane are remotely unloaded via FEP and stainless steel lines, respectively, and sent to two Capintec (New Jersey) hot cells, each containing a Labview-controlled Scansys (Copenhagen) automated radiochemistry module. \([^{11}\text{C}]\) activity can also be piped to the Waisman Institute for Brain Imaging and Research via a “tuned”\(^2\) 300 meter underground PTFE pipeline. Each Scansys module contains a syringe pump-fed 2-dimensional robot with access to reagent vials, two thermally heated, air-cooled reactors, and a microwave module. Customized inserts permit reaction vessels to range in size from 500 uL to 7 mL. Robotic access is provided to additional reagents through 4 banks of 3-way valves, a needle cleaning station, and HPLC injection loop. Three Rheodyne TitanEX 7-port selector valves direct flow through cartridges for in-line separations and filtration, all monitored by miniature Centronix ZP1300 GM tubes. The HPLC
system supports up to 5 separate columns via additional switching valves and includes a column heater as well as a linear scanner gamma viewing any column with one of 8 included ZP1300 (Centronic) GM tubes. Following HPLC purification, the Scansys module also includes a custom evaporator which is capable of removing 10 mL water in ~ 1 min. for reconstitution in appropriate solvents. Drydown, as well as fluid movement throughout the module, can be accomplished with 4 MFC-regulated gas channels, currently plumbed and calibrated for argon, nitrogen, and helium flow. Each module also contains two vacuum pumps capable of pulling approximately 50 mL/min through 1 m of 1/16” ID tube.

To date, we have successfully automated syntheses of [18F]FLT, [18F]FES, [11C]MHED and [11C]DTBZ for animal studies on these systems. Yields are comparable to those obtained with our prior manual chemistries. For [18F]FLT, yields average 10.1 ± 5.1% (decay corrected to QMA trapping, using 10 mg 3-N-Boc ABX precursor) with specific activities of 3.7 ± 1.8 Ci/umol (n=30). [18F]FES yields average 16.9 ± 4.2% (decay corrected to QMA trapping, using 2 mg ABX precursor) with 3.8 ± 1.5 Ci/umol (n=4). Syntheses of [18F]FMISO are planned to follow.

Conversion efficiency from [11C]CH4, produced in-target, to [11C]MeI by recirculating loop in the new module is 70.0 ± 0.4% (n=28). Automated syntheses of [11C]MHED and [11C]DTBZ on the Scansys module average yields of 16.0 ± 5.8% (n=11) and 36.3 ± 11.6% (n=3) respectively (decay corrected to methylation). Specific activities for both syntheses, decay corrected to EoB, are 8.4 ± 0.3 Ci/umol. [11C]WAY, produced manually from the [11C]CO2 target, averages 1.4 ± 0.6 Ci/umol at end of synthesis (n=8); decay correction puts EoB specific activity from this target at 9.8 ± 3.3 Ci/umol.

Conclusion

The natural evolution of production capacity at Wisconsin has been driven by the increased demand for PET tracers for molecular imaging, both in basic research and in the clinic. The new PETtrace, bunkered in new facilities, easily handles the call for conventional radionuclides, freeing up the legacy prototype CTI RDS 112 for a new life concentrating on the production of 64Cu for distribution,18F2 for electrophilic fluorination (F-DOPA, FMT), and target development for the production of orphan isotopes.

1 Roberts A D, Armstrong I S, Kay B P, Barnhart T E (2004). Improved strategies for increased [18F]F- yield via the 18O(p,n)18F reaction with thin target windows and bodies. Presentation at the 10th Semi-Annual Workshop on Targetry and Target Chemistry, Madison, WI.

Sustainable PET tracer production at Wisconsin

13N target

18F water

11C gas targets

Wisconsin Institute for Brain Imaging and Research, Madison, USA

Scansys Copenhagen DK

Waisman Institute for Brain Imaging and Research, Madison, USA

University of Wisconsin, Madison, USA

The University of Wisconsin-Madison
Targets mounted on the UW PETtrace

Scansys Radiochemistry Box

Scansys box and interface

Capintec Hot Cells
1. Manufactured targets
   - Cheaper
   - Same yields
   - Stainless steel target experience

   Manufactured targets
Production of Cl-34m via the (d,α) reaction on Ar-36 gas at 8.4 MeV.

Jonathan W. Engle, Todd E. Barnhart, Onofre DeJesus, and Robert J. Nickles

University of Wisconsin, Madison, USA

Introduction

The radioisotope 34mCl (β+, t1/2=32.2 m) is of interest to the medical community, especially in drug development. However, 34mCl production is currently limited to facilities capable of accelerating alpha particles.1 Proton-only accelerators can make use of reasonable yields for enriched 34S targets, but must contend with the poor thermal and electrical properties of sulphur and its compounds, which reach the molten state at even limited beam currents. The utility of the 20Ne(d,α)18F reaction2 suggests an alternative route to 34mCl via the corresponding noble gas, argon. The excitation function and yield measurements for 36Ar(d,α)34mCl near 8.4 MeV, the nominal deuteron energy on a PETtrace cyclotron, elude a careful search of the literature.

Test Irradiations of natArgon

A gas target (21 cm x 1.4 cm ID) was built with removable endplates for rapid removal of a quartz tube with trapped 38,34mCl- from 40,36Ar(d,α). Exploratory deuteron irradiations were conducted on a thick target of natAr 130 psig. Following irradiation, the target was “cooled” briefly to allow the overwhelming 511 keV gammas from 16O(d,n)17F in the quartz tube to decay and then flushed twice into a 1 L syringe to remove 41Ar prior to target disassembly and analysis. The quartz tube was removed and assayed with an HPGe detector (spectra shown below). Gamma spectroscopy revealed the production of 0.9 ± 0.1 mCi/uA of 38Cl (t1/2=37.2 m) and 5.1 ± 0.4 mCi/uA of 41Ar (t1/2=109 m) at end of saturated bombardment (EoSB). More importantly, the production of 34mCl in approximately 1:300 ratio with 38Cl mirrors the abundance ratios of their target isotopes.

Yield Measurements with 36Argon

Enriched 36Ar (99.993%, 1 L at STP) was obtained from Isoflex (San Francisco). The high cost (~$5000/L) of the target material necessitated cryotrapping 36Ar post-irradiation in a 50 mL stainless steel vessel.3 Vacsorb greatly improved the cryorecovery of argon at -196°C (<1 mm Hg) compared to vapor pressures achievable in its absence (0.3 atm), in agreement with the Clausius-Clapeyron relation’s prediction. A second target (21 cm x 1.9 cm ID) better accomodated the width of our deuteron beam, albeit at some cost in target pressure. The 36Ar-filled target was irradiated at an initial pressure of 68 ± 1 psig by beam currents between 5 and 20 uA for 30 minutes. After the run, 10 minutes of cryotrapping recovered >99.5% of target material at -196°C. The target was vented and the quartz insert removed for analysis. To date, 12 irradiations have been completed, revealing radionuclidically clean production of desired 34mCl trapped in the quartz tube. EoSB yields and decay over more than 3 decades are shown below, averaging 1.8 ± 0.2 mCi/uA for thick-target runs, reflecting the larger ID target’s accomodation of the PETtrace deuteron beam. The target appears to thin beyond 10 uA, reducing effective yield. Phosphor plate imaging of the quartz tubes’ adsorbed activity confirms this hypothesis, as the activity peak progresses steadily towards the back of the target with increased beam currents.
Conclusion

These results suggest the possibility of subsequent labeling with $^{34m}$Cl; nucleophilic test reactions to confirm the reactivity of the product will follow.


Production of $^{34}$mCl via $(d,\alpha)$ on $^{36}$Ar gas at 8.4 MeV.

Jonathan W Engle, Todd E Barnhart, Onofre J DeJesus, Robert J Nickles.

The University of Wisconsin, Madison

Expected products from a deuteron irradiation at 8.4 MeV:

- $^{41}$Ar
- $^{38}$Cl
- $^{34/34m}$Cl

Expected products from a deuteron irradiation at 8.4 MeV:

- $^{41}$Ar
- $^{38}$Cl
- $^{34/34m}$Cl

Yields for both reactions of interest are presently absent from the literature.

Three experiments with $^{36}$Ar were conducted for extraction of target.

Preliminary experiments with $^{36}$Ar.

A test reaction $^{36}$Ar$(d,\alpha)$.

Target has removable endplate for extraction of quartz.

Tube assayed with HPGe (FWHM @ 1333 keV = 2.5 keV).

Experimenter irradiations at 130 psig, 8 MeV.

$^{34mCl}$

$^{38Cl}$

$^{34mCl}$

$^{38mCl}$

$^{39Cl}$

Atmospheric Radiation

Table of Results

- $^{34mCl}$
  - Yield: $5.1 \pm 0.4 \text{ mCi/µA}$ at 8.4 MeV
  - Production: $1/2 t = 32.2 \text{ min}$, $\beta^+$ energy = 4.5 MeV

- $^{34mCl}$
  - Production: $1/2 t = 32.2 \text{ min}$, $\beta^+$ energy = 4.5 MeV

- $^{34mCl}$
  - Production: $1/2 t = 32.2 \text{ min}$, $\beta^+$ energy = 4.5 MeV

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  - Production: $1/2 t = 32.2 \text{ min}$, $\beta^+$ energy = 4.5 MeV

- $^{34mCl}$
  - Production: $1/2 t = 32.2 \text{ min}$, $\beta^+$ energy = 4.5 MeV

Production of $^{34mCl}$ via $(d,\alpha)$ on $^{36}$Ar
Recovery: >99.5% in 10 min after EoB

Beam moves from left to right

Stainless and aluminum foils show activity on the top of quartz insert.

Cl EoSB Activity Trapped on Quartz Insert (MBq/uA)

1.4 ± 0.2 mCi/μA at EoS (not shown)
30Ci yields increase from initial levels to different layers.

Drop in yield at higher currents initially for 5 and 10 μA.
30 Ci yield: 1.8 ± 0.2 mCi/μA at EoS

Additional Vacsorb quartz or foil ports cooling jacket torr end plate

Electron energy deposition of beam from 1 to 10 μA.
15 to 120 psig and beam currents consistent yields at different pressures from 15 psig.
Stainless and aluminum foils show.

Figure shows end-of-range for deuteron beam (~ 7 mm FWHM, tailing to 10 mm).

Additional Vacsorb allows pressure in the target tube, suggesting an upward convective flow of gas within the tube.

Drop in yield at higher currents initially for 5 and 10 μA.
15 psig
45 psi (counts)
59 psi (counts)
60 psig

Bourdon Convectron
Pressure
Ar in/out

360C C
Recovery: >99%

Figure shows end-of-range for deuteron beam (~ 7 mm FWHM, tailing to 10 mm).

Electronic energy deposition of beam

34Cl yields with quartz, liners and 36Ar.

18 irradiations from 5 to 20 μA at 60 ± 1 psig.

Recovery: >99.5% in 10 min after EoB
Pressure after addition of Vacsorb ~ 1 mm Hg
Pressure in 196°C Cl target 15 psi vacuum, 0.3 atm.

Electrolyte recovery tests using 60 psig in the target.

A Second Target

Cryotrapping 36Ar Gas (99.993%)

<table>
<thead>
<tr>
<th>Beam</th>
<th>Water</th>
<th>Removable cooling jacket</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartz Ultra-Removal Plate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3AR Foil</td>
<td>0.001&quot;</td>
<td></td>
</tr>
<tr>
<td>2AR Foil</td>
<td>0.001&quot;</td>
<td></td>
</tr>
<tr>
<td>1AR Foil</td>
<td>0.001&quot;</td>
<td></td>
</tr>
</tbody>
</table>

Cooling Plate
Wash stainless foil with 40 ml water, load onto QMA prepped with 0.6 ml KHCO3 and 5 ml water.

Elute with 0.5 ml K2,2,2, 1 ml MeCN

Add 0.1 ml 1 N HCl (carrier) and 0.1 ml TEAOH, azeotropically distill with 2 x 1ml MeCN at 90°C

Cool to < 80°C and add 1 ml MeCN and 0.1 ml MeI

Flush product into syringes by bubbling low psi argon through sealed vessel. Analyze by GC.

Poropak Q column (80/100, 6' x 0.125" x 0.085" SS), Shimadzu 8610B running 0.5 ml/min He at 110°C

Decay Corrected Yield 82 ± 8% (max 9.4 mCi following a 30 min, 20 uA bombardment).

To our knowledge, this work is the first demonstration of radiochemically clean form suitable for further chemistry.

Future Directions

Conclusions and Acknowledgements

1. Pros and Cons
   - No Cl chemistry observed
   - High 24mCl positron energy

2. Challenge: cross sections measurement

We gratefully acknowledge the support of NIH Grant NS05933 (OTD) and NIH Radiobiological Sciences Training Grant T32 CA009206 (TJH). Using these methods, more than 50 mCi 34mCl has been produced in the 36Ar(d,2p)34mCl with useful yields. This work is the first demonstration of
OPTIMISATION OF AN ELECTROPLATING PROCESS TO PREPARE A SOLID TARGET FOR (p,n) BASED PRODUCTION OF COPPER-64

C. Jeffery\textsuperscript{1,2}, S. Chan\textsuperscript{1}, D. Cryer\textsuperscript{1}, A. Asad\textsuperscript{1}, RAPID Group\textsuperscript{1}; R.I. Price\textsuperscript{1,3}

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Introduction
Research into the production of copper-64 from a nickel-64 solid target utilising a semi-automated solid target assembly coupled to an IBA 18/9 MeV proton cyclotron is ongoing. The target is prepared using an electroplating method adapted from McCarthy et al (1997), which uses a solution of nickel ammonium sulfate (adjusted to pH 9 with ammonium hydroxide) to plate nickel onto a gold substrate. While this method of production is sometimes very successful, it has also proved unreliable, producing poorly plated disks in approximately 50% of experiments. The irregularities observed in the nickel surface include - flaking, crazing, formation of spheres or pits, loose/powdery Ni, poorly adhered Ni, a lack of ‘lustre’ and a black deposit forming on the anode. An article from Kim et al (2009) described the black anode deposit, and suggested that ammonium hydroxide and/or ammonium sulfate added to counter residual acidity in the nickel ammonium sulphate solution was the cause. Kim et al suggested an electroplating method to resolve this issue. Further work was carried out to optimise our electroplating procedure, based on their method.

Aim
To develop a method that reliably and reproducibly generates a solid target for copper-64 production by electroplating nickel-64 onto gold; and to optimise the electroplating conditions to enable maximum nickel deposition for minimal time and use of nickel-64.

Method
Preparation of purified NiSO\textsubscript{4} [adapted from Kim et al (2009)]
Nickel metal is dissolved in nitric acid and evaporated to dryness. The solid is treated with sulfuric acid and dried to a yellow solid. The residue is dissolved in milliQ water and recrystallised by adding acetone. The solid is collected by vacuum filtration, and dried over vacuum for two hours, followed by drying in an oven at 120°C for a minimum of two hours. The resulting yellow-green solid is NiSO\textsubscript{4}.

Preparation of electroplating solution
Purified NiSO\textsubscript{4} (0.13770g to 0.30079g) was dissolved in milliQ water (5mL, 10mL, or 15mL). Ammonium sulfate (~0.06g) was also dissolved into the solution.

Electroplating experimental conditions
Anode: initially carbon rod (rotating), then platinum rod (non-rotating)
Cathode: initially 2mm x 20mm gold disk, then 125µm x 15mm gold foil
Solution: initially nickel ammonium sulfate, pH 9, with ammonium sulfate buffer, Ni concentration ~3mg/mL (McCarthy et al, 1997); then nickel sulfate, pH 4.5, with ammonium sulfate buffer, Ni concentration ~5mg/mL (Kim et al, 2009)
Plating area: 10mm diameter, 78mm\textsuperscript{2}
Current: Constant 6mA
Time: 12 hours (10 experiments, varying masses of NiSO\textsubscript{4}), plus 6 experiments with time varied from 12-96 hours (constant mass of NiSO\textsubscript{4})
Results
16 experiments were conducted with nickel sulfate - 14 considered were successful.

Discussion and Conclusion
Fourteen of the 16 NiSO$_4$ experiments resulted in a lustrous, well-adhered layer of nickel, with no black residue on the platinum anode. The two failures were the result of variation in the constant current applied to the cell, and a change in the volume of water (increased to 15mL). Some divots have been observed in the nickel surface, indicating that bubbles have adhered to the surface during plating, but they are small and not considered a defect. The electroplating solution is stable over time (ie. no precipitate formed), and it is easy to prepare. The average yield of nickel plated using NiSO$_4$ is much lower than that achieved with Ni(NH$_4$)$_2$.2SO$_4$ (37-63%, versus ~70-95%), which is a disadvantage.

Effect of time (constant NiSO$_4$ concentration): Figure 1 shows the amount of nickel plated plateaus rapidly. Doubling the time (12 to 24 hours) results in a 1.1x increase in Ni plated, while quadrupling the time (12 to 96 hours) only results in 1.7x more nickel plated. Run times less than 24 hours are therefore most efficient.

Effect of varying NiSO$_4$ concentration (constant time): Figure 2 shows a low yield was achieved using a volume of 5mL. One experiment using 15mL of water resulted in a poor nickel surface despite a reasonable amount of nickel plated. The best yield with minimal amount of nickel in solution was achieved with a 10mL solution of 8.5mg/mL of nickel.

Overall, we are satisfied with the reliability and reproducibility of our method.

References

Streamlined measurement of the specific radioactivity of in-target produced $[^{11}\text{C}]$methane by on-line conversion to $[^{11}\text{C}]$hydrogen cyanide.

1) Jacek Koziorowski and 2) Nic Gillings

1) Herlev Hospital Copenhagen University, Denmark, 2) Copenhagen University Hospital, Rigshospitalet

Abstract

A simple method for the direct measurement of in-target produced $[^{11}\text{C}]$methane specific radioactivity is described. The method is also suitable for the production of $[^{11}\text{C}]$cyanide for radiosynthesis. Specific activities up to 13 000 GBq/µmol are reported.

Introduction

For monitoring and optimization of the specific radioactivity of in-target produced $[^{11}\text{C}]$methane it is desirable to have a simple method for measurement of the mass of carbon without having to performed a complete radiosynthesis. Quantification of $[^{11}\text{C}]$methane using gas chromatography (GC) is rather cumbersome and if using a flame ionisation detector (FID) it is necessary to wait until the activity has decayed before performing the measurement. Such a delay gives rise to the possibility of losses of methane, thus leading to an over-estimation of the specific activity. Furthermore, a reliable measurement of such small masses of methane is challenging.

$[^{11}\text{C}]$hydrogen cyanide can be easily produced on-line from $[^{11}\text{C}]$cyanide by passing over platinum at 1000 °C in the presence of ammonia. Since ammonia is produced in situ during irradiation of the $[^{11}\text{C}]$methane target by the radiolysis of nitrogen in the presence of hydrogen, this further simplifies the procedure. Cyanide can be quantified down to ppb levels by HPLC using an electrochemical detector (1) or by the use of colorimetric methods.

Experimental

Target

The target consists of a water cooled, quartz lined aluminium body (length 250 mm, i.d. 19.8 mm) (2). The target volume is 75 mL.

Irradiations

Irradiations were performed using the Scanditronix MC-32 cyclotron at Copenhagen University Hospital, Rigshospitalet. H- ions were accelerated to 17.2 MeV, giving an target entrance energy of ca. 16 MeV. The target gas consisted of ultra pure gases of 10% hydrogen in nitrogen (AGA, Sweden, grade 6.0 [>99.99995%]). The target fill pressure was 26 bar giving a gas volume of 2L at NTP.
Analysis
Following irradiations, the gases were released from the target by simply opening a valve and transferred to a hotcell. A mass-flow controller was set at 100mL/min and the gasses were passed over 3.37g of platinum wire (20m L x 0.1mm Ø) in a 6mm ID quartz tube at 1000°C. The produced $[^{11}\text{C}]$cyanide was trapped in a 20mL vial containing 20mL of pure water. After the vial an Ascarite trap (for measuring cyanide trapping efficiency) and a gas collection bag (to prevent the escape of radioactive gasses) was attached. After decay the amount of cyanide was measured using the pyridine-barbituric acid colorimetric test (Koenig reaction, EPA method 335.4-1) (3,4).

Results
Not optimized conversion from $[^{11}\text{C}]$methane to $[^{11}\text{C}]$cyanide were 50%. Trapping was quantitative (no radioactivity was found in the Ascarite trap) and 20GBq (n=4) of activity was trapped and the concentration of cyanide in the solution was below the detection limit (2μg/L = 77nM/L). This corresponds to a specific activity of >13 000 GBq/mol (EOB). For radiosynthesis the residual ammonia is easily removed by a trap filled with Dowex 50W (200-400 mesh) followed by Sicapent (to dry / remove water), for multi-runs, or a smoke tube (Draeger air current tube; silica impregnated with fuming sulfuric acid) for a single run.

Outlook
Experiments to increase the conversion and minimize the trapping volume are planned.

References


4) Method 335.4, Determination of total cyanide by semi-automated colorimetry, Rev.1.0, James W. O'Dell (Ed.) Inorganic Chemistry Branch, Chemistry Research Division, August 1993
Streamlined Measurement of Specific Radioactivity of in Target Produced 

- Mass of methane: 0.143 µg (based on 50 GBq)
- 12C/11C ratio: 38:1
- Maximum we have measured: 9 TBq/µmol (EOB)
- Theoretical maximum: 34.1 TBq/µmol

Specific Activity of [11C]Methane

- Theoretical maximum: 341 TBq/µmol
- Maximum we have measured: 9 TBq/µmol (EOB)
- 12C/11C ratio: 38:1

- Mass of methylene: 0.143 µg (based on 50 GBq)
- 12C/11C ratio: 38:1

Neuroreceptor Ligand Binding

- Non-radioactive compound will compete for active binding sites
- Less than 5% occupancy is normally used as a cut-off for tracer studies.
- Higher affinity neuroreceptor ligands labeled with

Why Measure Specific Activity?
**Experimental Set-up**

- Mass Flow Controller
- Pt Oven
- 980 ºC
- 10% H₂ in N₂
- 100 ml/min
- 20 ml
- Colorimetric test (König reaction)
- Jacek (artist's impression)

### Measurement of Specific Activity

- Direct quantification of methane in target gas at end of bombardment using gas chromatography with FID
- Bombardment with gas chromatography with FID
- Specific Activity a end of bombardment (EOB)
- Conversion to a [11C]-labelled compound and quantification with HPLC
- Quantification of cyanide using HPLC with UV detection, colorimetric methods or HPLC with fluorometric or electrochemical detection
- Sensitivity: Cy anide Test Kit -- 2 µg/L (fluorometric) -- LOD: 0.05 µg/L (electrochemical) -- LOD: 0.27 µg/L
- Aim: A simple method to determine SA of target gas without the need to perform a full radiosynthesis.
Perspectives

More sensitive methods for analyzation of cyanide are required to truly quantify SA of target gas. Specific activity of target gas appears to be very high (>13000 GBq/µmol).

Conclusions

Specific activity >13000 GBq/µmol
Cyanide concentration >2 µg/L (<0.04 µg total)
50% conversion, quantitative trapping
[^14C]CN yield: 20 GBq (EOB) in 20 ml water (ca. 14.1 min)
Irradiation 20 µA for 20 min (n=4)

Results

• UV vs visual inspection
• Go through the system to avoid it
• Important order among conversion and production of cyanide

Repeat experiments to test the effect of different target parameters (e.g., beam current) on specific activity may be possible with this method.

Trapping [^14C]cyanide in a smaller volume can be achieved by trapping first in a cryotrap then transferring to a small vial with a low helium flow.
Recent advances and developments in IBA cyclotrons

Jean-Michel Geets, Benoit Nactergal, Michel Abs, Claudy Fostier, Eric Kral

IBA Molecular, IBA Technology group, www.iba-group.com

Various development and enhancement to the existing IBA cyclotron range were accomplished last year including the launch of new cyclotrons and the revival of the oxygen machine.

To reply to the strong demand of F-18 radiopharmaceuticals in PET nuclear medicine, IBA has achieved a development program on the Cyclone® 18/9 PET cyclotron with the aim of increasing beam current and reliability. The strippers were replaced by a ‘drop-in-place’ designed to ease the maintenance. The uncritical internal ion source system was doubled so as to provide redundancy and lower maintenance schedule in the Cyclone® 18 TWIN with two proton sources. Since almost all of the PET tracers are today produced by protons, the same concepts were reused to develop the Cyclone 11 TWIN compact self-shielded machine for hospital-scale production of PET tracers.

The well-know Oxygen generator, a positive deuteron machine known as Cyclone® 3d, is under redesign for installation in Japan in early 2011. The aim is to provide a continuous flow of \(^{15}\text{O}_2\) without disrupting the PET production schedule of the main hospital cyclotron. The production is carried out on natural nitrogen as target with 3.6 MeV deuteron.

In the high energy range, following the Cyclone® 70 XP multiparticules machine installation in Nantes (France), a small brother was designed in the 30 MeV proton-alpha range, the Cyclone® 30 XP for Jülich (Germany). While proton (15-30 MeV) and deuteron (8-15 MeV) are produced and extracted in the well-known negative ion mode with stripping extraction in the Cyclone® 30, the positive alpha beam (nucleus of helium atom \(\text{He}^+\)) is accelerated and extracted in positive ion mode using an electrostatic deflector. The \(\text{He}^{2+}\) acceleration needs specific external source and adjustments to the cyclotron magnetic field and acceleration frequency (RF). The energy of the alpha beam will be fixed in the 29-30 MeV range to maximize At-211 production. Redesign of the magnet system was needed in order to leave free space for the alpha deflector and to reuse magnetic ‘flaps’ for field correction as it is done on the IBA-Cyclone® 18/9. Some technical challenges were solved to fit the two RF acceleration modes in the same machine with external ion sources platform for the different ions species. The innovative new RF design was patented by IBA.

The well-know Cyclone® 30 used by most of the SPECT producers worldwide was upgraded to higher current mainly to deal with the Tl-201 needs. A new external powerful \(\text{H}^+\) ion source was used, a redesigned injection line and central region was installed onto a standard 30 MeV cyclotron. The acceleration power (RF) was upgraded to 100 kW using the IBA in-house expertise giving the power extra supply for acceleration of 2mA of proton beam. Auxiliaries systems were upgraded (extraction, collimators...) to handle the new beam power. Consequently, the high power solid target system is proposed with an optimized full process (plating, separation and recovery of isotope).
Recent advance and development in IBA cyclotrons

Geets Jean-Michel

WTTC #13

© 2006

Machine with vertical plane, self resonating RF on top, no valleys

Improvements from the old design (ref. Turku)

4 machines sold > discontinued in 90’s

One gas target

3.6 MeV D+ beam, ESD extraction

Revival of the Cyclone®

150 generator : Main specifications

Redesign of the main systems
Central region redesign, TWIN sources

Extended Remote diagnostics

More feedback and datalogging

Self-tests: before batch & after maintenance

Full automatic production mode

More automation

Zephiris® control system for PET cyclotrons

Introduction of the Cyclone® 11

The self-shielded « little brother »

11.5 MeV proton TWIN source

Using Cyclone 18 components & parts

8 targets, 8 extractors (x 2 foils)

Drop-in-place strippers

Maintenance

Extended lifetime

TWIN proton sources system

8 targets with 8 extractors (x 2 foils)

Redundancy
We learned a lot of interesting things above the 30 MeV.

Cyclone® 70 in Arronax, Nantes.
Multiparticule machine for research & $^{211}$At production

Design of Cyclone 30 XP

- Use standard magnet
- New main coils
- New internal switching with modifications
- Opening in median plane
- Flaps for field adjustment
- New main coils
- Opening in median plane
- New internal switching with modifications
- Use standard magnet
- □ Phased RF system
- □ Moving contacts

Deep Valley with Flaps and Pole Extensions

What's inside the Vaults

30 MeV alpha beam on the Cyclone@30 XP
The high current Cyclone® 30

- Finally the 1.5 mA proton beam – 30 MeV machine
- Higher RF power for 2 mA beam
- Optimisation of central region injector
- Optimisation of external ion source
- Optimisation of external ion source

External source + injection line
Production of therapeutic quantities of $^{64}$Cu and $^{119}$Sb for radionuclide therapy using a small PET cyclotron

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Introduction

In the recent years the use of radionuclides in targeted cancer therapy has increased. In this study we have developed a high-current solid target system and demonstrated that by the use of a typical low-energy medical cyclotron, it is possible to produce tens of GBq's of many unconventional radionuclides relevant for cancer therapy such as $^{64}$Cu and $^{119}$Sb locally at the hospitals.

Materials and methods

The irradiations were performed using a slightly modified GE PETtrace cyclotron equipped with a beam line. The PETtrace is originally specified to deliver > 75 $\mu$A 16.5 MeV protons or > 60 $\mu$A 8.4 MeV deuterons on target but has been shown to be capable of accelerating > 200 $\mu$A protons by careful adjustment of the central region and with much attention to vacuum conditions.

The target consists of a 2 mm thick silver plate with 8 cooling fins (height 2 mm, width 1 mm) which is mounted on top of an aluminium base with a stainless steel mounting ring (see figures). The back side of the silver plate is cooled by water flow through the rectangular channels between the cooling fins (1 mm × 2 mm) with a water flow rate of 14 l/min and a water inlet temperature of ~3°C.

Two different target materials were used for the irradiations. Either enriched $^{64}$Ni for the direct production of $^{64}$Cu via the
The calculated temperature profile on the target face for a 203 µA beam corresponding to 180 µA on the target.

$^{64}$Ni(p,n)$^{64}$Cu reaction or $^{nat}$Sn to demonstrate the capability of producing high amounts of the Auger-electron-emitter $^{119}$Sb via the $^{119}$Sn(p,n)$^{119}$Sb reaction. The electroplating of the $^{64}$Ni targets were done using a $^{64}$Ni ammonium sulphate plating solution and the $^{nat}$Sn targets were made according to our newly developed method (Thisgaard and Jensen, Appl. Rad. Isot. 67, 2009) with a hot $^{nat}$Sn potassium hydroxide solution.

The targets were irradiated several times with the 16 MeV proton beam collimated to Ø5 mm. Both target materials were initially irradiated with a net target current of 180 µA with a collimator spill between 10–15%, i.e. with approximately 200–210 µA beam current before the Ø5 mm collimator to test the thermal performance of the targets. After the irradiations the targets were stored for a few days to let the produced activity decay and then inspected with a microscope and weighted. For production yield measurements, the targets were irradiated several times with peak target currents of 150 µA, again with a collimator spill between 10–15%, with irradiation times up to 76 minutes.

The temperature profile and the thermal induced stress (data not shown) in the silver plate were modelled using Comsol Multiphysics 3.3. The code uses a finite-element analysis (FEA) of the silver plate with 24096 mesh elements.

**Results**

The target was capable of withstanding the 180 µA Ø5 mm proton beam with both target materials tested. No sign of melting was seen on the target surfaces and no losses of target material were found from weighing the targets after EOB. This means that the surface temperature had not been above 231.93 °C during the Sn irradiations (the melting point of Sn) and probably not during the Ni irradiations either due to the higher thermal conductivity of Ni – in good agreement with the modelled results (see figure below).

From the 150 µA peak current irradiations the produced $^{64}$Cu activity was measured to be 8.2 ± 0.7 GBq at EOB for the 76 min. irradiation (mean current of 121 µA), corresponding to 54 ± 5 MBq/µAh using 98% enriched $^{64}$Ni with a plated target thickness of 8.5 mg/cm$^2$. This corresponds to the proton energy interval of 16.0 → 14.3 MeV, i.e. well above the maximum cross section of the excitation function for the $^{64}$Ni(p,n)$^{64}$Cu reaction at approximately 11 MeV.

By increasing the plated target thickness to e.g. 30 mg/cm$^2$ of enriched $^{119}$Sn or $^{64}$Ni (resulting in a surface temperature increase of less than ~25 °C), it will be possible to produce ~46 GBq of $^{119}$Sb or ~174 GBq of $^{64}$Cu, respectively, in 3 hours using 150 µA target current as above. In both examples, the total amount of enriched target material required to obtain the 30 mg/cm$^2$ thickness will be less than 60 mg due to the extremely focused proton beam (Ø5 mm), thus keeping the specific activity high and the metal impurities low.

**Conclusion**

In the current study we have developed a high current solid target system and shown that by the use of a typical low-energy, medical cyclotron, it is possible to produce tens of GBq’s of unconventional therapeutic radionuclides locally at the hospitals.
Matching the beam to the target:

1) Solid targets with high currents and high spot beam spot

2) Get the "long lived" stuff away from the cyclotron

3) Neutron production (for (n,p) and (n,g) reactions)

Why & Isotope production?

"A beamline for the PETtrace cyclotron"

Highest power efficiency (C/kWh)

Smallest target (high SA, low volume chemistry)

If (p,n) is available, it gives:

1 MBq 1 A

1 GBq 1 nA

1 TBq 1 pA

"The nuclear battery" in our vials

Energy efficiency of a cyclotron: 800 W / 80 kW = 1%

Energy efficiency of target: (200 GBq * 1.5 MeV) / 800 W = 0.006%

The rest goes into heat.

Overall energy efficiency: 0.00006%

Only a small fraction is stored as nuclear energy:

16 MeV 54 a delivers 800 Watts of kinetic energy to the target

"A beamline for the PETtrace cyclotron"

Presentation for WTTC 13

Production of therapeutic quantities of 64Cu and 119Sb for radionuclide therapy

Using a small PET cyclotron
Water flow is 14 liters/minute, 6 deg. C inlet.

Target base is Silver 2 mm thick, with fins.

6 degrees grazing incidence of a Ø 10 or Ø 5 mm beam.

Target mounting...
Target with electroplated Tin - survives 200 uA.
At present we are hitting the target with 16.5 MeV. That is too high. We could use thick Ni-64 targets to degrade or strip at lower radius.

What do we want that for? Therapy?

74 GBq of 64Cu in 3 hours using 150 μA.

WTTC XIII – Presentation Discussions

1. Ag target: materials
   - May force all materials (even) screws to be Ag
   - Anodized Al as isolator: no scratches = no problems
   - Key focus all materials (very) smooth to be Ag

2. Collimator?
   - 10mm, 30% loss, good cooling necessary

3. Purification
   - Identification of residuals is important
   - Be careful with benzenes, etc.

The calculated temperature profile on the target face for a 233 fs pulse.
The chemistry of high temperature gas phase production of methyl iodide

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Veenstra Instruments, Joure, The Netherlands, *University Hospital, Center for Radiopharmaceutical Science, Zurich, Switzerland,

A methyl iodide system was set up to react iodine and methane at high temperature in the gasphase (Larsen).

\[ \text{CH}_4 \uparrow + \text{I}_2 \uparrow \rightarrow \text{CH}_3\text{I} \uparrow \]

The apparatus consists of an iodine vaporizer, a high temperature (about 700º C) reactor and a Porapak-N methyl iodide trap. The length of the tube which is heated to the high temperature can be varied.

A known quantity of methane is added from an injection loop or from a methaniser which is fed with carbon dioxide from the injection loop. The methane is transported by a controlled flow of helium through a carbosphere column, which is needed to remove hydrogen from the methane (which is present when starting with methane from a cyclotron and after methanisation). Behind the iodine oven a UV spectrometer is positioned to measure the absorbance in the glastube and the iodine absorbance is used as feedback to regulate the temperature of the vaporizer and thus control the iodine concentration (Link, Clark).

Scheme:

This way all relevant parameters are under control and known quantitatively. The initial amount of methane was chosen as 9 µl, which is the amount of carbon delivered from a cyclotron when producing carbon-11 of moderate specific activity.
The relation between the iodine concentration and the absorbance was calibrated, by collecting the iodine at a stable absorbance during a defined time and weighing the absorbed iodine.

The MeI is collected in methanol (> 90 % is known to be trapped in the first bottle) and analysed by HPLC over an ACE 5 C18 column (15 x 4.6 mm, particle size 5 µm) eluting with methanol / water 60/40 (v.v.) and UV detection (240 nm). A standard solution containing Methyl iodide (MeI) and diiodomethane (MeI₂) was used for calibration.

Results

The results given here are preliminary and have to be more precisely calibrated

Transport flow (He-flow) dependence:

The MeI yield decreases at high and low transport flow. Over a broad flow range, the variation in yield was not significant.

<table>
<thead>
<tr>
<th>Various flows with a I₂ abs of 0.10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow [ml/min]</td>
</tr>
<tr>
<td>Peak area</td>
</tr>
<tr>
<td>MeI [µMol]</td>
</tr>
<tr>
<td>Yield [%]</td>
</tr>
</tbody>
</table>

Iodine concentration dependence:

The MeI yield increases with increasing iodine gas concentration, the maximum concentration still has to be determined:

<table>
<thead>
<tr>
<th>Various flows with and I₂ concentrations resulted in the following yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10 I₂abs</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>23 ml/min</td>
</tr>
<tr>
<td>30 ml/min</td>
</tr>
<tr>
<td>38 ml/min</td>
</tr>
</tbody>
</table>

References


Aim

- Better understanding of the chemistry
- Robust in usage
- Small footprint
- Dimensions of the reaction oven
- Low heat dissipation
- Longer usage of the iodine

Multi-pass
- Single pass
- Specific activity
- Concentration methane
- Parameters: I₂, T, Flow, ...
- H₂

Critical points

Bettter Understanding Chemistry

- Critical points
  - H₂
  - Concentration methane
  - Parameters: I₂, T, Flow, ...
  - Specific activity
  - Robust in usage
  - Dimensions of the reaction oven
  - Low heat dissipation
  - Longer usage of the iodine

Bettter Device

- Better understanding of the chemistry
- Robust in usage
- Small footprint
- Dimensions of the reaction oven
- Low heat dissipation
- Longer usage of the iodine

Bettter Understanding Chemistry

- Critical points
  - H₂
  - Concentration methane
  - Parameters: I₂, T, Flow, ...
  - Specific activity
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Bettter Device

- Better understanding of the chemistry
- Robust in usage
- Small footprint
- Dimensions of the reaction oven
- Low heat dissipation
- Longer usage of the iodine

Bettter Device
Reactions

\[ \text{Methaniser} \]

\[ \text{CO}_2 + 4\text{H}_2 \rightarrow \text{CH}_4 + 2\text{H}_2\text{O} \]

\[ \text{Cold trap} \]

\[ 2\text{CH}_4 + 2\text{I}_2 \rightleftharpoons 2\text{CH}_3\text{I} + 2\text{HI} \]

\[ 2\text{CH}_3\text{I} + \text{I}_2 \rightleftharpoons 2\text{CH}_2\text{I}_2 + 2\text{HI} \]

Methods

- Test set up
  - Two flow controllers
  - Spectrophotometer
  - Methane injector
  - Trap product in pure MeOH
- HPLC
  - C18 column
- Methaniser
Results

Parameters compared: \( I_2 \), Flow and Me concentration

Acknowledgement

• Calle Sjoberg
• Jaring Huitema
• Teake Bijkerk
• And others colleagues

from Veenstra Instruments
from COSAB engineering

Temperature dependence:

Results
1. Challenge: Why not make a nano-reactor?
Target Performance – $[^{11}\text{C}]\text{CO}_2$ and $[^{11}\text{C}]\text{CH}_4$ Production

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Introduction
A systematic investigation on $\text{N}_2$ (0.1 % $\text{O}_2$) and $\text{N}_2$ (5 % $\text{H}_2$) target performances is presented in terms of saturation yields as function of target body temperature and irradiation current.

Materials and methods
Identical aluminium target bodies were used for both $[^{11}\text{C}]\text{CO}_2$ and $[^{11}\text{C}]\text{CH}_4$ productions. The conical chambers measured 11.2 x 90.0 x 19.4 mm (front I.D. x length x back I.D.) and 16.9 cm$^3$. The inlet foil was supported by a metallic grid having a transparency of ~ 70 %. In all irradiations the chambers were loaded at 20 °C to 35 bar pressure and irradiated for 20 minutes. Variable parameters were the target body temperature (10, 40, 70 °C), regulated with a cooling fluid circuit and a heat exchanger, and the irradiation current (10, 20, 30, 40 µA). For the data points $n = 2$.

The proton beam was generated with a fixed energy (17 MeV) negative ion cyclotron (CC 18/9, D.V. Efremov Scientific Research Institute of Electrophysical Apparatus, St. Petersburg, Russia).

The irradiation product was directed to a hot cell via a capillary and valve arrangement and a mass flow controller. The main $^{11}\text{C}$-species was first separated from the target gas using a selective trap: Porapak N column in Ar(Liq) for the $[^{11}\text{C}]\text{CH}_4$ and an Ascarite column at room temperature for the $[^{11}\text{C}]\text{CO}_2$. The traps were placed in a dose calibrator and the irradiated gas that passed a trap was collected as gas. The collected volume was readable from the gas trap and an aliquot could be taken for radioactivity measurement.

The $^{11}\text{C}$ main product yield was thus measured on-line with the dose calibrator containing the first trap. The content of $^{11}\text{C}$ and $^{13}\text{N}$ in the second trap was determined by iterating the decay curve fitting to the radioactivity values at early and late time points. Yields for the $^{11}\text{C}$ main product and $^{11}\text{C}$ and $^{13}\text{N}$ by-products were calculated as saturation activities ($A_{\text{sat}} [\text{GBq/µA}]$).

![Figure 1. Pressure versus irradiation current at different target body temperatures](image-url)
Results
The pressure increase as function of beam current was similar for both targets (figure 1). A slight
difference was observed at higher currents.

The main component yield is practically constant for the $^{11}$C$\text{CO}_2$ (figure 2, pane A) across the
range of varied target body temperature and irradiation current. The $^{11}$C$\text{CH}_4$ yield (figure 2, pane
B) is directly proportional to the temperature and inversely proportional to the current.

$^{11}$C$\text{CO}$ generation in the N$_2$ (0.1 % O$_2$) target is low and inversely proportional to temperature and
constant across the investigated current range. $^{11}$C by-product generation is negligible in the N$_2$
(5 % H$_2$) target.

$^{13}$N generation is constant across the range of current and temperature using either N$_2$ (0.1 % O$_2$)
or N$_2$ (5 % H$_2$) target gases. However, $^{13}$N production is slightly lower for the N$_2$ (5 % H$_2$) target.

![Figure 2. Yield of the main component as a function of irradiation current at 10 – 70 °C.](image)

Conclusions
Production of $^{11}$C$\text{CO}_2$ is practically independent of the irradiation current and the target body
temperature, whereas $^{11}$C$\text{CH}_4$ production was found to be strongly dependent on the current and
target body temperature.

Acknowledgement
The study was conducted within the "Finnish Centre of Excellence in Molecular Imaging in
Cardiovascular and Metabolic Research" supported by the Academy of Finland, University of Turku, Turku University Hospital and Åbo Akademi University.

References
volume, high pressure gas targets. Radiochim Acta, 88, pp. 201–205
Introduction

- Target chamber temperature control
- Experimental setup

- Fixed: Target composition, etc.
- Varied: I, T, E

Aim
- Better yields with higher body temperature
- Systematic investigation of selected parameters

Theoretical [11C] yields
- Background

Background performance – production

Tunuk PET Centre, Finland
Jussi Aromaa, Olof Solin
Semi Hellen, Evelina Arponen, Johan Rajander

WTTC X11, Risø, 28.7.2010, #25

Investigated parameters

<table>
<thead>
<tr>
<th>Category A</th>
<th>Category B</th>
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<tr>
<td>N[10%] H</td>
<td>17</td>
</tr>
<tr>
<td>N[5%] H</td>
<td>35</td>
</tr>
<tr>
<td>C</td>
<td>17</td>
</tr>
</tbody>
</table>

Average 19.6 21.4 10.0 18.0 22.6
SD 0.3 0.4 0.03 0.8 0.3
RSD (%) 1.4 2.0 0.3 4.3 1.1

Results, set A

System repeatability

Results, set B

At 10-70°C

Measurement & data collection

Experimental setup

Exact actual values for various parameters

Produced radioactivity

1st trap for the main 11C-product

Irradiation log file

Sampling available

- Irradiated target gas, irradiation log file
- 2nd trap for the unretained gas
- 1st trap for the main 11C-product inside a dose calibrator
Conclusions

Knowledge for optimization and design

- balance of consuming reactions
- hydrogen reserve
- current dependence
- wall effect
- temperature dependence
- beam current dependence

For \([{}_{11}^{13}C]CH_4\) production:

- predicted range of parameters varied
- predicted range quite constant within

- predicted yield of \([{}_{11}^{13}C]CH_4\) as function of

- temperature and irradiation current

- Predicted yield of \([{}_{11}^{13}C]CH_4\) as function of

\(I \cdot \left(\frac{I \cdot \left[{}_{11}^{13}C]CH_4\right]}{I \cdot \left[{}_{11}^{13}C]CO_2\right]} \right) \cdot \text{predicted yield} \cdot \text{predicted yield} \cdot \frac{g \cdot \text{yr}}{\text{yr}} \)

- Other factors inherent to the larger setting in case

- Beam current, temperature, and gas chamber wall

- Steaming from nuclear reaction, proton energy

- \(I \sim 1\)

- \(N_2 \sim 1\)

- \({}_{11}^{13}C \sim 1\)

- \({}_{11}^{13}C + 2H_2 \leftrightarrow {}_{11}^{13}C \sim 1\)

- \(2NH_3 \leftrightarrow 3H_2 + N_2\)
This study was conducted within the "Centre of Excellence in Molecular Imaging in Cardiovascular and Metabolic Research" supported by the Academy of Finland, University of Turku, Turku University Hospital and Åbo Akademi University.

---

1. Low yield
   • Can $^{11}$C be produced but stay in target walls?
   • Can $^{11}$C be produced but stay in target walls?
   • Can gas quality/quantity or temperature help?
A Solid $^{114m}$In Target Prototype with Online Thermal Diffusion Activity Extraction - Work in Progress
Jonathan Siikanen$^{a,b}$ and Anders Sandell$^b$

$^a$Lund University, Medical Radiation Physics, Barngatan 2:1, 221 85 Lund, Sweden
$^b$University Hospital in Lund, Radiation Physics, Klinikgatan 7, 221 85 Lund, Sweden

Introduction
A solid target system is under development for indium isotope production. Pure $^{114m}$In ($T_{1/2}=45$ d, $E_γ=190$ keV, 15.6%) can be produced from proton irradiation on natural cadmium foils if the simultaneously produced $^{110}$In-$^{111}$In activity is allowed to decay several days. $^{114m}$In decays to $^{114}$In ($T_{1/2}=71.9$ s, $β^-=99.5$%). This work focuses on $^{114m}$In production/extraction.

Material and methods
A target holder was constructed to match a MC 17 Scanditronix cyclotron with a wide beam. The beam fits into a collimator of 40x10 mm$^2$. The foil holder is a 30° slanted cooling/heating block with a three side frame mounted to the beam strike side (fig 4). On this frame a 25 µm niobium foil is placed to create a water tight cavity, of some ml volume, between the niobium foil and cooling/heating block. In this cavity the cadmium foils are placed. The slanting gives a beam strike area of 40x20 mm$^2$. This area is cooled with a 1.5 mm thick, 3 l/min water film. The system was loaded with natural cadmium foils and bombarded with 45 µA protons, under helium flush. After irradiation, the foils were heated to 280-310°C for 1 to 2 hours under argon flush in the cavity. The heating was performed with two heating elements (L=40 mm, ø=6.5 mm, P=160 W each) mounted symmetrically on the long sides to the beam strike area (fig 3). The temperature was measured, with two PT100 sensors (9.5x1.9x1.0 mm, -70…+500°C) mounted on the sides (fig 4), and displayed/controlled with two Shimaden RS32 controllers. The side temperatures were calibrated to the actual temperature under the cadmium foil with another PT 100 sensor. The activity extraction was made with a thermal diffusion technique [1]. This technique is based on heating close to the melting point of cadmium (320°C). At this temperature, the produced indium isotopes (melting point 150°C) are diffusing in the cadmium matrix. Gradually over time, the indium atoms concentrate on the foil's surface and can then be etched off with a weak acid (0.05 M HCl). The acid was pumped in and out with a peristaltic pump.

Fig 1. Target cooling/heating block back plate with water cooling in out and two heating elements.

Fig 2. 1: 25 µm Nb foil, 2: Cd-foil-Al-fork (fig 4) 3: Outer frame with He/Ar in/out and a hole in the bottom for activity extraction, 4: back plate 0.5 mm back wall to cooling water, 5: water in/out plate.

Fig 3. Cross section view of the back plate: 1: Beam strike area. 2: Heat element holes.
Fig 4. The foil is squeezed and stabilized into place under the flush tubes. This view is covered with a 25 µm Nb foil. HCl is pumped in/out from below, in the cavity between the back plate and the Nb-foil. The Cd-foils are mounted on an Al-fork with a silicone adhesive.

Fig 5: The target is loaded from its rear top simply by sliding down a Cd-Al-fork.

E_p on cadmium foils is ~12.3 MeV. 100 and 50 µm cadmium foils slanted 30° degrades 12.3 → 9.2 and 12.3 → 10.9 MeV. This correspond to theoretical ¹¹⁴ᵐIn activity yields of 0.2 MBq/µAh and 0.08 MBq/µAh for natural¹ cadmium foils [2].

**Preliminary Results**

Low activity yields indicated that a great portion of the beam had missed the actual target, i.e. the cadmium foil. Activity yields will be presented at the conference when new irradiation has been performed. Separation yields on the other hand are valid and are given in table 1.

Table 1: Extraction yields were either measured with a Capintec CRC 120 dose calibrator or a HPGe detector. Etching time was 1-2 min.

<table>
<thead>
<tr>
<th>Foil #</th>
<th>Thickness (µm)</th>
<th>Irradiation Time (min)</th>
<th>Heating time (min)</th>
<th>Extraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1=T116</td>
<td>100</td>
<td>~6.3</td>
<td>128</td>
<td>41</td>
</tr>
<tr>
<td>2=T117</td>
<td>100</td>
<td>~6.8</td>
<td>120</td>
<td>54</td>
</tr>
<tr>
<td>3=T118</td>
<td>100</td>
<td>~6.8</td>
<td>60</td>
<td>44</td>
</tr>
<tr>
<td>4=T119</td>
<td>50</td>
<td>~6.7</td>
<td>120</td>
<td>41</td>
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<td>5=T122</td>
<td>100</td>
<td>~7.0</td>
<td>60</td>
<td>40</td>
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<tr>
<td>6=T123</td>
<td>100</td>
<td>~6.8</td>
<td>120</td>
<td>49</td>
</tr>
<tr>
<td>7=T124</td>
<td>50</td>
<td>~6.7</td>
<td>120</td>
<td>56</td>
</tr>
</tbody>
</table>

**Discussion**

It was found that thermal diffusion extraction of indium from cadmium foils, which only requires temperatures around 300°C, is practically doable direct in the target without any dismounting of foils after irradiation. About 40-50% of produced activity could be extracted with heating times of 1-2 hours. Natural cadmium material for one target cost about 10 Euros.

**Acknowledgements:**

Thanks to Jan Hultqvist, University Hospital Lund, for machining the target pieces.

Thanks to Professor Hans Lundqvist, Professor Vladimir Tolmachev and Dr Lars Einarsson Uppsala University for the separation technique and discussions.

**References:**


[2] IAEA Recommended cross sections for ¹¹⁴Cd(p,n)¹¹⁴ᵐIn reaction (http://www-nds.iaea.org/radionuclides/cd4p4in0.html)

¹ The yields are calculated to correspond to the abundance of ¹¹⁴Cd in natural Cd foil i.e. 28.73 %
**Background**

- Long lived isotope for therapy. $^{114m}$In is listed by IAEA as an emerging therapeutic isotope.

**Target**

- Target mass $\sim 1$ g
- Temperature resistant silicon adhesive (316°C)
- Mounted to an aluminium fork with a high temperature resistant silicon adhesive ($316^\circ$C)
- $100$ µm cadmium foils (92% $^{114}$Cd)
- $\text{natCd} + \text{p} \rightarrow \text{cd}^{114m} + \text{n}$ (29% $^{114}$Cd)
- Recommended cross sections for $^{114}\text{Cd}(p,n)^{114m}\text{In}$ reaction

**Remote activity handling**

- Personal protective equipment for handling to decrease dose burden to personnel.
- A solid target system for $^{114\text{In}}$ in an online thermal diffusion activity extraction system.
- Long lived isotope for therapy, $^{114\text{In}}$ is listed by IAEA.

**Work in progress**

- Thermal diffusion activity extraction prototype with online monitoring.
Activity extraction

1. Information

- Heating close to 320°C melting point of cadmium

2. Method

   1. Target site
   2. After EOB: Water cooling and He-flush switched
   3. Heating close to 300°C for 1-2 h and then cool
to Ar-flush
   4. Foil is etched with 5-6 ml 0.05 M HCl for about 2h
down to about 30°C

3. Material

   - Target Holder
   - Cooling/Heating Block

4. Activity extraction

   - remote handling to avoid personnel doses
   - online activity extraction with thermal diffusion
   - melting point of cadmium is 429°C
   - melting point of indium is 157°C

5. Controls

   - Displacement controlled with two Shimaden RS32
   - PT100 sensors (9.5x1.9x1.0 mm, -70...+500°C)
   - Two heating elements
   - 3 l/min water flow
   - Cooling block with 1.5 mm thick
   - Target holder-cooling/Heating Block

   The beam fits into a collimator of 4x10
   and another 25 µm Nb foil EP on target
   The foil fits into a double He-cooled Havar and 200 µm Ag
   and passes through a double He-cooled 25 µm Havar window
   and another 25 µm Nb foil EP on target

   1Lundqvist et. al
   2Tolmachev et. al
   3l/min water flow
   4Target site
   5Material
   6Method
   7Proton flux
   8Activity extraction
Results

• First set of experiments gave 40–50% extraction yield

\[ \text{eq} \]

\[ V=177 \text{ Kev} (90.6\%) \text{ and } V=245 \text{ Kev} (94.1\%) \]

\[ T=2.8 \text{ p} \]

- B=62 %

\[ T=171 \text{ Kev} (94.1\%) \]

In the future

Discussion

• It was found that thermal diffusion extraction of indium from cadmium foils, which only requires temperatures around 300°C, is practically doable direct in the target without any dismounting of foils.

- About 40–50% of produced activity could be extracted with heating times of 1–2 hours after irradiation.

- < 2% of cadmium material losses.

Natural cadmium material for one target cost about 10 Euros.

• Further investigation

- low activity yields (about 20% of theoretical) needs holder etc.

- Natural cadmium material for one target cost about 10 Euros.

- < 2% of cadmium material losses.

Table 2: \(110\text{In} \) yields of 0,25 MBq/µAh net-cd.

\[ \text{Table} 2: \text{\textsuperscript{110}In yields of } 0.25 \text{ MBq/µAh net-cd.} \]

\[ \text{Theoretical yield: } 100 \text{µm Cd foil stained 30º, f } 12.3 \text{ with } 8.4 \text{ MeV} \]

100 µm Cd foil stained 30º, f 12.3 with 8.4 MeV.

Heating 280–310°C (some problems with Pt100)

First set of experiments gave 40–50 % extraction yield.

• In this set all foils were heated for 2 h at 300°C.

In this set all foils were heated for 2 h at 300°C.

\[ 110\text{In} \] yields of 0,25 MBq/µAh net-cd.

\[ \text{Theoretical yield: } 100 \text{µm Cd foil stained 30º, f } 12.3 \text{ with } 8.4 \text{ MeV} \]
1. Why not a Niobium target?
   • Not tried

2. Diffusion/extraction
   • Process known in Russian literature
   • Stack could be used, but difficult to get the acid in there
Upgrade of a Control System for a Scanditronix MC 17 Cyclotron

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\textsuperscript{b}University Hospital in Lund, Radiation Physics, Klinikgatan 7, 221 85 Lund, Sweden

In order to extend the life time of the relatively old Scanditronix MC17 cyclotron (built 1980) an upgrade to the control system was commissioned. The existing system is a PM 550 Texas Instruments. It consist of a Central Control Unit (CCU, 4 KB), a programmer, 6 MT input(170)/output(120) modules (fig 1), 7MT analog input(16)/output(12), a 7MT parallel input(4)/output(4) module and a control consol interface (fig 3). The programming is ordinary ladder logic. The system works well but the lack of spare CCU:s forced an upgrade to the system.

The choice was the CTI 2500 system due the existing special interface card 505-5190 B. This card makes it possible to keep, and avoid rewiring of, all the 6 MT modules. CTI-2558/2562 N analog input/output modules replaced the old ones. The ADC:s were connected in parallel to the old ones. The old DAC:s and the new DAC:s were connected to a toggle switch. This simple rewiring was done in less than five hour. The 7MT parallel input/output were only used for display function and could be omitted in the new system. The installation makes it possible to change between the systems within less than 5 minutes. The CTI system runs under CTI P-SM505-CW N software (505 Workshop Single License). A new interface was written in Visual Basic instead of using a commercial SCADA program. The interface was used on a PC lap top. The upgrade was performed in collaboration with a Danish company Green Matic. Green Matic made the ladder programming. The total cost of the upgrade was less than 20 000 Euros. Testing and debugging of the new system took one day.

Fig 1: The 6MT modules

Fig 2: The new CTI system (In order from left: Power Supply, CPU, Interface card, 4 Analog 8 Channels IN/OUT cards)

Fig 3: The PM550 control consol

Fig 4: New interface written in visual basic
New software for the TracerLab Mx

D. Fontaine², D. Le Bars³, D. Martinot¹, V. Tadino⁴, F. Tedesco¹, G. Villeret⁴

1. 49h, 23 Rue du Vieux Mayeur, 4000 Liège, Belgium
2. Eosis, 33 Rue Lefebvre, 7000 Mons, Belgium
3. CermeP, 59 Bvd Pinel, 69003 Lyon, France
4. ORA, 337 Rue de Tilleur, 4420 St Nicolas, Belgium

Introduction: With almost 800 systems installed all over the world, the Coincidence/TracerLab Mx (General Electric, USA) is still the best seller among synthesizers for [¹⁸F]FDG production. This device is approved by relevant Authorities for most of the Marketing Authorizations and used in a GMP environment to produce pharmaceutical grade fluorodeoxyglucose. When FDG started to be commercialized, private laboratories were approved by the Authorities as “mono-product” producers allowed to prepare, sell and deliver only FDG. Further, following the increasing market demand for other radiopharmaceuticals, they were solicited to produce already published tracers under special license and under specific orders for approved clinical protocols. Today, more and more producers are very far in the development of new tracers and on their way to submit Marketing Authorizations.

Objective: On one hand, most of the production laboratories must adapt their license and organization to become “multi-product” and one major step of the file update is the demonstration that in one room, several different synthesis are managed at no risk for the final product (schedule, cross contamination, ...). On the other hand, most of technician teams are trained on the TracerLab Mx and the switch to any other system may easily take up to several months to recover the same reliability. Today, by using the TracerLab Mx in its original configuration, the above mentioned two points are not under control, mostly due to the inadequacy of the original software.

Features:

The purposes of a new software development were:

1) Availability of specific folders for each different produced radiopharmaceuticals
2) Use of kits commercially available from ABX (Dresden, Germany) for NaF, FLT, F-Miso, FET, F-acetate and F-choline
3) Avoidance of sequence problems, with reset of the PLC memory between each run
4) Specific kit test dedicated to the molecule
5) Display a specific flow path layout for each molecule
6) Creation of a specific report corresponding to the name of the molecule
7) Building of data base in order to manage and optimize the preventive maintenance
8) Implementation of different level of users that can log into the system (administrator, operator,...)
9) Safe and secure control of the TracerLab Mx from any computer through secured LAN (cabled and/or wifi) or secured internet connection
10) Open updatable list of compounds

Other useful features added to the software:

11) Addition of a 5th radioactivity detector
12) Possibility to connect a UV detector
13) Control of the 8 outputs still available on the back of the Mx
14) For the user willing to run synthesis including HPLC purification, dedicated screen displaying HPLC UV and radio detection, “Collect” and “Stop collect” button and the possibility to control an “Add On Reform”

Upgrade Procedure:
The upgrade of an existing TracerLab Mx is quite simple:
- Replacement of the RS232 cable by an RJ45 cable
- Replacement of the PLC control board
- Installation of a control server and a WIFI router

From that configuration, any computer loaded with standard browser (Firefox for example), can control the TracerLab Mx.

User Procedure:

**Step 1:**
Start WebBrowser → Connect machine http://10.10.... → Login → Select Molecule in the list

**Step 2**
Enter batch Data → PLC Reset → **Automatic Upload of the correct sequence**

**Step 3 :**
HW Test → Kit Test → Synthesis → Report → DB Recording

Results:

<table>
<thead>
<tr>
<th></th>
<th>Duration</th>
<th>Uncorrected Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kit Only</strong></td>
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<td></td>
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<tr>
<td>NaF</td>
<td>&lt;10 min</td>
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</tr>
<tr>
<td>FLT</td>
<td>54 min</td>
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</tr>
<tr>
<td>F-Miso</td>
<td>54 min</td>
<td>22%</td>
</tr>
<tr>
<td>F-choline</td>
<td>32 min</td>
<td>17%</td>
</tr>
<tr>
<td>FET</td>
<td>54</td>
<td>17%</td>
</tr>
<tr>
<td>F acetate</td>
<td>42</td>
<td>39%</td>
</tr>
<tr>
<td>FDG</td>
<td>26</td>
<td>61%</td>
</tr>
<tr>
<td><strong>HPLC</strong></td>
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<tr>
<td>MPPF</td>
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<tr>
<td>FLT</td>
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</tr>
<tr>
<td>Fallypride</td>
<td>Under Progress</td>
<td></td>
</tr>
<tr>
<td>Licensed 1</td>
<td>Under Progress</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion:
By using the new software the Tracer Mx has now become a flexible platform dedicated not only to FDG production, but also to most of the fluorinated tracers with clinical demand.
WHY?

- FDG only!
- Other kits available but...
- New radiotracers?
- 8 year old software :-(

HOW?

1. Web connect
2. Select
3. Visualize
4. Launch syntheses
5. Monitoring

AND NOW?

1. Web connect
2. Select
3. Visualize
4. Launch syntheses
5. Monitoring

New software for the TraceLab MIX

Tips & Tricks

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AND NOW?

1. web connect
2. select
3. visualize
4. launch synthesis
5. monitoring
Optimized Radiochemical Applications

Research Development
Scientific Survey
Technological Survey
Feedback

Radiochemical Synthesis Modules

New Products
Optimization

Maintenance
Regulatory Affairs

Experience
Production

Cooperation
Radiopharmaceutical cGMP

13th International Workshop on Targetry and Target Chemistry
Risø National Laboratory, Roskilde, Denmark – 26 July 2010

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INTRODUCTION: There is growing interest in the Australian research community for new PET radioisotopes with relatively long half lives. $^{64}\text{Cu}$ is a candidate, since; (i) it can be produced in cyclotrons found in a medical setting; (ii) the translational energy of its emitted positron is moderate (0.65MeV), and; (iii) its half life is sufficiently long (12.7h) to be used to radiolabel a range of molecular targeting agents (including monoclonal antibodies) and for the isotope to be transported across continents.

The RAPID Lab produces $[^{18}\text{F}]$FDG on a daily basis (~4500 doses per year), plus other clinical radiopharmaceuticals based on biogenic PET isotopes. The radioisotopes for these products are produced using standard targetry of an 18/9 MeV IBA cyclotron. As the productions of $^{64}\text{Cu}$ and $^{89}\text{Zr}$ both require an external beam, the RAPID team has devised a purpose built solid targetry system to suit this setting. The new targetry system consists of a 30cm long external beam line fitted with a 50μm Havar vacuum window plus an independent vacuum and cooling system (chilled water plus helium) for the target and beam degrader. Proton energies and currents can be controlled between 4–17.3MeV (using beam degraders) and 10-30μA, respectively.

The preferred approach for the production of $^{64}\text{Cu}$ using a medium-energy cyclotron uses enriched $^{64}\text{Ni}$ as the target in the reaction $^{64}\text{Ni}(p,n)^{64}\text{Cu}$. A yield of 248MBq/μA.h has been reported [2]. However, for a natural nickel (natNi) target the yield is considerably less, since the abundance of $^{64}\text{Ni}$ in natNi is only 0.91%. This study investigated the production and purification of the radionuclides $^{64}\text{Cu}$, $^{55}\text{Co}$ and $^{57}\text{Co}$, (the latter two arising from $^{58,60}\text{Ni}[p,\alpha]^{55,57}\text{Co}$) using a natNi thin-foil target, as a preliminary ‘proof-of-principle’ study prior to the bombardment of more expensive isotopically enriched targets formed by electroplating $^{64}\text{Ni}$ onto a gold substrate.

METHODS: A high purity natNi foil (99.99%) of nominal thickness 50μm and 15mm diameter was weighed on a 5-decimal-place balance to determine true average thickness prior to proton bombardment. Three separate runs were performed. The target foil was cooled by both chilled water and helium. The accessible proton beam energy of 17.3 MeV was moderated to 11.7MeV at the target surface by using a 1020μm graphite degrader placed in the collimator of the solid targetry beam line.

Bombardment elapsed times were 8, 19, and 20 minutes with beam currents of 10.4, 19.1 and 14 μA, respectively. Beam currents were uncorrected for secondary electron emission. At end of bombardment (EOB) the irradiated nickel target was left to decay for 3-4 hours to remove the short half-life radioisotopes $^{60}\text{Cu} & ^{61}\text{Cu}$.

The target was then dissolved in concentrated acids at 100°C and then loaded on to either a cation or an anion exchange column (1x 20cm). Nickel from the target plus Cu and Co radioisotopes were separately eluted using a range of solvents mixed with
hydrochloric acid. The fractions containing the radioisotopes of Cu and Co were characterized for radionuclidic purity and activity by calibrated gamma spectrometry (cryo-HPGe gamma spectrometer; Genie2000 software).

**RESULTS:** The table summarises the activities for $^{64}$Cu, $^{57}$Co and $^{55}$Co for each natNi target for 3 consecutive runs. It compares the activity for each radioisotope (corrected to EOB) with values calculated using reaction cross sections reported in the literature [1, 2 and 3].

**Table:** Activities for $^{64}$Cu, $^{55}$Co and $^{57}$Co, as a percentage of their respective predicted values calculated using published reaction cross sections plus targetry and beam parameters.

<table>
<thead>
<tr>
<th>Nickel Foil Thickness</th>
<th>Proton Energy; Current</th>
<th>Irradiation Time</th>
<th>$^{64}$Cu (% of Predicted Activity) [using ref. 2]</th>
<th>$^{55}$Co (% of Predicted Activity) [using ref. 1]</th>
<th>$^{57}$Co (% of Predicted Activity) [using ref. 3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>(µm)</td>
<td>(MeV; µA)</td>
<td>(min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>11.7; 10.4</td>
<td>8</td>
<td>80.2</td>
<td>94.8</td>
<td>86.4</td>
</tr>
<tr>
<td>47</td>
<td>11.7; 14.0</td>
<td>20</td>
<td>84.4</td>
<td>84.8</td>
<td>88.7</td>
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<tr>
<td>47</td>
<td>11.7; 19.1</td>
<td>19</td>
<td>64.7</td>
<td>78.6</td>
<td>97.2</td>
</tr>
</tbody>
</table>

**CONCLUSION:** We have performed preliminary ‘proof-of-principle’ experiments (prior to the use of an enriched target) on the production of Cu and Co isotopes using a natNi target and a medium-energy cyclotron in a medical setting. The activities produced are in reasonable agreement with predicted activities. For the three runs, activities of $^{64}$Cu ranged from 64.7 to 84.4% of the predicted values calculated from [2]. Activities of $^{55}$Co and $^{57}$Co varied from 78.6% to 94.8% and 86.4% to 97.2%, respectively, of those values calculated from [1,3]. Work is proceeding to understand the variability in results between runs, particularly in the ratio of $^{55}$Co to $^{57}$Co, since these isotopes are eluted under identical chemical conditions.

**REFERENCES**

Production of No Carrier Added $^{64}$Cu & $^{55}$Co

Introduction

Rapid advances in radioimmuno-diagnosis & therapy techniques have focused interest on longer lived PET isotopes such as $^{64}$Cu (9/2+; $^{1/2}_{\beta+}$=12.7 h) and $^{55}$Co. $^{64}$Cu is now being produced over the past two decades, cyclotron-based production of $^{64}$Cu has been optimized, and $^{64}$Cu is now being produced using several medical and research cyclotrons at a medium energy level available in a major hospital.

$^{64}$Ni is of low abundance (1%) and must be enriched prior to use.

Excitation Functions for Selected $^{64}$Cu Production Strategies

\[
\begin{align*}
64Ni(d,2n) & \rightarrow 64Cu \\
64Ni(p,n) & \rightarrow 64Cu \\
68Zn(p,x) & \rightarrow 64Cu \\
64Zn(d,2p) & \rightarrow 64Cu
\end{align*}
\]

The three decay paths of $^{64}$Cu are:

- $^{64}$Ni (stable) with emission of $\beta^{+}$ (39.03%) and EC (42.63%)
- $^{64}$Zn (stable) with emission of $\beta^{+}$ (37.86%) and EC
- $^{64}$Ni (p,n) with emission of $\beta^{+}$ (17.86%) and EC

$^{64}$Cu decays via two paths:

- $^{64}$Ni (stable) with emission of $\beta^{+}$ & EC (42.63%)
- $^{64}$Zn (stable) with emission of $\beta^{+}$ (39.03%)

The most common path for the production of $^{64}$Cu is

- $^{64}$Ni(p,n) to $^{64}$Cu

It requires a medium energy cyclotron, often available in a major hospital.

Use of natNi targets yields more complex mixture of radioisotopes.

The $^{64}$Ni is of low abundance (1%) and must be enriched prior to use.

It requires a medium energy cyclotron, often available in a major hospital.

Use of natNi targets yields more complex mixture of radioisotopes.
Characteristics of Products from Reactions

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Energy (MeV)</th>
<th>Cross section (mb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60Cu</td>
<td>23.2</td>
<td>0.06</td>
</tr>
<tr>
<td>61Cu</td>
<td>3.41</td>
<td>0.03</td>
</tr>
<tr>
<td>55Co</td>
<td>17.54</td>
<td>0.04</td>
</tr>
<tr>
<td>57Co</td>
<td>271</td>
<td>0.02</td>
</tr>
<tr>
<td>64Cu</td>
<td>12.7</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Cross sections (0) for natNi(p,x) reactions

Isotopic Abundances of Ni Targets

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Abundance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>58Ni</td>
<td>27.27</td>
</tr>
<tr>
<td>60Ni</td>
<td>10.17</td>
</tr>
<tr>
<td>64Ni</td>
<td>94.8</td>
</tr>
<tr>
<td>61Ni</td>
<td>1.13</td>
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<tr>
<td>62Ni</td>
<td>3.59</td>
</tr>
<tr>
<td>64Cu</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Aims

- To re-evaluate cyclotron based production of 64Cu
- To test feasibility of the co-production & purification of 64Cu & 55Co from proton bombardment of natNi, partly aiming at reducing cost of targetry
- To re-evaluate cyclotron based production of 64Cu
Methods: Radionuclides Production

- **IBA 18/9 cyclotron** provides the primary beam
- In-house built solid targetry system for up to 30 μA at 18MeV
- Cooled by chilled water & helium, independent vacuum
- Achievable proton bombardment energy = 17.3 MeV
- Graphite beam-energy collimator & degrader (to 11.7 MeV for 64Cu)
- Ni & enriched 64Ni used as target

**Experimental Precision of Beam Energies**

- The mean primary beam energy is 18.08 (0.09) MeV (SD) (0.5% CV)
- Calculated using both EXFOR & IAEA regimes for 63Zn & 65Zn data from replicate stacked Cu-foil runs
- Graphite disc of thickness 1020 μm, inserted in front of 50mm Havar window, is used to reduce energy of incident beam to 11.68 (0.18) MeV (1.5% CV)

**Graphite beam-energy collimator**: Normal incident (degraded) beam energy = 11.7 MeV, where normally incident (degraded) beam energy = 11.7 MeV.

**Methods**: Experimental for 64N(p,n)64Cu

**In these experiments**: 64Ni & enriched 64Ni used as target

- Graphite beam-energy collimator & degrader (to 11.7MeV for 64Cu)
- Achievable proton bombardment energy = 17.3 MeV
- Cooled by chilled water & helium, independent vacuum
- In-house built solid targetry system for up to 30μA at 18MeV
- IBA 18/9 cyclotron provides the primary beam
Methods: Production of ⁶⁴Cu from nat Ni-foil (I)

- Production from Ni-foil (I)
  - Activation of target; chemical separations & identification of radioactive products
  - Insert the target in a target holder
  - Determine beam current (over time of bombardment)
  - Wash column with 0.3M HCl & Ethanol to extract Co-fraction
  - Elution of Ni ions in 0.3M HCl & Ethanol (no need to recycled nat Ni)
  - Wash column with 0.3M HCl & Ethanol to extract Co-fraction
  - Evaporate the 3 fractions Ni, Co, and Cu, adjusted to 1ml
  - Dissolve Ni-target into heated 6M HCl, then transferred to ion-exchange column
  - Wash column with 0.3M HCl & Ethanol to extract Co-fraction
  - Evaporate the 3 fractions Ni, Co, and Cu, adjusted to 1ml

Methods: Production of ⁶⁴Cu from nat Ni-foil (II)

- Irradiate nat Ni-foil [Diam=15mm, thickness=50um]
  - nat Ni 100 times lower abundance of ⁶⁴Ni than enriched ⁶⁴Ni target
  - Place in Al target cradle [thickness=1.2mm]
  - ¹¹.7MeV protons with various current and time
  - Target stayed in a cyclotron bunker for 2-3 hours to let short half-life isotopes [⁶⁰Cu and ⁶¹Cu] decay
  - Target is transferred to a cyclotron bunker for 2-3 hours to let short half-life isotopes [⁶⁰Cu and ⁶¹Cu] decay

Methods: Production of ⁶⁴Cu from nat Ni-foil (III)

- Elution of Ni ions in 0.3M HCl & Ethanol
  - ³⁶⁵Cu 24.5 Tanaka, 1972
  - ⁵⁵Co 13.00 ⁵⁷Co 0.002 0.000 Kaufman, 1960
  - ⁶⁴Cu 1102 Szelecsenyi, 1993

Results: Calculated Comparative Yields

<table>
<thead>
<tr>
<th>Method</th>
<th>EOB (MBq/µA.h)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>nat Ni-foil</td>
<td></td>
</tr>
<tr>
<td>⁶⁴Cu</td>
<td>1</td>
<td>Szelecsenyi, 1993</td>
</tr>
<tr>
<td>⁶⁰Cu</td>
<td>365</td>
<td>Tanaka, 1972</td>
</tr>
<tr>
<td>⁵⁵Co</td>
<td>13.00</td>
<td>Ewart, 1964</td>
</tr>
<tr>
<td>⁵⁷Co</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

Methods: Production of ⁶⁴Cu from nat Ni-foil (II)

- Dissolve Ni-target into heated 6M HCl, then transferred to ion-exchange column
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- Dissolve Ni-target into heated 6M HCl, then transferred to ion-exchange column
- Wash column with 0.3M HCl & Ethanol to extract Co-fraction
- Evaporate the 3 fractions Ni, Co, and Cu, adjusted to 1ml
- Elution of Ni ions in 0.3M HCl & Ethanol (no need to recycled nat Ni)
Results: Experimental – 64Ni Target

Production & purified separation of 64Cu, 55Co & 57Co from bombarded natNi, in reasonable agreement with calculations

Future work aimed at combining the capacity to separate aluminium, targets, and the electroplated foil

Production of 64Cu from electroplated 64Ni target in good agreement with calculations

Electroplating 64Ni on Au-foil has been successful in constructing an enriched target

However there is still inter-run variability in our hands

Production & purified separation of 64Cu, 55Co & 57Co from bombardment of enriched 64Ni! In reasonable agreement with calculation, reproducibility of three isotopes

Acknowledgments

RAPID Team, Perth

Australia Nuclear Science & Technology Organisation (Dr Suzanne Smith & Co-workers)

Organisers of WTTC13, Rosekilde, Denmark

Summary & Discussion
1. (p,n) reaction
   - 117 MeV to reduce isotopic impurities
   - 11 MeV to reduce isotopic impurities
   - Energy degradation by graphite (1020 μm)
   - 64Ni electroplated on gold

2. Separation: ethanol method
   - Separates Ni, Co, Cu (checked by gamma spectroscopy)
   - Column as big as 20 x 1

3. Why not (the cheaper) nat Ni?
   - Less production more problems
   - OK only for testing

4. Graphite degradator? What kind of graphite?
   - Less beam divergence (Monte Carlo)
   - Pyro? Better heat transfer, more expensive
   - 117 MeV to reduce isotopic impurities

5. Why keep using He flow?
   - Keep oxidation (nitridation) away
   - Possible by neutrons but only to 117 MeV (16 MeV too much)

6. Target material direct to cyclotron vacuum?
   - Dangerous: Ni is magnetic
   - Dangerous: Ni is magnetic
   - Target material directly to cyclotron vacuum?
Reportback from iThemba LABS: Some tales of broken targets, split beams and particle tracking

C. Vermeulen, G.F. Steyn, N. Stodart, J.L Conradie, A Buffler, I Govender

iThemba Laboratory for Accelerator Based Sciences, Cape Town, South Africa

Introduction

iThemba LABS started 2006 with one bombardment station handling batch targets with 66MeV protons up to a maximum 100uA. In 2010 we have four bombardment stations and the ability to split beam to two stations increasing the total intensity on target to 350uA. We have reported in previous meetings on the vertical bombardment station for large batch targets at high currents as well as the degrading system to produce F-18 on a commercial water target. This report will look at some successes and failures of these systems and highlight the new developments at the lab.

Broken targets etc.

The vertical bombardment station (VBTS) at iThemba LABS has now been in operation for 4 years and has seen just over 1 million micro-amp hours of beam. We have experienced a number of target (Fig 2) and infrastructure (Fig 1) failures, especially of gallium metal targets. We have implemented a number of measures (Fig 3) to reduce the frequency of breakage of these.
Beam Splitter

We have implemented an electrostatic channel and a septum magnet (Fig 5), to obtain separated but simultaneous beams for the vertical and horizontal bombardment stations. This is based on the system for splitting employed at the Paul Scherrer Institut. (Conradie et al. 2007)

Fig 5: Split Beamline

PEPT

Positron emission particle tracking (PEPT) was developed at the University of Birmingham (Hawkesworth et al., 1991; Parker et al., 1994). Since the arrival of the ECAT ‘EXACT3D’ (Model: CTI/Siemens 966) PET camera (Fig. 6), from Hammersmith Hospital Cape Town now boasts the second dedicated PEPT lab in the world.

Initial runs (Fig 7) with tumbling mills, flotation cells and even an angle grinder have proven very successful and development of tracer manufacture using both ion-exchange labelled particles and directly activated particles is continuing well.

Fig 6: EXACT3D in its new home Fig 7: First PEPT run

References


Beam Splitter

Beam Splitter

Beam Splitter
• New Cyclotron Facility

Vertical Target Station
Technical pitfalls in the production of $^{64}$Cu with high specific activity

J. Rajander$^1$, J. Schlesinger$^1$, M. Avila-Rodriguez$^{1,2}$ and O. Solin$^1$

$^1$Turku PET Centre, Turku University and Åbo Akademi University, Finland

$^2$Unidad PET/CT-Ciclotrón, Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico-City, Mexico

Introduction

In 2008, we initiated production of $^{64}$Cu aiming at high specific activities and high quantities. Routine production of $^{64}$Cu as well as the reproducible and economical preparation of the $^{64}$Ni target material with ultra-low metal contamination was established. Some technical pitfalls had then to be overcome. We faced a) aggressive corrosion by concentrated acid solutions, b) flaking of the target material during the irradiation, c) contamination of the target material with cooling water, d) formation of insoluble $[^{64}\text{Ni}]\text{NiO}$ during the irradiation and e) incomplete dissolution of the irradiated target material.

Methods

Using the $^{64}\text{Ni}(p,n)^{64}\text{Cu}$ reaction with an optimized beam profile and proton energy (13.0±0.2 MeV), we routinely produce high quantities of $^{64}$Cu (10-38 GBq) on our CC 18/9 cyclotron (Efremov Scientific Research Institute of Electrophysical Apparatus, St. Petersburg, Russia) as previously described (Avila-Rodriguez et al., 2008). A semiautomatic processing of the irradiated $^{64}$Ni target material and a remote controlled separation of $^{64}$Ni and $^{64}$Cu has been developed, which yields $^{64}$Cu with a high specific activity of 3 TBq/µmol. Using four miniature Geiger-Müller tubes, which are placed within the processing module, we monitor the distribution of activity and control the separation process of $^{64}$Cu (Rajander et al., 2009). The recovery of the $^{64}$Ni target material and the preparation of the $^{64}$Ni electrolyte solution are done in a dedicated rotary evaporator. The computer controlled electrochemical deposition of the $^{64}$Ni target material starts with a stepwise increase of the deposition voltage from 2.0 V to 2.5 V within 5 h, followed by a constant voltage of 2.5 V for 40 h.

Results

a) The use of concentrated acid solutions for preparing the $^{64}$Ni electrolyte solution as well as for separating $^{64}$Ni/$^{64}$Cu caused serious corrosion problems in the fume hood and in the hot cell. This problem was partly solved by using a closed and remote-controlled module for the processing of the irradiated $^{64}$Ni target material, which includes dissolution, separation of $^{64}$Ni/$^{64}$Cu and concentration of the acidic $^{64}$Cu fraction. For recovery of the $^{64}$Ni target material from the concentrated hydrochloric acid solution, a dedicated rotary evaporator is used inside a fume hood. Acidic vapour from the evaporation process is neutralized by passing the vapours through an alkaline aqueous solution in a flask.

b) Flaking of the $^{64}$Ni material from the Au-backing was twice observed during the irradiation. Thus, we included an additional cleaning step for the gold disk in the target preparation procedure. After
cleaning with Deconex®, the gold disk is briefly soaked in 6 M HNO₃ and then rinsed subsequently with DI water to efficiently remove traces of metallic and organic contamination from the gold surface. After this step was included in target processing, no flaking of ⁶⁴Ni target material from the gold surface during the irradiation has occurred. Also the electroplating process is controlled with a computer program in order to obtain more reproducible results in the target preparation.

c) Due to scratches on the back of the gold disk and thus, insufficient sealing of the O-ring against the cooling water, contamination of the target material with cooling water was twice observed after the irradiation. Due to this, lower specific activities were obtained for ⁶⁴Cu. In order to solve this problem, the gold disks were henceforth visually inspected and serious scratches were removed by sanding.

d) A first series of targets was irradiated under ambient atmosphere. We then observed twice the formation of insoluble, greenish [⁶⁴Ni]NiO particles on the target material surface, resulting from an oxidation of ⁶⁴Ni during the irradiation. In order to avoid oxidation of nickel in the presence of atmospheric oxygen, we henceforth applied a stream of helium on the target material during irradiation. Subsequently, we have not observed formation of [⁶⁴Ni]NiO.

e) In some cases, a thermal treatment of the irradiated target material with 10 M HCl at 100 °C for 20 min was insufficient to dissolve the target material. This might be a result of a passivation of the ⁶⁴Ni surface during the irradiation. This problem was solved by applying a stream of helium on the target material during irradiation, and also by extending the period of thermal treatment with concentrated HCl from 20 to 40 min.

Acknowledgement

The study was conducted within the "Finnish Centre of Excellence in Molecular Imaging in Cardiovascular and Metabolic Research" supported by the Academy of Finland, University of Turku, Turku University Hospital and Åbo Akademi University. This work was also supported by the EU-FP7 integrated project Betalimage contract no.: 222980.

References


Technical pitfalls

- Incomplete dissolution of the irradiated target material
- Formation of insoluble {\[^{64}\text{Ni}\]NO} during the irradiation
- Contamination of the target material with cooling water
- Leaking of the target material during the irradiation
- Aggressive corrosion by concentrated acid solutions

64Cu production

- Reproducible {\[^{64}\text{Ni}\]}-target preparation with ultra-low metal contamination
- Semiautomated {\[^{64}\text{Ni}/^{64}\text{Cu}\]} separation yields {\[^{64}\text{Cu}\]} with high specific activity (3000 GBq/\mu mol)
- Adapted proton energy and beam profile yields high specific activity (38 GBq) {\[^{64}\text{Cu}\]} in high quantities (95\% recovery rate)
- Recycling of {\[^{64}\text{Ni}\]} for economical {\[^{64}\text{Cu}\]} production

64Cu in high quantities (95\% recovery rate)

- 95% recovery rate
- Economical {\[^{64}\text{Cu}\]} production
- Recycling of {\[^{64}\text{Ni}\]} for an economical {\[^{64}\text{Cu}\]} production
- High effective specific activity
- Post- and prelabeling techniques
- High specific activity
- Economic large scale production
- Micro-PET studies in vivo
- Preclinical investigations
- Post- and prelabeling techniques
- High specific activity
- Economic large scale production

Supported by:

- EU 7th Framework Programme
- Automated radiosynthesis
- R	ext{ey Clin} of 64Ni for an economical 64Cu production (95\% recovery rate)
Cooling water leakage

Corrosion in the fume hood

Insoluble NiO on the gold disc

Flaking of the target material from the gold backing
1. Problems in Cu production
   - Hotcell oxidation/corrosion caused by acidic environment

2. Target material
   - Gold?
     - NiO found in gold, but removable by He flux
   - Silver?
     - Rust, impurities if not very high quality silver
   - Gold coating?
     - Scratching can be a problem
   - Rhodium?
     - Easy to plate, hard, no problems found by users

3. Energy degradation on target?
   - Just to 13 MeV
   - Protons?
   - No found in gold, but removable by He flux

WTC XIII - Presentation Discussions
Supported Foil Solution for Legacy Helium-Cooled Targets
When An Alternative to Havar Foil Material is Desired

Benjamin R Bender and G. Leonard Watkins
PET Imaging Center, University of Iowa Health Care, Iowa City, IA 52242, USA

For any given radionuclide target system, the choice of targetry is often made as a compromise between Quantity and Quality. Quantity refers primarily to higher target yield or in the case of smaller volumes, higher specific activity. Quality, for the purpose of this discussion, refers to radionuclidic and chemical purity. Most recent target system design innovations have been driven by the need for increased target yield per run. In no application is this more evident than in the evolving design of $^{18}$F targetry [Eriksson, et al; Zyuzin, et al]. This pursuit of “quantity” has resulted in numerous target design innovations. Most notable are improvements in target geometry, optimization of target cooling thermodynamics and designs modifications intended to reduce proton beam loss due to interceding structures and foils. But for those facilities whose overall production does not require target yields beyond a few Curies, the helium-cooled, two-foil target systems (fig 1) have remained in service, even if only for backup or research $^{18}$F production. These legacy targets are characterized as having two foils along the beam path terminating in the target volume (gas or liquid). The front foil separates the tank vacuum from a helium cooling flange. The back foil separates the helium cooling flange from the target volume chamber.

Our facility produces $^{18}$F and other radionuclides solely for our own clinical and research needs; thus our production needs are modest. But to satisfy our low-level research production needs while also improving the yield of our low-efficiency radiopharmaceutical syntheses (eg. $^{18}$FFLT) we have directed our targetry efforts towards reduction of radionuclidic and chemical impurities. Regardless of target type, improvement in product purity may have significant implications to the efficiency of radiopharmaceutical syntheses as well as patient/participant dosimetry. To achieve this we have retrofitted our two-foil $^{18}$F target to utilize Niobium for both the back foil (0.003” thick) and the body material of the target volume chamber [Nye, et al]. The significantly lower strength of Niobium when compared to Havar for the back foil presented an additional hurdle to the retrofit. Additionally, local heating of the Niobium foil by the proton beam further threatens its ability to perform without failure. To address these issues we opted to include another modern target feature, the grid support. This became the evolution of our novel retrofit grid support solution (fig 2). Support grids in modern targetry are generally made from copper or aluminum and cooled by the same water that cools the target volume chamber. This observation brings to light the final hurdle in our design – grid cooling. The solution is the existing Helium cooling system, but since a grid support, placed to support the Niobium foil, would block the flow of the Helium cooling, the grid must be modified. Therefore, we have included a vent hole through the grid perpendicular to the beam path to allow helium flow which now becomes the grid cooling mechanism of this retrofit design.
The primary benefit of this design is its low cost. Commercially available targets may cost as much as $50,000, but the direct cost for this design was less than $3,000 for materials and machining. To achieve this inexpensive solution, the aluminum grid foil support we designed requires only that the beam aperture in the helium flange be widened slightly to hold the grid support captive. Additionally, this grid support can be fabricated using standard machining practices and a simpler rectangular grid design. This significantly reduced the expense when compared to the commercial copper or aluminum hex-grid supports which utilize a more expensive EDM machining technology.

A second benefit of this design is its ease of incorporation into the existing target. It may be either slipped or press fit into the widened Helium flange beam aperture.

Yet a third benefit is the utilization of the existing Helium cooling. Where previously the Helium flow was directed to cool both the front and back foils, that flow will now pass through the vented support grid to conduct its heat away. Because the grid is in direct contact with the back foil, it also acts as a heat sink to conduct heat away from the localized point where proton beam heating may weaken it. Also, because we utilize the existing helium cooling, it need not be defeated as a target interlock, as it is on many older cyclotrons. And lastly, there is no need to make additional modifications to the target to cool the grid using the water cooling system as is common in the commercially available systems.

As a final site specific benefit, our older, self-designed target allows easy replacement of the target insert (ie. the target load chamber). This has allowed us to very easily convert this target at any time for the in-target production of $^{13}$NAmmonia [Krasikova, et al] by simply replacing the Niobium insert and foils with Aluminum versions of each and overpressuring with CH$_4$. Without the support grid, it would likely be impractical to use such thin (0.005” thick) aluminum foils, as they would be far too weak. In conclusion, this grid foil support design is an economical solution allowing the use of more chemically advantageous, though weaker, foils materials while easily maintaining integrity, even with overpressure in excess of 300 psi. Additionally, no negative impact on the overall yield of the target was observed.

**Acknowledgement:** University of Iowa Medical Instruments shop and Tim Weaver for design support.

**References:**


Supported Foil Solution for Legacy Helium-Cooled Targets

When An Alternative to Havar Foil Material is Desired

Benjamin R Bender, G. Leonard Watkins
University of Iowa Health Care, Iowa City, Iowa, USA

Introduction

Target Selection Criteria

Quantity: More Chemically Compatible Target Foil Materials

Quality: Fewer Target Foils

Target Improvements

Quantity: Fewer Target Foils

Quality: Better Target Cooling

Better Target Geometry

Target Choice

Quantity: (newer target designs)

• Commercial Radionuclide Production Facilities
• High Volume In-House Clinical Needs

Quality: (modify existing target)

• Higher Synthesis Production
• Higher Synthesis Production
• More Chemically Compatible Target & Foil Materials

Introduction
**Introduction**

**Design**

**Application**

**Problem #1:**
- Havar Foils Leave Contaminants during FDG and FLT syntheses.

**Solution:**
- Niobium Foil Instead of Havar.

**Problem #2:**
- Niobium is much weaker than Havar.

**Solution:**
- Grid Support for Target Foil.
- Thicker Foil.

**Design Development**

**Grid Cooling:**
- Conductive cooling of both foils & grid.
- Existing helium system left intact.
- Helium flow-through holes.

**Quality:**
- Helium flow aperture slightly widened.
- Outer walls are outside target aperture.
- Designed so grid walls avoid beam.

**Vacuum End (front)**

**Foil End (back)**
### Foil Considerations

#### Stopping Power:
- Havar = \( \sim 157 \text{ MeV/cm} \)
- Niobium = \( \sim 144 \text{ MeV/cm} \)
- Aluminum = \( 60.6 \text{ MeV/cm} \)

#### Beam Energy Loss:

<table>
<thead>
<tr>
<th>Material</th>
<th>Thickness ((\mu)m)</th>
<th>Beam Energy Loss (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Havar</td>
<td>0.001&quot;</td>
<td>400</td>
</tr>
<tr>
<td>Niobium</td>
<td>0.002&quot;</td>
<td>( \sim 730 )</td>
</tr>
<tr>
<td>Niobium</td>
<td>0.003&quot;</td>
<td>( \sim 1095 )</td>
</tr>
<tr>
<td>Aluminum</td>
<td>0.005&quot;</td>
<td>( \sim 770 )</td>
</tr>
<tr>
<td>Havar</td>
<td>0.001&quot;</td>
<td>( \sim 530 )</td>
</tr>
<tr>
<td>Niobium</td>
<td>0.002&quot;</td>
<td>( \sim 300 )</td>
</tr>
<tr>
<td>Niobium</td>
<td>0.003&quot;</td>
<td>( \sim 280 )</td>
</tr>
<tr>
<td>Aluminum</td>
<td>0.005&quot;</td>
<td>( \sim 430 )</td>
</tr>
</tbody>
</table>

#### Thermal Conductivity:
- Havar: 14.7 W/m*K
- Niobium: 53.7 W/m*K
- Aluminum: 237.0 W/m*K

#### Other:
- Better nuclide conversion
- Reduced localized boiling
- Better heat transfer to grid

#### Thermal Conductivity:

<table>
<thead>
<tr>
<th>Material</th>
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<td>( \sim 770 )</td>
</tr>
<tr>
<td>Havar</td>
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<td>( \sim 530 )</td>
</tr>
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<td>Niobium</td>
<td>0.002&quot;</td>
<td>( \sim 300 )</td>
</tr>
<tr>
<td>Niobium</td>
<td>0.003&quot;</td>
<td>( \sim 280 )</td>
</tr>
<tr>
<td>Aluminum</td>
<td>0.005&quot;</td>
<td>( \sim 430 )</td>
</tr>
</tbody>
</table>

### Beam Transmission

#### Beam Current Blocked by Grid:

<table>
<thead>
<tr>
<th>Material</th>
<th>Thickness ((\mu)m)</th>
<th>Beam Current Blocked by Grid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Havar</td>
<td>0.001&quot;</td>
<td>&gt; 530%</td>
</tr>
<tr>
<td>Niobium</td>
<td>0.002&quot;</td>
<td>( \sim 300 )</td>
</tr>
<tr>
<td>Niobium</td>
<td>0.003&quot;</td>
<td>( \sim 280 )</td>
</tr>
<tr>
<td>Aluminum</td>
<td>0.005&quot;</td>
<td>( \sim 400 )</td>
</tr>
</tbody>
</table>

#### Beam Energy Loss:

<table>
<thead>
<tr>
<th>Material</th>
<th>Thickness ((\mu)m)</th>
<th>Beam Energy Loss (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Havar</td>
<td>0.001&quot;</td>
<td>400</td>
</tr>
<tr>
<td>Niobium</td>
<td>0.002&quot;</td>
<td>( \sim 730 )</td>
</tr>
<tr>
<td>Niobium</td>
<td>0.003&quot;</td>
<td>( \sim 1095 )</td>
</tr>
<tr>
<td>Aluminum</td>
<td>0.005&quot;</td>
<td>( \sim 770 )</td>
</tr>
<tr>
<td>Havar</td>
<td>0.001&quot;</td>
<td>( \sim 530 )</td>
</tr>
<tr>
<td>Niobium</td>
<td>0.002&quot;</td>
<td>( \sim 300 )</td>
</tr>
<tr>
<td>Niobium</td>
<td>0.003&quot;</td>
<td>( \sim 280 )</td>
</tr>
<tr>
<td>Aluminum</td>
<td>0.005&quot;</td>
<td>( \sim 430 )</td>
</tr>
</tbody>
</table>

### Stopping Power:

- Aluminium = 60.6 MeV/cm
- Niobium = 144 MeV/cm
- Havar = 157 MeV/cm

### Burst Pressure

- Havar: \( \sim 18 \text{ MPa} \)
- Niobium: \( \sim 25 \text{ MPa} \)
- Aluminum: \( \sim 15 \text{ MPa} \)
Conclusions

Benefits of Grid Design

Cost:
• Low-Cost Machining Techniques Used vs expensive EDM machining methods used for hex grid in commercial targets
• Modification Far More Inexpensive Than New Target

Ease of Implementation:
• Simple Design
• Grid Fits in Helium Flange with Slip-or Press-Fit
• Target Not Significantly Modified

Other:
• Careful with impurities in foil material
• Ti can be used, Va trapped in Sep-pak

Better Foil Cooling:
• Conductor Cooling of Foil (with contraindicated)

Adapts to Design:
• Niobium-Have preferred to Niobium-Havar (experience)

Conclusions

Benefits of Grid Design

1. Which one is the best foil?
• Ni vs Havar: no yield difference
• Ni vs Havar: no yield difference
• Careful with impurities in foil material
• Ti can be used, Va trapped in Sep-pak
• Niobium-Havar preferred to Niobium-Niobium (experience)

References


A Simple Target Modification to Allow for 3-D Beam Tuning

J.S. Wilson, K. Gagnon and S.A. McQuarrie

Edmonton PET Centre, Cross Cancer Institute, University of Alberta, Edmonton, AB, CANADA

Introduction: The TR19/9 cyclotron at the Edmonton PET Centre (EPC) is a variable energy machine with a proton beam energy range from 13 to 19 MeV and a deuteron beam energy range from 6.5 to 9 MeV. The energy and trajectory of the extracted beam is determined by the orbital at which the beam is intercepted by the extractor foil and it is essential, especially with the longer gas targets, that the beam is being directed down the centre of the target. To ensure optimal beam alignment, more feedback on the angle of beam entry to the target was desired than could be offered by the 2 dimensional target port collimators.

Aim: To provide a means of monitoring the beam position during normal operation. This would allow for interactive real-time target alignment to assure that the beam is centred on target.

Methods: The nosepiece of the target was lengthened to provide a 1 cm cylindrical beam port extending 5 cm prior to the target body. (Extended nosepiece with current pickup and original nosepiece, pictured opposite) The nosepiece was fabricated from anodized aluminum so that with insulated attachment, electrical isolation from the target body was possible. Use of insulated bolts and plastic washers during target assembly enabled separate current pick-ups to be attached to the target body and the nosepiece.

A solid target plate was prepared which had a hole drilled in the top to allow a temperature probe to be inserted to the middle of the plate. This enabled the temperature of the target plate to be monitored between the beam spot and the water cooling on the back of the plate.

Results: Beam alignment was easily achieved on gas targets equipped with the extended nosepiece and the irradiation pressure was readily optimized on true aligned conditions. The effect of varying different ion source, radiofrequency and magnet parameters was also readily observed and all while the beam was at maximum normal operating specifications.

Solid target irradiation (no nosepiece present): We found a very linear relationship between the beam current and the target plate temperature. It became increasingly difficult, however, to maintain this linear relationship at higher beam currents indicating that the registered beam was not hitting the plate. As beam spread is more pronounced at higher currents, it is probable that the 1 cm target aperture was no longer accommodating the entire beam. Use of an isolated nosepiece would maintain alignment and show at what point maximum beam on target had been reached.

Recently the nosepiece has been put onto the high current water targets and we will be evaluating the saturated yields vs observed nosepiece currents to determine the extent of beam expansion.

Conclusions: The isolated nosepiece allows for facile beam tuning and gives useful real time information on beam size and alignment.
**Beam Extraction**

Variable energy extraction determined by depth of extractor probe.

- Extractor depth
- Azimuthal angle of extractor
- Magnetic field (temperature)
- Ion source parameters

Beam trajectory affected by:

- Beam trajectory related to extractor depth
- Pivot point of artifactual target head
- Collimators

**Extractor Arm with Azimuthal movement**

- 19 MeV
- 13 MeV

**Beam trajectory related to extractor depth**

Variable energy extraction determined by depth of extractor probe.

- Extractor depth
- Azimuthal angle of extractor
- Magnetic field (temperature)
- Ion source parameters

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- Magnetic field (temperature)
- Ion source parameters

Beam trajectory affected by:

- Beam trajectory related to extractor depth
- Pivot point of artifactual target head
- Collimators

**Extractor Arm with Azimuthal movement**

- 19 MeV
- 13 MeV
Beam Collimation

Pivot point and target collimators are designed with separate current pick-up sensors for each section with sufficient beam position monitoring.

Extended Isolated Nosepiece

Extended isolated nosepiece were extended from 1 cm to 5 cm in length with 1 cm cylindrical hole for electrical isolation. Two current pickups used.

Results

- Water targets were fairly aligned.
- C-11 gas target ruptured.

Extended Nosepiece

Intended for gas targets to provide more space at target head and to confirm target alignment.

Results

- C-11 gas target ruptured.
- Water targets were fairly aligned.
- Maximized pressure on slightly misaligned targets.
- Routine saturated yield determination.

Pressure Maximization

Maximize pressure fast and accurate.

Sufficient beam position monitoring.

12 cm between the 2 collimators. Both have a 1 cm circular aperture divided into 4 sectors each with pivot point and target collimators are extended for gas targets to provide more space at target head and to confirm target alignment.

Extended Nosepiece

Intended for gas targets to provide more space at target head and to confirm target alignment.

Results

- Pressure maximization. All targets were subsequently fitted with the specifications.
- The effect of varying different ion source, radiofrequency and magnet parameters was also readily observed and while the beam was at maximum normal operating specifications.

Extended Isolated Nosepiece

Anodized aluminum for electrical isolation. Length with 1 cm cylindrical hole in target nosepiece extended from 1 cm to 5 cm in length with 1 cm cylindrical hole for electrical isolation. Two current pickups used.
Solid Tar et Conclusions

Solid Target Conclusions

Pivot Point Collimator

Solid Tar et

Solid tar gets

No pressure indicator

No pressure indicator

linear relationship not maintained at higher beam currents (100 uA)

linear relationship not maintained at higher beam currents (100 uA)

Electrically isolated, water cooled. He window temperature rise was not hitting the plate.

Electrically isolated, water cooled. He window temperature rise was not hitting the plate.

Solid target beam indicators desirable at low current, critical at high currents. Solid target beam indicators desirable at low current, critical at high currents.

Solid target beam indicators desirable at low current, critical at high currents.

Solid target beam indicators desirable at low current, critical at high currents.

Solid target beam indicators desirable at low current, critical at high currents.


Higher intensity beams – larger not smaller.

Higher intensity beams – larger not smaller.

Higher intensity beams – larger not smaller.

Over collimator apertures, collimator apertures.

Over collimator apertures, collimator apertures.

Over collimator apertures, collimator apertures.
Evolution of a High Yield Gas Phase $^{11}$CH$_3$I Rig at LBNL
James P. O’Neil, James Powell, Mustafa Janabi
Biomedical Isotope Facility, Lawrence Berkeley National Laboratory, Berkeley CA USA

After working with a home built “wet method” $^{[11]}$C methyl iodide system for a number of years, an effort was made towards the in-house development of a gas phase rig. This began with personal communication and visits to both TRIUMF and the University of Washington, Seattle PET centers for many helpful discussions, photos, drawings and hints that only years of experience can provide. The culmination of this was the construction of a first iteration single pass, gas phase $^{[11]}$C methyl iodide system that closely resembled the Seattle system described by Link$^{[1]}$.

The Biomedical Isotope Facility (BIF) at the Lawrence Berkeley National Laboratory houses the prototype CTI RDS111 ($E_{proton} = 11$MeV) negative ion cyclotron. We run an original 7mL aluminum-body target filled to 300psi with 1% O$_2$/N$_2$ to produce $^{[11]}$C CO$_2$. Typical production irradiations are 40 minutes in duration at 35uA beam current and provide on average 1.5Ci of $^{[11]}$C CO$_2$ that is most often converted to $^{[11]}$C CH$_3$I. Operation of the $^{[11]}$C CH$_3$I system is as follows: (a) Post irradiation, target gas is rapidly unloaded through a Carbosphere trap (60-80 mesh, 1.4g) at room temperature. Discussions with Bruce Mock led us to choose this trapping medium over molecular sieves for the chromatographic properties providing trapping of the $^{[11]}$C CO$_2$ and separation from target gas and side products. (b) After static heating of the trap to >80°C, the trap is swept with helium (50mL/min) and combined with hydrogen (50mL/min). (c) The mixture is passed through a heated (400°C) nickel catalyst (Harshaw) and the resulting $^{[11]}$C CH$_4$ is trapped on a PoroPak-Q trap (100mg in aluminum u-tube, 2mm id x 90mm tall) at -196°C. (d) The $^{[11]}$C CH$_4$ is released by raising the trap from the liq-N$_2$ dewar and flushing with helium (80mL/min) directing the gas stream through a quartz reaction tube (10mm id x 350mm). The head of the tube is packed with solid iodine that is heated to provide I$_2$ vapor which mixes with incoming $^{[11]}$C CH$_4$ and is pushed further downstream into a high temperature segment (100mm long) where conversion takes place. (e) The resulting $^{[11]}$C CH$_3$I exits the quartz reactor, is passed through a dry ascarite column (7mm id x 150mm), and is trapped on a glass test tube (4mm id x 50mm) immersed in liq-N$_2$.

**Single-Pass Optimization**
Significant optimization of the single pass system was initially required to generate useable yields and purity of $^{[11]}$C CH$_3$I. There are primarily three parameters that govern the overall conversion of $^{[11]}$C CH$_4$ to $^{[11]}$C CH$_3$I in the system, namely: (1) iodine oven temperature (I$_2$ concentration); (2) flow through the reactor tube (residence time); and (3) temperature of the reactor (energy potential). These three factors are highly interdependent, thus changing any one parameter requires a re-optimization of the other two. For example, higher quartz tube (reactor) temperatures may require a faster flow rate and lower iodine oven temperature to decrease the co-production of $^{[11]}$C CH$_2$I$_2$ and maintain $^{[11]}$C CH$_3$I yield. Through this process we experimentally determined a push gas flow of 80mL/min and I$_2$ oven temperature of 70°C and then re-explored a range of reactor temperatures. Over a range of 625-775°C, the undesired production...
of $[^{11}\text{C}]\text{CH}_2\text{I}_2$ increased linearly from 1.5-15%. Over the same temperature range (625-775°C), $[^{11}\text{C}]\text{CH}_3\text{I}$ yield started at 15.5%, peaked at 32% (680°C) and fell back to 21%. Total conversion of methane to iodinated species followed a similar curve as shown in Figure 1. Consistent yields of 25-30% were realized for production runs for a number of months.

**Recirculation System** In order to increase the conversion yield we installed a recirculation pump in the system, passing the unconverted $[^{11}\text{C}]\text{CH}_4$ back to the reactor as described by Larsen[2]. In addition, we have separated the conversion oven from the $[^{11}\text{C}]\text{CH}_4$ and $[^{11}\text{C}]\text{CH}_3\text{I}$ trapping station allowing vertical placement on the hotcell side wall thus saving space. At the exit of the oven, a vortex chiller (-8°C) rapidly condenses I$_2$ vapor ensuring nearly complete iodine recovery. Other refinements to the system include a low mass Kapton resistive heater on the I$_2$ reservoir and a LED/photodiode based I$_2$ concentration detector.

With very little modification to either equipment or parameters we were able to realize a significant gain in conversion yield as compared to the single-pass setup. Optimized conditions provide 64-73% decay corrected yield of $[^{11}\text{C}]\text{CH}_3\text{I}$ based on trapped $[^{11}\text{C}]\text{CO}_2$ with >98% purity. The high purity is attributed to cryogenically trapping the iodinated methane in a glass loop, releasing the $[^{11}\text{C}]\text{CH}_3\text{I}$ while the glass warms, and recooling the glass before the $[^{11}\text{C}]\text{CH}_2\text{I}_2$ is pushed to the reaction vial.

Over the past 5 years we have seen 50-60% conversions on a daily basis. Maintenance is minimized by having the $[^{11}\text{C}]\text{CH}_4$ Poropak trap outside of the recirculation path, trapping iodine at -8°C, and cold trapping the $[^{11}\text{C}]\text{CH}_3\text{I}$ on a glass trap. We have routinely used this system to produce a variety of $[^{11}\text{C}]$ labeled PET tracers at or above literature yields and high specific activity (5-12Ci/umol eos).

References:
Evolution of a High Yield Gas Phase

Background

Biomedical Isotope Facility, Lawrence Berkeley National Laboratories

James P. O’Neil, James Powell

MUSTHANA JANNABI, Mustafa Janabi

National Laboratory, Berkeley CA USA

CO2→Cp*2→H2→N2→Cool

LBNL Single Pass Gas Phase Methyl Iodide Rig circa 2004


For a fixed flow rate, the production of [11C]CH2I2 increases steadily.

Optimized for these conditions

Original system single pass modeled after Link’s work

After discovery trips to Seattle and Vancouver a gas phase rig established

Methyl iodide 
Diiodomethane Total
Conversion

Methyl iodide
Diiodomethane

40 50 60 70 80 90

Methane

0 10 20 30 40

Quartz Oven Temperature (°C)


For a fixed flow rate, the production of [11C]CH2I2 increases steadily.

At higher temperature [11C]CH3I production yield drops rapidly.

At higher temperature [11C]CH3I production yield drops rapidly.

0 20 40 60 80

% of [11C]Methane

Optimizations for these conditions

Original system single pass modeled after Link’s work

The old system was implemented by making starting up

Example some mistakes they made/starting up

Take home message: go to the experts/experienced for advice.

After discovery trips to Seattle and Vancouver a gas phase rig established.

Tried our hands a decade ago wet method methyl iodide

Original aluminum bodied 7 mL internal volume CO2 target

Prototype CTI ROSETTA Cyclotron

Evolution of a High Yield Gas Phase [11C]CH3I Rig at LBNL
For an optimized set of parameters it is important to maintain consistency and pumping speed.

Sample sequence of operation as seen by radiation detectors:

1. Cold trap, valves, recirculating pump
2. Split system for space utility
3. System separation
4. Lower iodine concentration and oven temperature
5. Flow limited by pump capacity (500 mL/min)

Re-optimized parameters:

- CH₄ trap left out of recirculation loop to avoid contamination/trapping of CH₄
- Added KNF micro-diaphragm pump
- Lower concentration of iodine

Importance of optimization, consistency, and pumping speed.
### The Numbers

- Iodine Trap
- 80 cm³/min of iodine vapor
- 0.1 cm³/min of air

**Summary**

- Key system attributes and components for success:
  - Low system volume: less contact, more passes, mild reaction conditions
  - Low cost LED based absorbance detector
  - Efficient post oven iodine trapping
  - Iodine concentration adjustment
  - Post oven iodine trapping

**System Operation**

- Iodine trap
- 9 mm EOC 10 Cl²/Ch²
- 25-30 mL recirculating path
- Recirculation time: 4-5 sec per pass (3.5 min)
- System volume: 30 mL recirculating path

**Monitoring Iodine Concentration**

- Quick adjustments
- Iodine concentration, less passes, milder reaction conditions

**System Separation**

- Free up hot cell floor space for chemistry and other clutter
- Iodine reuse very important for purity
- Efficient post oven iodine trapping
- Less contact, more passes, milder reaction conditions

**The Numbers**

- System volume 25 - 30 mL
- Recirculation time 4 - 5 sec per pass (3.8 min)
- Runs between I² driveback 25 - 30 mL
- Time of production 9 min EOB to CH₃I complete delivery
- Typical tracer specific activities 5 - 20 Ci/umole (1.5 - 5 Ci CO₂)

**Iodine Concentration Adjustment**

- Typical tracer specific activities 5 - 20 Ci/umole (1.5 Ci CO₂)
- Time of production 9 min EOB to CH₃I complete delivery
- Runs between I² driveback 25 - 30 mL
- Recirculation time 4 - 5 sec per pass (3.5 min)
- System volume 30 mL recirculating path

**System Components**

- LED – Photo Diode Based Iodine Concentration Detector
- Photo Diode
- Absorber
- Detector

**Vortex Chiller as Iodine Trap Cooler**

- Inlet
- Exhaust
- 15 cm

**Webpage**

[www.newmantools.com/vortex.html](http://www.newmantools.com/vortex.html)
1. System can (also) do, at environment temperature
   • Methane triflate
   • Methane triflate
   • Raclopride

2. System performance
   • Running consistently = better performance on specific activity
   • After long stop, run cold couple of times before going hot

System (unexpected) do, as environment temperature
One Year Experience With a IBA 18/9 Cyclotron Operation for F-18 FDG Rutin Production

Nicolini J; Ciliberto J; Nicolini M A; Nicolini M E; Baró G; Casale G; Caro R; Guerrero G; Hormigo C; Gutiérrez H; Pace P; Silva L

Laboratorios Bacon S.A.I.C. Ururuguay 136 –B1603DFD- Villa Martelli, Bs. As. Argentina

This paper tries to encourage those countries that still do not have an industrial production system to supply FDG to PET centers. We show a compilation of performance data, maintenance and production yield. With the statistical analysis of these data we conclude that the whole system is robust and effective. This work also shows graphic performance of the ion source before and after maintenance and repositioning, and also performance of targets and chemical process yields. we include the layout of the installation which was designed to have visual control of the important areas from the control room of the cyclotron.

PERFORMANCE OF FDG PRODUCTION SYSTEM

\[ y = 1790.9 \ln(x) - 4938.1 \]

Integrated current on target (uAh) vs FDG activity EOS (mCi)
One-Year Experience with an IBA 18/9 Cyclotron Operation for F-18 FDG Routine Production

The Cyclotron Facility

- Designed to have visual contact with the Power Unit and Hot cells at the Radiochemistry Laboratory

The Facility Diagram

- The Bunker
- The Cyclotron
- Hot Cell
- Chemistry Synthesis Unit
- The Target

Ground Layout

Control Room
The bunker is designed to shield neutron and gamma radiation. Walls are made of concrete (density 235 g/cm²). During the irradiation the bunker is closed by a 14-ton concrete door.

The cyclotron Cyclone® 18/9- HC (high current) model.


The safety system locks the door if the dose rate inside the bunker is greater than 100 µSv/h.

The ventilation system keeps a depression greater than 100 Pa.

The shields are designed in order to limit the dose to the workers to 0.5 mSv/year.

The bunker is closed by a 14-ton concrete door.
Chemistry Synthesis Unit

- Synthera® nucleophilic substitution.
- FDG Synthesis time <25 min.
- Yield EOS 60% (70% corrected yield).
- Integrated Fluidic Processor (IFP™)
- Single use

Adjustable Parameters

- Reactor: temperature 30-150°C.
- Pressure: 0-2 bar.
- Timing: each step adjustable

Dispensing HOT cell

- Ventilation systems: 70% recycling.
- Completely efficient HEPA filters (>99.99%)

Synthesizing HOT cell

- The HEPA filter and charcoal filter are built to filter the exhaust air.
- A continuous radiation air monitoring system.
- Front lead shielding 75mm thickness.
- Side and back shielding 60 mm thickness.

Chemistry Synthesis Unit

- Single use
- Synthera® nucleophilic substitution.
- FDG Synthesis time <25 min.
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Adjustable Parameters

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Synthesizing HOT cell

- The HEPA filter and charcoal filter are built to filter the exhaust air.
- A continuous radiation air monitoring system.
- Front lead shielding 75mm thickness.
- Side and back shielding 60 mm thickness.
**Target Care**

- Do not use recycled enriched water to fill all the target windows at 5000 µm. Replace the o'ring and foil windows at 5000 µm.
- Keep the target/Tgt + Coll current ratio above 90%.

**Fill the volume**

- Large volume 2.4 ml
- 50 µm Havar fold
- Nibium body
- IBA commercial target

**Water Target**

- 98% enriched water
- 2,4 ml
- 50 µm Havar fold
- Large volume 2.4 ml
- Nibium body
- IBA commercial target

**System**

Performance of FDG Production

**Target Performance**

- Water Target Yield
- Theoretical Saturation Line
- Experimental Saturation Line

\[ y = 2884.9 \ln(x) - 7834.2 \]
\[ R^2 = 0.92144000 \]

\[ y = 1790.9 \ln(x) - 4938.1 \]

Integrated current on Target (µAh)
More than 200 runs

Average daily production of FDG: 2300 mCi.

Maximum FDG activity obtained in one run: 3970 mCi (147.54 μAh in 3.5 h).
Comparison of $[^{11}C]CH_3I$ yields from 2 in-house Methyl Iodide Production systems – Does size matter?

Salma Jivan, Ken R. Buckley, Wade English & James P. O’Neil
UBC/TRIUMF PET Program, 4004 Wesbrook Mall, Vancouver, B.C., Canada
1Lawrence Berkeley National Laboratory, 1 Cyclotron Road, Berkeley, CA, U.S.A.

The TRIUMF/PET Program is largely reliant on carbon-11 tracers for neurology studies. The reliability and high specific activity radiotracers are key components to the success of the program. Recently, we experienced low in-target $[^{11}C]CH_4$ yields which prevented us from synthesizing certain low radiochemical yield tracers. To circumvent the problem, a new module was constructed. We report our conversion yields obtained from 2 in-house built CH$_3$I modules and describe the changes made between the two systems.

$[^{11}C]CH_4$ is produced in a niobium target as previously described(1). The target contents and helium flushes (approximately 1.5 litres) are transported 50 metres in 3.2 mm stainless steel tubing to a hotcell in the radiochemistry lab that houses the CH$_3$I module. The target contents pass through phosphorous pentoxide to trap ammonia formed in target and are collected on 2 grams of Poropak N cooled at -196°C. Helium is used to flush nitrogen and hydrogen off the trap upon warming. After flushing, the recirculating pump is started and the $[^{11}C]CH_4$ is pumped through a 720°C quartz tube containing iodine vapour. An ascarite trap (9.5mm OD x 7mm ID x 12cm length) is placed between the quartz tube and CH$_3$I trap which is packed with 0.2 grams of Poropak N. Recirculation proceeds until the radiation level on the CH$_3$I detector levels off. The trap is heated to 180°C and helium elutes the $[^{11}C]CH_3I$ into precursor solution or solvent for quantifying CH$_3$I.

MethylIodide Systems Description

The first TRIUMF gas phase recirculating $[^{11}C]CH_3I$ system built in 1996 was based on works by Link and Larsen (2,3) with minor modifications. Our first system had a 19mm OD x 16.5mm ID x 30.5cm length quartz tube placed in a 15 cm horizontal oven. The I$_2$ vapour source was a heated side arm near the head of the quartz tube and temperature was varied from 50°C to 90°C to maintain a constant I$_2$ concentration. A copper coil with running water was placed at the end of the quartz tube to condense iodine and prevent migration through the system. System pressures during recirculation ranged from 2 to 4 psi and flows were 250-300ml/min for a period of 6 minutes. The $[^{11}C]CH_4$ trap was in the recirculation loop for this system. The conversion yields of $[^{11}C]CH_3I$ averaged 20% decay corrected based on $[^{11}C]CH_4$ production. The system worked reliably and made enough dose for injection until we experienced target problems and low yields from our Niobium target. With high demand for scanning tracers to be shared with multiple scanners, the need for another CH$_3$I system was pushed forward.

The new system was built with the same model oven rotated into a vertical orientation with a 12.75mm OD x 10.5mm ID x 38cm length quartz tube as the reactor and the flow upward through the tube. The I$_2$ is now inside a heated portion of the quartz tube (2.5 cm band heater set at 50°C) and sees the flow path directly. A Peltier cooler is used to condense and trap the I$_2$ vapor exiting the oven to prevent migration through the system. The relatively large volume diaphragm Cole Parmer pump from the original system was replaced with a micro diaphragm KNF pump as the recirculation pump. The system volume was further reduced by replacing the 3.2 mm stainless steel tubing to 1.6 mm teflon tubing where possible. Tubing from the outlet of the quartz tube to the ascarite trap was kept to 3.2 mm due to iodine plating out and causing high pressure and plugging of the system. Fittings were changed to PFA from stainless steel where possible to prevent corrosion in the system. The major difference between the two systems was the recirculation path. After CH$_4$ trapping, the trap contents were pressurized into the quartz tube. The CH$_4$ trap was isolated from the recirculation path and $[^{11}C]CH_4$ was recirculated for 3.5 minutes at a flow rate of 300 to 400ml/min. Pressures during recirculation ranged between 9 and 12 psi.
Results and discussion

The original CH$_3$I system provided conversion yields averaging 20%. Due to poor trapping of I$_2$ after the oven, the ascarite trap was changed between every run, while the I$_2$ pot was topped up every 20 runs. The system was given a complete cleaning after 60 runs. Upon cleaning of traps, it was found that the CH$_3$I Poropak packing appeared light yellow in colour proving the breakthrough of iodine and preventing efficient $[^{11}\text{C}]{\text{CH}}_3$I trapping. It was also noticed that the counts on the CH$_4$ trap radiation detector would rise during recirculation confirming breakthrough of the formed product. With routine maintenance of the system, high specific radioactivity was maintained and the mass of CH$_3$I produced ranged from 5 to 10 nmols.

With the new system we find the conversion yields increased close to 2 fold and averaged 40% with measured masses of CH$_3$I ranging between 15 and 25 nmols. We replace the ascarite trap at the beginning of each production day and can perform up to 6 batches with short turnaround time of 20 minutes. The iodine is scraped down the quartz tube for re-use periodically as the vapor concentration decreases thus avoiding the need to add fresh iodine. The system currently has operated with 100 runs without any intervention or I$_2$ filling.

A smaller recirculation volume allows for larger number of passes of $[^{11}\text{C}]$CH$_4$ through the reaction chamber over the same time period. The original system had a recirculation cycle time of 40 sec per pass providing approximately 10 to 12 passes for the given 6 to 8 minute recirculation time whereas the new system has a recirculation cycle time of 10 sec per pass providing approximately 18 to 24 passes in the 3 to 4 minute recirculation step. In addition, the removal of the CH$_4$ trap from the recirculation system avoids buildup, and therefore the loss, of any $[^{11}\text{C}]$CH$_3$I not trapped or bled from the $[^{11}\text{C}]$CH$_3$I trap. In conclusion, the changes made to the new system with smaller recirculation volume improved the conversion yield of the system.

References:

Comparison of $[11C]$CH$_3$I Yields from 2 In-house Methyl Iodide Production Systems – Does Size Matter?

Salma Jivan, Ken R. Buckley, Wade English & James P. O’Neil

UBC/TRIUMF, 4004 Wesbrook Mall, Vancouver, BC Canada

1Lawrence Berkeley National Laboratory Berkeley, CA USA

Motivation

Existing system not adequate, low conversions
Syntheses of low RC yield tracers
In-target $^{11}C$CH$_4$
Target issues
Low inherent target yield
Reliable but needed frequent maintenance
15-20 syntheses per week
Original system built 1997
System Hardware

Peltier cooler

Iodine heater

Flow

CH₄ trap

Pellet cooler

CH₄ trap

System Hardware

Radioactivity Trend

Old

New

Product vol.

MeI trap

Melting trap

Reload - flush

Warm

Recycled

Unloaded - flush

Time (min)

System volume reduction

Conversion based on 11CH₄ 15-20%

Water (18-20°C) Peltier (0°C)

Iodine source

Source

> 10 l/min

3-4 l/min

Recirculation pump

Large volume micro

56 ml

33 ml

Original

New

Summary

Original

New

Volume 65 ml

33 ml

Recirculation pump

Large volume micro

150 ml

80 ml

Number of passes

10-12

18-24

Water

Cooling source

Water (18-20°C) Peltier (0°C)

System volume reduction

System volume reduction

Removal of CH₄ trap

Increase in number of passes

Increase in conversion yield

Performed 200 runs without needing to replace traps or replenish iodine thus reducing maintenance requirements.

Size does matter!!
1. Temperature during synthesis
   - 720 °C in all synthesis
   - Too high temperature = problems

2. Specific activity
   - 7 Ci/umol
   - No difference observed between systems

3. Cold trap
   - Cold trap outside: decreased volume
Cyclotron production of $^{99m}$Tc via the $^{100}$Mo(p,2n)$^{99m}$Tc reaction

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¹ Edmonton PET Centre, Cross Cancer Institute, University of Alberta, Edmonton, AB, CANADA
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³ Lawson Health Research Institute, London, ON, CANADA
⁴ TRIUMF, Vancouver, BC, CANADA

Introduction: In light of the current world-wide shortage of reactor-produced $^{99}$Mo/$^{99m}$Tc, there is a growing interest in exploring the large-scale cyclotron production of $^{99m}$Tc via the $^{100}$Mo(p,2n)$^{99m}$Tc reaction (a method first proposed by Beaver and Hupf, *J Nucl Med*, 1971, 12: 739). In producing $^{99m}$Tc, knowledge of the cross sections and theoretical yields are essential for optimizing the high-current irradiation conditions and verifying the processing/recovery techniques. A review of the existing published cross section data for the $^{100}$Mo(p,2n)$^{99m}$Tc reaction however reveals large discrepancies in these measured values.

Aim: Given the large cross section discrepancies in the current literature, the goal of this work was to re-evaluate the cross sections for the $^{100}$Mo(p,2n)$^{99m}$Tc and $^{100}$Mo(p,pn)$^{99}$Mo reactions.

Methods: The $^{99m}$Tc and $^{99}$Mo cross sections were evaluated using both natural abundance (7.5 mg/cm²) and $^{100}$Mo enriched (97.42%, 7.4–11.1 mg/cm²) foils. Foils were individually irradiated with proton energies up to 18 MeV for 600 seconds on the Edmonton PET Centre’s TR 19/9 variable energy cyclotron (Advanced Cyclotron Systems Inc., Richmond, BC). A copper foil was in place for all irradiations for the purpose of monitoring the beam energy and irradiation current. Unless otherwise noted, all decay data were obtained from the NuDat 2.5 database.

The molybdenum foils were assayed multiple times (from a few hours to several days post-EOB) using an HPGe detector (sample distance ≥ 25 cm, dead time < 7%). The detector was calibrated using standard sources of $^{22}$Na, $^{54}$Mn, $^{57}$Co, $^{60}$Co, $^{109}$Cd, $^{133}$Ba and $^{137}$Cs. The $^{99}$Mo activity was determined using a weighted average of the 181 keV and 739 keV peaks. In determining the $^{99m}$Tc activity, the non-resolved 140/142 keV peak (89.06%/ 0.02%) was measured. Two additional contributing sources to the 140 keV peak were subtracted prior to evaluation of the direct $^{99m}$Tc cross section. Firstly, as $^{99}$Mo decays to $^{99m}$Tc, the $^{99}$Mo associated $^{99m}$Tc activity at the start of counting was determined from the measured $^{99}$Mo activity using the radioactive parent-daughter relationship described by Attix (*Introduction to Radiological Physics and Radiation Dosimetry*, 2004, pp. 105–106) with the branching ratio to $^{99m}$Tc taken as 87.6% (Alfassi et al., *Appl Radiat Isot*, 2005 63: 37). Next, as $^{99}$Mo gives rise to a 140 keV (4.52%) gamma ray upon decay, this peak contribution was calculated from the measured $^{99}$Mo activity of each respective foil. Cross sections were calculated using the standard activation formula (Krane, *Introductory Nuclear Physics*, 1988, pp. 169–170) with values normalized to 100 percent $^{100}$Mo enrichment.

Thick target yields were calculated from the measured $^{99m}$Tc cross sections assuming 100 percent $^{100}$Mo and fitting the cross-section data with a 2nd order polynomial. Values are reported for 18→10 MeV, and 22→10 MeV (cross sections extrapolated to 22 MeV from a polynomial curve fit).

Results: The following figures compare the evaluated cross sections for the direct production of $^{99m}$Tc and $^{99}$Mo to previously published cross section data. For the purpose of comparison, we have normalized the $^{99m}$Tc data of Challan et al. (*Nucl Rad Phys*, 2007, 2: 1) to 100 percent $^{100}$Mo by dividing by 9.63%. For both reactions, our results are in good agreement to values published by Levkovskij (1991). Good $^{99m}$Tc cross section agreement is also noted up to $E_p$ ~12 MeV when
comparing with Lagunas-Solar (IAEA-TECDOC-1065, 1999) and Challan et al. We believe that the elevated 99mTc cross sections for Lagunas-Solar for Ep > ~12 MeV may be attributed to the incomplete subtraction of the 99Mo 140 keV peak contributions due to underestimated 99Mo cross sections. Although Challan et al. mention that they have corrected for the growth and decay of the metastable and ground states, it is unclear if the 99mTc 140 keV peaks were corrected to account for 99Mo→99mTc contributions post-EOB. The absence of such a correction would similarly explain the elevated 99mTc cross sections for Ep > ~12 MeV. While the 99Mo cross sections are in good agreement, the 99mTc cross sections measured in this work are significantly higher than values published by Takács et al. (J Radioanal Nucl Chem, 2003, 257: 195) and slightly higher, by approximately 2σ, than values presented by Lebeda and Pruszynski (to be published in Appl Radiat Isot). An overall disagreement was noted for both reactions when comparing with the published cross sections of Scholten et al. (Appl Radiat Isot, 1999, 51: 69).

Throughout this experiment the beam current and detector efficiency were carefully monitored and we are confident with the 140 keV peak area corrections performed in this experiment as the evaluated 99mTc cross sections were consistent, independent of the time post-EOB upon which they were evaluated (i.e. calculated within a few hours post-EOB or >24 hours post-EOB).

Thick target yields were determined to be 14.2 mCi (526 MBq)/µAh for 18→10 MeV, and 18.2 mCi (674 MBq)/µAh for 22→10 MeV. These yields are higher than the value of 11.2 mCi (415 MBq)/µAh for 22→12 MeV reported by reported by Scholten et al., and are in good agreement with the value of 17 mCi (629 MBq)/µAh for 25→5 MeV given by Takács et al.

As we are not only interested in optimizing the yield of 99mTc, but also the purity, future work is planned to experimentally evaluate the 100Mo(p,2n)99mTc cross sections. Preliminary calculations using cross sections modelled with Empire–II suggest that a 99mTc/99m++99gTc ratio of 18% is possible for a 3 hour irradiation at 22→10 MeV. In comparison, assuming a 24 hour elution frequency and 5% retention, the 99mTc/99m++99gTc ratio calculated for the standard generator setup is 26% (Alfassi et al., Appl Radiat Isot, 2005 63: 37).

**Conclusion:** We have presented updated cross sections for the 100Mo(p,2n)99mTc and the 100Mo(p,pn)99Mo reactions. Results of this work suggest that production of large quantities of 99mTc via a cyclotron may be a viable alternative to the current reactor-based production strategy.

**Acknowledgements:** The authors would like to thank Advanced Cyclotron Systems, Inc. This work was supported through a grant from NSERC/CIHR (MIS 100934).
Motivation/Background

- Current / ongoing worldwide shortage of reactor-produced 99Mo/99mTc.
- Growing interest in exploring the large-scale cyclotron production of 99mTc via the 100Mo(p,2n)99mTc reaction.
- Knowledge of the cross sections and theoretical yields.
- Irradiations:
  - Thin foils, both natMo and 100Mo (97.42% enrichment).
  - Folds individually irradiated on the TR-19/9 at the EPC.
  - Irradiations:

Reaction scheme:

\[
\begin{align*}
\text{99Mo} & \rightarrow \text{99mTc} + \gamma \quad \text{140 keV photon used for imaging} \\
\text{100Mo} \rightarrow \text{99mTc} + n + n + \gamma \quad \text{3840 keV photon } \\
\end{align*}
\]

- Large discrepancy amongst published literature.
- Eff and current monitored.
- \( I = I_{\text{p}} t = 600 \text{ seconds} \)
- \( E_p \) and current monitored.
- Folds individually irradiated on the TR-19/9 at the EPC.
- Foils individually irradiated on the TR-19/9 at the EPC.
- Thin foils, both natMo and 100Mo (97.42% enrichment).
- Irradiations:
  - Thin foils, both natMo and 100Mo (97.42% enrichment).
  - Foils individually irradiated on the TR-19/9 at the EPC.
  - Ir \( I \approx 1 \mu A, t = 600 \text{ seconds} \)
  - \( E_p \) and current monitored using copper foils.
Results

Future/Ongoing

Alberta’s Radiogenic Isotope Facility:
- Folds will be analyzed via ICP-MS at the University of Alberta. These folds are currently waiting for decay of 99Mo, 99mTc, etc.
- Production of 99Mo and 99mTc have been measured for a few time points post-EOB.
- Folds were irradiated ~12,000 fmin (20 μA x 600 sec).
- Production of enriched 100Mo (p, 2n) 99gTc

Cross sections for enriched foil irradiations

Cross sections (p, x) production of 100Mo, 99mTc, and 97Nb also evaluated for enriched foil irradiations.

Thick Target Yields

Cross sections

Uncertainty due to determining 140 keV contribution from 99Mo, 99mTc, etc.

Note: HPGe calibration source included 57Co.

Correct for overlapping contributions from 99Mo.

Production of 99mTc within a few hours post-EOB. Typical assay times were 300 seconds.

To minimize contribution of 99Mo, assays for 99mTc.

Folds assayed at multiple time points post-EOB.

Planned measurement of the 100Mo(p, 2n) 99gTc excitation function.

Enriched foils irradiated ~12,000 μA x 600 hrs, June 2010.

Production of 99Mo and 99mTc have been measured for these folds.

Correct for overlapping 140 keV contributions from 99Mo, 99mTc, etc.

Currently awaiting for decay of 99Mo, 99mTc, etc.

Folds will be analyzed via ICP-MS at the University of Alberta.
We have presented updated cross sections for the 100Mo(p,2n)99mTc and 100Mo(p,pn)99Mo reactions. Experiments are underway to evaluate the calculated thick target yields. Suggest that cyclotron may be a feasible alternative to the current reactor-based strategy. Neutron measurements difficult in thin foil methodology.
Cyclotron Production of $^{99m}$Tc

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$^1$Advanced Cyclotron Systems Inc., Richmond, BC, Canada
$^2$Sherbrooke Molecular Imaging Center, Université de Sherbrooke, QC, Canada

Introduction. Current global interruptions of $^{99}$Mo supply, aging reactors, and the staggering costs of their maintenance have accelerated the search for alternative sources of $^{99m}$Tc. Direct production of $^{99m}$Tc via $^{100}$Mo($p$,2$n$)$^{99m}$Tc nuclear reaction can be considered as one of such alternatives. The feasibility of $^{99m}$Tc production with a cyclotron was first demonstrated in 1971 by Beaver and Hupf$^1$ and confirmed by a number of researchers.$^{2,3,4,5}$ Measured yields indicate that up to 2.1 TBq (56 Ci) of $^{99m}$Tc can be produced in 12 h using a 500 μA 24 MeV cyclotron. This amount will be sufficient to cover population base of 5-7 million assuming: 15 % $^{99m}$Tc losses, an average injected dose of 25 mCi and a 10 hrs decay. Initial results of the target development and thick target yields are presented in the “Mo-100 development for direct Tc-99m Production” abstract. In this work we compared the chemical and radiochemical properties and in vivo behavior of cyclotron- and generator-produced $^{99m}$Tc.$^6$

Experiment. Targets, 6-mm diameter discs, were prepared by melting $^{100}$Mo pellets (99.54% enrichment) onto tantalum backing supports. Targets were bombarded for 1.5–3 h with 15.5–17.0 MeV protons (14–52 μA), using a TR-19 cyclotron (ACSI). After bombardment, $^{100}$Mo targets were partially dissolved and purified by the method of Chattopadhyay et al.$^7$ The radionuclide purity of the $^{99m}$Tc was >99.99%, as assessed by γ-spectroscopy, exceeding USP requirements for generator-based $^{99m}$Tc. Although small peaks corresponding to $^{99}$Mo were observed in the initial solute, these were not detectable in the purified $^{99m}$Tc-pertechnetate solution. Minute amounts of $^{97}$Nb were also quantitatively separated from during target processing. The content of other technetium isotopes was measured after allowing sufficient time (4 days) for $^{99m}$Tc decay. The presence of 0.0014% $^{96}$Tc and 0.0010% $^{95}$Tc at the end of bombardment, was below USP requirements of 0.01% for generator-produced $^{99m}$Tc. No other radionuclidic impurities were found. The radiochemical purity of cyclotron-produced $^{[99mTc]TcO_4^-}$, as determined by instant thin-layer chromatography was >99.5%, well above the USP requirement of 95%. The content of ground state $^{99}$Tc ($T_{1/2} = 2.1 \times 10^5$ years) was not determined in these experiments and is one of the tasks for future work. For imaging studies, both cyclotron- and generator-produced $^{99m}$Tc were formulated as 3 different radiopharmaceuticals: $^{99m}$Tc-pertechnetate for thyroid imaging, $^{99m}$Tc-methylene diphosphonate ($^{99m}$Tc-MDP) for bone scanning, and $^{99m}$Tc-hexakis-2-methoxyisobutyl isonitrile ($^{99m}$Tc-MIBI) for heart imaging. These radiopharmaceuticals account for more than 75% of all routine $^{99m}$Tc scans currently used in diagnostic nuclear medicine. The latter two radiopharmaceuticals were prepared using commercially available kits. Labeling efficiency for the bone imaging agent $^{99m}$Tc-MDP and heart imaging agent $^{99m}$Tc-MIBI were 98.4% and 98.0%, respectively, well above USP requirements of >90%.

Animal Scans. The bio-distributions of $^{99m}$Tc-pertechnetate, $^{99m}$Tc-MDP, and $^{99m}$Tc-MIBI, prepared with either cyclotron- or generator-produced $^{99m}$Tc, were assessed in a healthy rat model. For each experiment 2 animals were simultaneously injected with a 0.3-mL physiologic saline solution containing 34–90 MBq of the selected $^{99m}$Tc-radiopharmaceutical, prepared either with cyclotron- or generator-produced $^{99m}$Tc. Dynamic acquisitions were continued over a 2 h period. At the end of scanning, the rats were killed and dissected to

**Figure 1.** Whole-body scintigrams of two rats 2 h after administration of: 90 MBq of $^{99m}$Tc-pertechnetate; 34 MBq of $^{99m}$Tc-MDP; 15 MBq of $^{99m}$Tc-MIBI, prepared from cyclotron- (right image) and generator-produced $^{99m}$Tc (left image).
measure activities of target tissues. Static images obtained 2 h after administration of each of these 
\(^{99m}\text{Tc}\)-radiopharmaceuticals show matching \(^{99m}\text{Tc}\) distribution patterns, clearly delineating the thyroid with \(^{99m}\text{Tc}\)-pertechnetate, skeleton with \(^{99m}\text{Tc}\)-MDP, and heart with \(^{99m}\text{Tc}\)-MIBI (Fig. 1). Uptake kinetics calculated over the target organs (thyroid, bones, and heart), show identical uptake patterns for the cyclotron- and generator-produced \(^{99m}\text{Tc}\)-radiopharmaceuticals (Fig. 2). Tissue activities from dissected samples collected 30 min after the end of imaging with \(^{99m}\text{Tc}\)-MDP and \(^{99m}\text{Tc}\)-MIBI also show matching patterns between cyclotron- and generator-derived \(^{99m}\text{Tc}\) preparations (Fig. 3).

**Conclusion.** The results of these in vivo experiments and quality control tests support the concept that cyclotron-produced \(^{99m}\text{Tc}\) is suitable for preparation of USP-compliant \(^{99m}\text{Tc}\) radiopharmaceuticals. Establishing decentralized networks of medium energy cyclotrons capable of producing large quantities of \(^{99m}\text{Tc}\) may effectively complement the supply of \(^{99m}\text{Tc}\) traditionally provided by nuclear reactors, at a fraction of the cost of a single nuclear reactor production facility, while sustaining the expanding need for other medical isotopes, including short-lived positron emitters for PET imaging.

2. Lagunas-Solar M C. Accelerator production of \(^{99m}\text{Tc}\) with proton beams and enriched \(^{100}\text{Mo}\) targets. In: IAEA-TECDOC-1065. Vienna, Austria: International Atomic Energy Agency; 1999:87
5. Lebeda, O. et al. New measurement of excitation functions for (p,x) reactions on \(^{96}\text{Mo}\) with special regard to the formation of \(^{95}\text{Tc}\), \(^{96m}\text{Tc}\), \(^{99m}\text{Tc}\) and \(^{99}\text{Mo}\). Appl. Radiat. Isot., in press
Cyclotron Production of Tc-99m

**ACSI TR24 Cyclotron**

The measured production yields @24 MeV:

- 75 Ci (two 6 hr runs)
- 56 Ci (one 12 hr run)

500 µA TR-24 can generate -150 µCi/mA at saturation

**History**

- May 2009: Recent isotope crisis begins: NRU Shutdown
- Jun 2009: NRCan calls for Expressions of Interest
- ACSI propose to implement direct Tech production of 99mTc
- Jul 2009: NRC submits to NRCCan National Cyclotron Network
- Current using network of TR24 cyclotrons
- NRC calls for Expressions of Interest
- Recent isotope crisis begins: NRU Shutdown

**Tc99m Production Yields**

<table>
<thead>
<tr>
<th>Month</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 2009</td>
<td>Recent isotope crisis begins: NRU Shutdown</td>
</tr>
<tr>
<td>Jun 2009</td>
<td>NRC calls for Expressions of Interest</td>
</tr>
<tr>
<td>Jul 2009</td>
<td>NRC submits to NRCCan National Cyclotron Network</td>
</tr>
<tr>
<td>Aug 2009</td>
<td>ACSI propose to implement direct Tech production of 99mTc</td>
</tr>
<tr>
<td>Sep 2009</td>
<td>Current using network of TR24 cyclotrons</td>
</tr>
<tr>
<td>Oct 2009</td>
<td>NRC calls for Expressions of Interest</td>
</tr>
<tr>
<td>Dec 2009</td>
<td>NRCan commits to develop non-fission solution</td>
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<tr>
<td>Feb 2010</td>
<td>NRCan calls for proposal on development and demonstration of non-fission solution</td>
</tr>
<tr>
<td>Mar 2010</td>
<td>Two Canadian organizations purchase 24 MeV cyclotron</td>
</tr>
<tr>
<td>Dec 2010</td>
<td>NRCan commits to develop non-fission solution</td>
</tr>
</tbody>
</table>

**ACSI TR24 Cyclotron**

**100Mo(p,2n)99mTc Production Yield**

The measured production yields @24 MeV:

- 75 Ci (two 6 hr runs)
- 56 Ci (one 12 hr run)

500 µA TR-24 can generate -150 µCi/mA at saturation

**Graph**

- Particle energy, MeV
- Physical yield, mCi/µA
- Physical yield, GBq/C

**Graph Description**

- The graph shows the relationship between particle energy and physical yield for the production of 99mTc using the TR24 cyclotron.
- The measured production yield is approximately 150 µCi/µA at saturation.
- The yield for a 12-hour run is estimated to be around 56 Ci.
- The yield for two six-hour runs is approximately 75 Ci.

**Equation**

\[100Mo(p,2n)99mTc \]
How many 99mTc doses can we make?

Sat Yield 24 MeV 150 mCi/u

A Measured y yields @ 24 MeV

Beam on TA 500 µA Hrs / day 12 hrs Production 56 Ci / day 37 Ci in 6 hours (75 Ci in 2 x 6 hrs)

AV 25 Ci AD 20-30 mCi for cardiac and NPT bone scans

Av. t EOB 10 hrs Tc losses 15% Av. dose @ EOB 93 mCi

Doses per site 602 Dose/day Tc-99m Req 600 Ci/day For entire Canadian Population

Daily requirements for Canada

Cost of Production

Cyclotron production of 99mTc can be economically viable, if it can effectively supplement and possibly compete with reactor based supply:

- Cyclotron production can be economically viable if it can
- Supplement and possibly compete with reactor based supply
- Cost of production

Challenges. Radionuclidic Purity

NUCLIDE HALF-LIFE REACTION COMMENTS

99mTc (21 E + 5 y)

99mTc deca y 99mTc eluted from generator after 24 h growth time

98Tc (4.2E+6 y)

97mTc (91.4 d)

97mTc decay

96mTc (51.5 min)

96mTc decay

99Mo (2.75 d)

97Nb (72.1 min)

96Nb (23.3 h)

95Nb (35 d)

99Mo (2.75 d)

97Nb (72.1 min)

96Nb (23.3 h)

95Nb (35 d)

99Mo (2.75 d)

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95Nb (35 d)

99Mo (2.75 d)

97Nb (72.1 min)

96Nb (23.3 h)

95Nb (35 d)
Challenges. Specific Activity

Cyclotron 99mTc specific activity is 2.5-3 (EOB) times lower than 99mTc eluted from a generator after 24 hr growth in period:
- 24 hr generator ~ 28%
- 12 hr run cyclotron ~ 9%
- 6 hr run cyclotron ~ 12%

Measured by ICP MS 6 hrs @16.4 MeV 99mTc/Tc ~19% equivalent to 36 hr generator.

Labeling with specific activity as low as 2.8% has been studied for HMPAO, TF, MAG3 ECD and MIBI as model compounds. All the standard quality control indicators, radiochemical purity and labeling efficiency values were unaffected.


Work in Progress

First experiments on direct 99mTc production started in October 2009 at University of Sherbrooke. The main objective was:
1. to demonstrate the feasibility of 99mTc production using a cyclotron
2. to compare the chemical and radiochemical properties and in vivo behavior of cyclotron- and generator-produced technetium
3. to prepare the cyclotron-produced technetium for heart imaging

Mo-100 (99.54%) targets were bombarded with 15.5-17.0 MeV protons (14–52 uA) using TR-19 cyclotron.

Radionuclidic purity: 0.0014% 96mTc, 0.0010% 99mTc and 0.0003% 95mTc.

No 97mTc were detected.

99mTc was formulated as 3 different radiopharmaceuticals:
- 99mTc-pertechnetate for thyroid imaging
- 99mTc methylene diphosphate (99mTc-MDP) for bone scanning
- 99mTc hexakis-2-methoxyisobutyl isonitrile (99mTc-MIBI) for heart imaging

The radiochemical purity of cyclotron produced [99mTc]TcO4- was 99.5% (USP requirement of 95%).

The labeling efficiency (potentially affected by ground state technetium):
- 99.5% (USP requirement of 95%)

Whole-body scintigrams of two rats 2 hr after administration of:
- 90 MBq of 99mTc-pertechnetate
- 34 MBq of 99mTc-MDP
- 15 MBq of 99mTc-MIBI prepared from cyclotron- (right) and generator-produced 99mTc (left).

Guerin et al. J Nuclear Med 2010;51:13N-16N
Conclusion

- World-wide interest in this model
- PET Imaging
- Expanding availability for other medical isotopes, including for PET
- Cyclotron production of 99mTc can be economically viable. It can address new demands in a few weeks or even days
- Flexible solution, as production demand changes sites can react
- Is an attractive alternative to regional supply of 99mTc
- Make the use of safe and relatively low-cost cyclotron technology

WTTC XIII - Presentation Discussions

1. Specific activity
   - Generator 24h: 28%
   - Cyclotron 12h: 9%
   - Cyclotron 6h: 12%
   - Carefull with Tc96: bad energy to collimators

2. Supply of Mo100
   - Max 10Kg available worldwide
   - Price will depend on demand

3. Final price
   - Mo100 price decisive in overall process price
   - GMP compliance: 2$ USD / dose

4. Alternative processes
   - Nuclear reactor will start again (n, gamma)M99: 10Ci/g but still not profit wise for power plants
Targets for Cyclotron Production of Tc-99m

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Introduction: The measured yields of direct 99mTc production via 100Mo(p,2n)99mTc suggest that 99mTc can be produced in quantities sufficient for supplying regional radiopharmacies i, ii, iii, thereby reducing our reliance on reactor-derived 99Mo. Cyclotron- and generator-produced 99mTc-radiopharmaceuticals were shown to be radionuclidically, chemically and biologically equivalent, giving matching images and identical kinetic and biodistribution patterns in animals, indicating that a medical cyclotron can produce USP-compliant 99mTc-radiopharmaceuticals for nuclear imaging procedures.iv, v In this work, several different 100Mo target configurations were investigated and thick target yields were measured, validating the production of clinically useful quantities of 99mTc on a medical cyclotron.

Target Holders: Two different solid target holders were used to measure the thick target yields of the 100Mo(p,2n)99mTc nuclear reaction. The straight 90° target holder has a heat removal capacity of 1.5 kW and while the 30° tilted solid target holder has a heat removal capacity of 3.0 kW. Two different solid target holders (Advanced Cyclotron Systems Inc., Richmond, BC, Canada) were installed on three compact medical cyclotrons (TR-19, Cross Cancer Institute, Edmonton, AB, TR-19 Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke QC, Canada, GE PETTrace, Lawson Health Research Institute, London ON, Canada).

30° Solid Target Holder
Straight Solid Target Holder

100Mo Targetry. Molybdenum has been a metal of choice in accelerator targetry for several decades. With a high melting point, good thermal conductivity and chemical stability, molybdenum is nearly an ideal material for manufacturing high power targets. While a number of low and medium current cyclotron targets that use natural and enriched molybdenum isotopes have been developed and used for production of technetium isotopes: 94Tc, 96Tc and 99mTc, a reliable process for preparation of enriched molybdenum targets has not yet been implemented. A number of standard target manufacturing techniques are being evaluated: melting, sintering, pressing/pelletizing, rolling, plating from solutions or molten salts, formation of low melting temperature Mo alloys, brazing or soldering 100Mo to a target substrate, coating molybdenum with a protective layer, development of a thick target, plasma sputtering and other coating techniques.

Mo Target Preparation: Between 100-450 mg natural and enriched 100Mo (99.5%) were pressed into 6 and 9.5 mm pellets at between 25,000 N and 100,000 N. The pellets were sintered in wet or dry hydrogen at 800-900ºC, and subsequently mounted into a tantalum substrate, either by pressing or arc melting or electron beam melting at currents between 40-70 mA with different sweeping / focusing patterns.
99mTc Production: 99mTc was produced via the 100Mo(p,2n)99mTc nuclear reaction on a 19 MeV medical cyclotron using an incident proton energy of 15-17 MeV at current between 14-52 μA. After bombardment targets were subjected to electrochemical dissolution, 99mTc was purified by ion-exchange chromatography and recovered as pertechnetate.

Results: Up to 44.7 GBq (1.2 Ci) (EOB) of 99mTc was produced after a 6-h bombardment at 16.4 MeV and 39 μA. This corresponds to a thick target production yield of 0.25 GBq/μA/h (6.8 mCi/μA/h) and 2.3 GBq/μA (63 mCi/μA) at saturation and is in good agreement with literature data. The radionuclide purity of the cyclotron-produced 99mTc was >99.99%, as assessed by γ spectroscopy, exceeding USP requirements for generator-based 99mTc. The content of other technetium isotopes was measured after allowing sufficient time (4 days) for 99mTc decay and was below USP requirements of 0.01% for generator-produced 99mTc. No other radionuclidic impurities were found. The radiochemical purity of cyclotron-produced 99mTcO4– was >99.5%, well above the USP requirement of 95%.

Conclusion: This study confirms that clinically useful quantities of 99mTc can be produced on medical cyclotrons installed worldwide. Extrapolating these results to the optimal energy of 22-24 MeV indicates that over 2 TBq of 99mTc can be produced daily for regional distribution on a high-current medium-energy cyclotron. Implementing networks of high-current medium energy cyclotrons would reduce reliance on nuclear reactors and attenuate the negative consequences associated with the use of fission technology.

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5 Zyzuin, A.; Guérin, B.; van Lier, E.J.; Tremblay, S; Rodrigue, S.; Rousseau, J.A.; Dumulon-Perreault, V.; Lecomte, R.; van Lier, J.E.; Cyclotron production of 99mTc WTTC 13, Abstract
6 Qaim, S.M., Production of high purity 94mTc for positron emission tomography studies, Nuclear Medicine and Biology, 27, 4, 2000, 323-328
Overview

**Cross-Section measurements**
- **Target Stations:** 40 µA – 500 µA
- **Targets for Cyclotron Produced Tc-99m**
- **Arc Melting Molybdenum**
- **E-Beam Melting Molybdenum**

**Thick Target Yields**

1. **100Mo(p,2n)99mTc Cross Section**
   - **Gagnon et al. WTTC13**
   - **Target Stations**
     - **Straight Target:** 40 µA
     - **30° Target:** 80 µA
     - **PET:** 1.3 Ci in 6 hrs
     - **TR24:** 2.8 Ci in 6 hrs
     - **High Current:** 500 µA
     - **Medium Current:** 200 µA
     - **PET:** 6.6 Ci in 6 hrs
     - **TR24:** 14 Ci in 6 hrs

**Future Work**
- Results
- Processed Molybdenum Powder
- E-Beam Melting Molybdenum
- Arc Melting Molybdenum
- Targets for Cyclotron Produced Tc-99m
- Target Stations: 40 µA – 500 µA
- Cross-Section measurements
Pressed Molybdenum Powder

- 100-450 mg Mo (nat. and enriched 100Mo 99-99.5%)
- 6 and 9.5 mm diameter pellets
- Force: 27-107 kN

---

Molybdenum Targets – Arc Melting

**Pros:**
- Good thermal contact Mo/Ta
- Easy to manufacture
- Can run up to 65 µA

**Cons:**
- Difficult to control arc
- Potential alloy formation
- Slow dissolution of target
- Slow dissolution of target
- Critical Temp Mo melting (mp 2617°C)
- No Bonding Mo/Ta

---

Molybdenum Targets – E-beam

**Pros:**
- Accurate control of E-beam
- 50-70 mA Electron beam

**Cons:**
- No Bonding Mo/Ta
- Critical Temp Mo melting (mp 2617°C) and Ta deformation (mp 3017°C)

---

Bulk Density of Molybdenum Pellet vs. Force

![Graph showing bulk density vs. force]
Molybdenum Targets – Pressed

- Mo pellets pressed into Al ring then to 24 mm Ta disk
- Mo pellets pressed directly into 24 mm Al disk

Pros:
- Relatively Inexpensive
- Easy to dissolve Mo
- Can run up to 40 µA
- Relatively inexpensive

Cons:
- Brittle Mo pellets
- Poor thermal contact
- Mo pellets pressed directly into Al disk
- Mo pellets pressed into Al ring then to 24 mm Ta disk

Thick Target Yields

Results – Thick Target Yields

Pros:
- Relatively Inexpensive
- Easy to dissolve Mo
- Can run up to 40 µA
- Relatively inexpensive

Cons:
- Brittle Mo pellets
- Poor thermal contact
- Mo pellets pressed directly into Al disk
- Mo pellets pressed into Al ring then to 24 mm Ta disk

Conclusion

Target Yields:
- Thick target yields agreement with previously measured PET cyclotron yields can produce multi-Ci Tc-99m
- High Current TR24 cyclotron could complement generators
- Preliminary results (3.8 – 1.25 MeV, 5 min, 1.94 µA)
- 2.3 GBq/µA (63 mCi/µA) (scaled to 24–100 MeV)
- 4.6 GBq/µA (125 mCi/µA) (measured)
- Saturated yield
- Saturated yield
- Thick target production yield
- Thick target, 14 MeV → 0 MeV, 39 µA 6 hrs

Results – Thick Target Yields

Preliminary results (3.8 – 1.25 MeV, 5 min, 1.94 µA)
- 2.3 GBq/µA (63 mCi/µA) (measured)
- 4.6 GBq/µA (125 mCi/µA) (measured)
- Saturated yield
- Saturated yield
- Thick target production yield
- Thick target, 14 MeV → 0 MeV, 39 µA 6 hrs

Molybdenum Targets – Pressed
Future Work

- Continue to study targets:
  - Pressed Targets
  - Ebeam/Arc Melting
  - Foils
  - Plating
  - Vap or deposition / Plasma spray

- Select most appropriate method
  - Scalable with overall process integration
  - Cost effective
  - Reliable / Robust

Notes:
- Tc/Mo separation?
  - Next step
  - But: 500uA cyclotrons...
  - FDA approval 3 decades ago...

- Cyclotrons needed to replace nuclear production of Tc99m?
  - 5-8 TR/24 for Canada, 10x more for the USA
  - Plasma spray / Plasma spray
  - FDA approval? It was approved 3 decades ago...
A further exploration of the merits of a Niobium/Niobium vs Niobium/Havar target body/foil combination for $[^{18}\text{F}]$Fluoride production: A detailed HP $\gamma$-spectrometry study

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In the current nuclear medicine environment, both the Molybdenum crisis and FDA regulation, are driving the PET community to look more closely at the production of $[^{18}\text{F}]$NaF for PET imaging. This situation has led the University of Iowa to design and construct a targetry unit and a synthesis/purification module designed to obtain highest purity $[^{18}\text{F}]$NaF. In this study we investigate the radionuclidic purity of $[^{18}\text{F}]$NaF from this module with $[^{18}\text{F}]$NaF produced from both a Nb/Havar and Nb/Nb target/body combination. The rationale for the targetry comes from the recent observations of the Wisconsin and Edmonton groups$^{1,2,3}$.

As can be seen from the schematic in Figure 2 $[^{18}\text{O}]$H$_2$O was irradiated in a Nb target body equipped with either a Nb or Havar front foil. The target water was emptied into a target collection vessel (TCV). Under N$_2$ overpressure the contents were passed sequentially through a CM cation SPE cartridge and a QMA anion SPE cartridge to an $[^{18}\text{O}]$H$_2$O recovery vessel. Any non-anionic material was then flushed from the QMA with water (5 mL) to waste. The $[^{18}\text{F}]$NaF and any other anionic species were then eluted into the final product vial with isotonic saline (15 mL).

To assess radionuclidic purity, the Nb/Niobium body/foil combination was bombarded at 30 $\mu$A for 5, 10, 20 and 80 minutes. The Nb/Havar body/foil combination was bombarded at 30 $\mu$A for 80 minutes. In all cases the TCV, CM, QMA, and Product Vial were quantitatively assessed for radionuclidic content using an GEM20P4-70. ORTEC GEM Coaxial P-type HPGe Gamma-Ray Detector. Results are summarized in Figure 2.

The Nb-Nb body/foil combination spectrum was simple; 30 $\mu$A for 10 minutes created minute quantities of $^{56,57,58}$Co and $^{52}$Mn (<0.1 nCi) from the trace quantities of iron and chromium in the Nb foil, but approximately 1 $\mu$Ci of $^{93m}$Mo from the $^{93}$Nb(p,n)$^{93m}$Mo reaction (Figure 1). The CM cation cartridge quantitatively bound the cobalt isotopes, while the $^{93m}$Mo, initially trapped by the QMA anion cartridge, eluted quantitatively with the $[^{18}\text{F}]$NaF. Under similar conditions, the Nb/Havar body/foil created 12 radionuclides at 10-100 nCi levels. The CM/QMA cartridge combination served to eliminate 6 of 12 contaminants, and reduce the quantities of the remaining nuclides substantially, but not completely. The product vial from the Nb/Nb combination had only $^{93m}$Mo, while the product vial from the Nb/Havar target resulted in $[^{18}\text{F}]$NaF with $^{51}$Cr, $^{95,96}$Tc, $^{181,182}$Re, and $^{93m}$Mo (from Nb target body) contaminants with activities ranging from 1-30 nCi.

References:
Figure 1. Radionuclidic Impurities associated with 30A, 10 minute and 80 minute bombardments on Nb-Nb and Nb-Havar.

Figure 2. [18F]NaF Synthesis schematic with radionuclidic impurities.
A Further Exploration of the Merits of a Niobium/Niobium vs. Niobium/Havar target body/foil combination for [18F]Fluoride Production: A detailed HPGe γ-spectrometry study


PET Imaging Center, University of Iowa Health Care, Iowa City, IA

Project Rationale

1. In the current nuclear medicine environment, both the Molybdenum crisis and FDA regulation are driving the PET community to look more closely at the production of [18F]NaF. This situation has led the University of Iowa to design and construct a targetry and a synthesis/purification module designed to obtain [18F]NaF from this module with [18F]fluoride produced.

2. In this study we investigate the radionuclidic purity of [18F]NaF from both a Nb/Havar and Nb/Nb target/body.

3. This study was performed using HPGe γ-spectrometry for [18F]fluoride production. A detailed HPGe γ-spectrometry study for [18F]fluoride production.

4. A Further Exploration of the Merits of a Niobium/Niobium vs. Niobium/Havar target body/foil combination.
In all cases the Target (TCV), CM cartridge (CM), and Product Vial were quantitatively assessed for radionuclidic contaminants. From the Nb/Nb combination, no measurable quantities of radionuclidic impurities remained in the QMA. The Nb/Nb combination resulted in only Co and Mo radionuclidic contaminants. The Co radionuclides resulted from trace impurities in the Nb foil, while the Mo-93m resulted from the (p,n) reaction on Nb. The Havar foil spawned radionuclidic contaminants were on the order of 100–1000X the absolute quantities from Nb foil. Typical Target Water Spectra from Nb-Havar Comb.
1. The University of Iowa [18F]NaF synthesis/purification system produced a final product with acceptable radionuclidic purity regardless of whether the Nb-Nb or Nb/Havar target body/foil combination was used.

2. Order of magnitude calculations suggest that additional radiation dose resulting from the picoCurie levels of radionuclidic contaminants will result in substantially less than 1 mR additional whole body radiation for both target body/foil combinations using highly conservative assumptions that:
   a) All particulate and gamma radiation emitted in the body are absorbed.
   b) Biological half-lives are infinite.
   c) No attempt to model biodistribution was included in the calculation.

3. It is NOT clear which of the two target body/foil systems is optimal.

**Mo-97m** has a short half-life (6.85 hours) but it also has intermediate energy gamma emissions of approximately 1 MeV. This poses a significant challenge to the purification process.

4. The University of Iowa [18F]NaF synthesis/purification system removes the vast majority of radionuclidic contaminants from the Nb roll from the final product. It is likely that we will never to be able to remove the Mo-97m produced by the Havar, and the system fails to remove the Mo-97m produced by the Nb-Nb system. However, the University of Iowa [18F]NaF synthesis/purification system also removes the vast majority of radionuclidic contaminants from the Nb roll from the final product. It is likely that we will never to be able to remove the Mo-97m produced by the Nb-Nb system. However, the University of Iowa [18F]NaF synthesis/purification system also removes the vast majority of radionuclidic contaminants from the Nb roll from the final product.

5. As the University of Iowa [18F]NaF synthesis/purification system removes the vast majority of radionuclidic contaminants from the Nb roll from the final product. It is likely that we will never to be able to remove the Mo-97m produced by the Nb-Nb system. However, the University of Iowa [18F]NaF synthesis/purification system also removes the vast majority of radionuclidic contaminants from the Nb roll from the final product.

6. The Nb-Nb or Nb/Havar target body/foil combination was used.

**Conclusions**

- **Ni** vs **Havar**
  - No yield difference
- **Ni** vs **Niobium**
  - No yield difference
- Careful with impurities in foil material
- Ti can be used, Va trapped in Sep-pak
- Niobium Havar preferred over Niobium-Niobium (experience)
- Nb-Nb or Nb/Havar target body/foil combination was used.

7. The University of Iowa [18F]NaF synthesis/purification system produced...
A multi-wire proportional counter for measurement of positron-emitting radionuclides during on-line blood sampling

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Introduction. Pharmacokinetic analyses of PET data require the exact determination of the input function, i.e. the determination of radioactivity concentrations in blood and plasma. Silicon diodes have been used for the measurement of blood radioactivity during PET imaging of rodents [1]. Conventional BGO detectors are widely used for blood radioactivity measurements in human studies (Allog Ab, Sweden). The purpose of the present study was to develop a flow-through multi-wire proportional counter with high sensitivity for positrons emitted from the commonly used positron emitters ¹¹C, ¹⁵O, ¹⁸F and ⁶⁸Ga. The proportional counter used in this work was a multi-wire flow-through detector filled with argon-methane gas (P10). The detector system was tested for measurements of ¹¹C, ¹⁵O, ¹⁸F and ⁶⁸Ga with mean positron energies in the energy interval 250 - 830 keV. Although the sensitivity of a gas-filled detector is low for 511 keV photons, positrons in the mentioned energy range will give an efficient signal when they interact with the detector fill gas. This type of detector requires only light lead shielding and the detector system can be installed very close to the animal or patient. The detector was used in studying time-activity curves in rats after i.v. injection of [¹⁵O]water. Our measurements indicate that the conventional proportional counter technique is useful for routine on-line analyses of blood samples obtained during PET studies of rodents and humans.

Materials and Methods. The multi-wire proportional counter (Fig. 1) was constructed in our laboratory. The electronics was purchased from Oxford Instruments Analytical Oy (Finland). The detector was equipped with an aluminium tube window (thickness 100 µm, diameter 13 mm, length 78 mm). The detector was filled with argon-methane gas (P10) and closed at 1060 mbar pressure. The counter electronics, preamplifier, linear amplifier and high-voltage power supply were all placed in the same aluminium box. The counter A/D converter and software for data collection were custom made. The detector was shielded with 50 mm of lead (25 kg). The background count rate was 2-4 cps. The stability and working conditions of the detector were tested with a ²⁴¹Am X-ray source. The performance of the multi-wire proportional counter was tested with known activities of ¹¹C, ¹⁵O, ¹⁸F and ⁶⁸Ga in water solutions. Oxygen-15 was produced with the Cyclone 3 cyclotron (IBA, Belgium) of the Turku PET Centre. [¹⁵O]water was produced with a Hidex Radiowater Generator (Hidex Oy, Finland). ¹¹C and ¹⁸F sources were produced with the MGC-20 and CC-18/9 cyclotrons of the Turku PET Centre. ⁶⁸Ga-chloride solution was obtained from a ⁶⁸Ge/⁶⁸Ga generator (Obninsk, Russia).

The rats were anesthetized with isoflurane. [¹⁵O]water (50 - 60 MBq, 500 µL) was manually injected via tail vein using a cannula. The blood sampling tube (Teflon, i.d. 0.5 mm, o.d. 1.0 mm) was installed through the detector. A peristaltic pump was used for blood sampling from the artery femoralis. The blood-flow rate through the detector was 500 µL/min. The animals were placed in a PET scanner (HRRT, Siemens) in order to get a reference input function from the heart left ventricle.

Results and Discussion. Fig. 2 shows the detector efficiency as a function of the mean energy of positrons. The radionuclides ¹¹C, ¹⁵O, ¹⁸F and ⁶⁸Ga in water solutions in the Teflon tubing (i.d. 1.5 mm, o.d. 2.5 mm) were used as positron sources. The graph reflects a linear relationship between the detector efficiencies and the mean energies for positrons of the four radionuclides (R² = 0.9982). The multi-wire proportional counter responses to ¹¹C, ¹⁵O, ¹⁸F and ⁶⁸Ga activities in the Teflon tubing are shown in Fig. 3. The detector response was linear for ¹⁵O in the range 5 - 80 kBq/mL with the i.d. 1.5 mm Teflon tubing and in the range 100 - 1300 kBq/mL with the i.d. 0.5 mm Teflon tubing. These ranges cover the radioactivity concentrations for both human and...
rat studies. Radioactivity levels in humans are about 20 times lower but still well above the signal to noise level.

Blood time-activity curves (arteria femoralis) were recorded for $[^{15}\text{O}]$water in rat studies. Our results show that a multi-wire proportional counter setup can be used for measurements of blood time-activity curves in PET studies with $[^{15}\text{O}]$water. Blood radioactivities with injection of $[^{11}\text{C}]$, $[^{18}\text{F}]$ and $[^{68}\text{Ga}]$ labelled tracers can also be measured. The detector efficiency for $[^{18}\text{F}]$ is low (0.9 - 4.0 %, depending on wall thickness and i.d. of sampling tubing), which limits the use of the detector in $[^{18}\text{F}]$ applications. Taking into account the abundance of positron decay of $[^{68}\text{Ga}]$ (86%) the actual detector efficiency for $[^{68}\text{Ga}]$ is slightly less than for $[^{15}\text{O}]$ (positron decay 100%).

**Fig. 1.** Exploded view of multi-wire proportional counter.

**Fig. 2.** Detector efficiency versus mean energy of positrons. Radionuclides $[^{11}\text{C}]$, $[^{15}\text{O}]$, $[^{18}\text{F}]$ and $[^{68}\text{Ga}]$ were used as positron sources.

**Fig. 3.** Multi-wire proportional counter response to $[^{11}\text{C}]$, $[^{15}\text{O}]$, $[^{18}\text{F}]$ and $[^{68}\text{Ga}]$ activities in Teflon tubing.

A multi-wire proportional counter for measurement of positron-emitting radionuclides during on-line blood sampling.

- Low background
- Low sensitivity for 51 keV photons
- Gas proportional counter = position sensitive detector
- Position-sensitive, position-sensitive detector
- Good geometry - flow-through detector
- Low 51 keV photon sensitivity
- High 51 keV photon background
- Low activity
Black line: measured blood curve; Red and green plot: measured blood curve with dispersion correction by Munk's and Iida's methods, respectively. Blue line: Image based input. by Nobu Kudomi. WTTCXIII, July 2010, Riso, Denmark.
Liquid target system for production of $^{86}\text{Y}$

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Introduction
Radionuclide $^{90}\text{Y}$ is a widely used tool for cancer therapy due to its suitable half-life, ready availability in high specific activities at relatively low cost. As it is a pure $\beta^-$ emitter with no associated $\gamma$ rays, there is a need for a tracer of $^{90}\text{Y}$. Promising candidate for these purposes is $^{86}\text{Y}$, since it is a positron emitter with half-life of 14.74 h. This radionuclide has been usually produced by the (p,n) reaction on enriched $^{86}\text{Sr}$ solid targets (SrCO$_3$) [1]. Handling and processing of those targets have several disadvantages. There is an interesting alternative to this approach, namely irradiation of a liquid target filled with aqueous solution of strontium nitrate [2]. It makes the target processing significantly easier and allows for automation of the process. Separation step can be also simplified, since usual electrolysis can be replaced by filtration of yttrium colloid in alkaline milieu [3].

Materials and methods
Strontium carbonate (96.3% $^{86}\text{Sr}$) was purchased from JV Isoflex, Moscow. Trace select ultra grade HNO$_3$, HCl and NH$_4$OH were purchased from Sigma-Aldrich. Puratronic grade (NH$_4$)$_2$CO$_3$ was purchased from AlfaAesar. High purity de-ionized water was used (specific resistance 18.2 M$\Omega$ cm).

The main part of target assembly was water cooled chamber (volume 2.4 ml) made out of pure Nb with Ti entrance foil. The concentration of irradiated solution of strontium nitrate was 35% (w/w). After irradiation, the solution was transferred to separation unit, target was washed with 10 mM nitric acid and water. All parts were collected together, pH was set to 10, filtered through PVDF filter and washed with 50 ml water. Filtrate was collected for Sr recovery. Yttrium was eluted from the filter with 10 ml 1M HCl. Eluate was evaporated to dryness and re-dissolved in 100–300 µl of 0.05M HCl as a stock solution for labelling.

Radionuclidic purity and activity of produced yttrium was measured with $\gamma$-ray spectrometry (HPGe detector GMX45, Ortec).

Content of chemical impurities (for $^{86}\text{Y}$ – Fe, Cu, Zn, Al, $^{86}\text{Sr}$) was determined via ICP-MS at the Institute of Chemical Technology Prague. We used two alternative methods for determination of the purity of the produced $^{86}\text{Y}$: differential pulse voltametry and labelling efficiency of DOTATOC. Ca. 40 MBq of $^{86}\text{Y}$ stock solution was mixed with 20 µg of DOTATOC in 300 µl of 0.4 M sodium acetate and heated in for 30 min at 80 °C. The labelling yield was monitored with TLC, using silica gel plates (Merck, Germany) developed with 10 % NH$_4$OAc aq. / MeOH = 1:1, $R_f$ = 0.46, and measured on a Cyclone autoradiography system (Perkin-Elmer).

Enriched $^{86}\text{Sr}$ was recovered by precipitation of strontium carbonate with ammonium carbonate [1]. The precipitate was decanted with water and acetone. Strontium carbonate was than dissolved in concentrated nitric acid, evaporated to dryness and re-dissolved in water for further irradiations.

Results
The yield of irradiation was 33 MBq/µAh. It corresponds well to the published data [1] and given content of $^{86}\text{Sr}$ in the target matrix. Radionuclide purity was excellent ($^{86}\text{Y}>99.4$ %, $^{87}\text{Y}<0.55$ %, $^{88}\text{Y}<0.025$ %). Separation yield was more than 90 %, about 4–5 % is left on the filter. Less than 0.1 % of $^{86}\text{Y}$ stays in filtrate. Also losses during evaporation of 1M HCl are under 1 %. Table 1 shows comparison of methods used for determination of copper concentration as a example of impurity. Labelling efficiency reflects well the copper concentration.
TABLE 1 Comparison of different analytical methods for estimating the copper content in the product

<table>
<thead>
<tr>
<th>Batch</th>
<th>Polarography [µg/ml]</th>
<th>ICP-MS [µg/ml]</th>
<th>Labelling efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.7</td>
<td>8.9</td>
<td>51.0 %</td>
</tr>
<tr>
<td>2</td>
<td>5.7</td>
<td>5.3</td>
<td>77.3 %</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>0.4</td>
<td>96.6 %</td>
</tr>
</tbody>
</table>

Recovery of enriched strontium was nearly quantitative, all solution used in recycling process were collected and reprocessed.

Discussion/Conclusion This work presents a compact, fully automated system for production of $^{86}$Y in activity and quality suitable for radiopharmaceuticals production. Transport of irradiated target matrix via a capillary to a separation unit minimizes problematic handling of radioactive material and losses of expensive enriched $^{86}$Sr. It also reduces significantly personnel radiation burden.

Acknowledgement The project was supported by Nuclear Physics Institute under the NPI research plan AV0Z10480505 and Ministry of Education, Youth and Sports, grant no. 2B061665.

90Y is a widely used radionuclide for cancer therapy due to its suitable half-life ($T_{1/2} = 64$ h, $I_{β^-} = 100\%$) and availability in high activities in carrier-free state at relatively low cost ($E_{β^- \text{max}} = 0.99$ MeV and availability in high activities due to its suitable half-life ($T_{1/2} = 64$ h). 90Y is a widely used radionuclide for cancer therapy.

**Yttrium-86**

**Decay Properties of 86Y**

<table>
<thead>
<tr>
<th>$E_γ$ (keV)</th>
<th>$I_γ$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>443.14</td>
<td>16.9</td>
</tr>
<tr>
<td>627.72</td>
<td>32.6</td>
</tr>
<tr>
<td>1076.64</td>
<td>83</td>
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<tr>
<td>1153.01</td>
<td>30.5</td>
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<tr>
<td>1724.9</td>
<td>63</td>
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<td>1854.35</td>
<td>32.6</td>
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<tr>
<td>1920.72</td>
<td>20.8</td>
</tr>
<tr>
<td>2277.35</td>
<td>33.3</td>
</tr>
</tbody>
</table>

- $E_{β^- \text{ave}} = 213.1$ keV
- $E_{β^- \text{max}} = 3141.3$ keV
- Half-life = 14.74 h

**System Design of the Liquid Target**

- Helium cooling of target foils made of pure Nb with Ti entrance foil
- Water cooled chamber (volume 2.4 ml)
- Automated operation (filling and processing)
- An integrated colimator at the beam entrance
- Suitable liquid target system

**Liquid Target System for 86Y Production**

- 90Y liquid target system.
- Water cooled chamber (volume 2.4 ml)
- Suitable liquid target system.
Production

Separation of $^{86}$Y

- Solution ready for labelling
  - Dissolved in 100-300 ml of 0.05 M HCl (stock)
  - Elute was evaporated to dryness and redissolved in 10 ml 1 M HCl

- Elution was collected for Sr recovery
  - Filtrate was washed with 10 ml of water
  - pH was set to 10, filtered through PVDF filter
  - Irradiated solution was transferred to separation unit

- Solution was transferred to separation unit
  - Target was washed with 10 ml nitric acid
  - Filtrate was collected for Sr recovery
  - Eluate was evaporated to dryness and redissolved in 100-300 μl of 0.05 M HCl

Cyclotron irradiation on beam line of U-120M isochronous cyclotron, and the content of $^{86}$Sr in the target matrix, which corresponds well with the published data for $^{86}$Sr ($^{99}$Sr) and $^{99m}$Tc. The achieved thick target yield was 33 MBq/µAh.

Typical irradiation conditions were 1 - 2 hours, 10 - 15 µA, AECB 500 - 1000 MBq.

Liquid Target System

Liquid Target System
Separa
tion of 86Y

Recovery of 86Sr

Methods for quality control of 86Y

SLT (standard labelling test) based on the determination of the labelling efficiency of the product, 86Y with DOTATOC (DOTA-Tyr3-Octreotide). 20 µg of DOTATOC in 300 µl of 0.4 M sodium acetate, heated for 30 min at 80 °C, Cu detm. by polarography [µg/ml], batch No. Cu detm. by ICP-MS [µg/ml]. Sensitivity of SLT

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Cu detm. by</th>
<th>ICP-MS [µg/ml]</th>
<th>Polarography [µg/ml]</th>
<th>Sensitivity of SLT [%]</th>
</tr>
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<tr>
<td>93.6</td>
<td>0.5</td>
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<tr>
<td>73.3</td>
<td>5.3</td>
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<th>Batch No.</th>
<th>Cu detm. by</th>
<th>ICP-MS [µg/ml]</th>
<th>Polarography [µg/ml]</th>
<th>Sensitivity of SLT [%]</th>
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</thead>
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<tr>
<td>225</td>
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<td>5.3</td>
<td></td>
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</tr>
<tr>
<td>30.5</td>
<td>--</td>
<td>93.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

According to the sensitive reactivity of DOTATOC with various metal impurities in the product, 86Y, SLT is a suitable method for quality control. According to the sensitive reactivity of DOTATOC with various metal impurities in the product, 86Y, SLT is a suitable method for quality control.
Conclusion

- Fully automated system for production of 86Y in amounts and quality appropriate to usual requirements for labelling very fast and efficient
- Possibility of transport of irradiated target matrix via a capillary to a separation unit
- Minimizes handling of radioactive material and losses of expensive enriched 86Sr
- It also reduces significantly personnel's radiation burden
- Very fast and efficient
- Fully automated system for production of 86Y in adequate amounts and quality appropriate to usual

Acknowledgements

Department of Radiopharmaceuticals

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MSc. J. Štursa

Assoc. Prof. František Melichar, D.Sc.

The project was supported by the Academy of Sciences of the Czech Republic under the NPI research plan AV0Z10480505 and by the Ministry of Education, Youth and Sports, grant no. ZB061665.
Can Half-life Measurements Alone Determine Radionuclidic Purity of F-18 Compounds?

THOMAS JØRGENSEN1, MILLE ANKERSTJERNE MICHEELSEN2, AND MIKAEL JENSEN1

1Hevesy Lab, Risoe-DTU, Technical University of Denmark, DK-4000 Roskilde, Denmark
2Dept. Clinical Physiology and Nuclear Medicine, Koege Hospital, DK-4600 Koege, Denmark

Current revisions of monographs for F-18 pharmaceuticals in the European Pharmacopoeia call for a radionuclidic purity (RNP) of or better than 99.9%. If (debatably) this requirement is put at end of shelf life, typically 10 hours EOS, the requirement can be very difficult to assure by actual measurements, if all possible radionuclide contaminations should be considered. Clearly, gamma spectroscopy can do much, but only if the contaminant has strong gamma emissions above 511 keV. We have tried to analyse mathematically to what extent that half-life measurements alone can establish RNP for F-18 compounds. The method could in principle be extended to other isotopes. The current method of half-life determination in the Ph.Eur with two measurements at 6h interval is not sufficient nor effective for testing the required RNP level.

We present a theoretical model leading to a practical procedure for testing RNP of F-18 compounds with a confidence of 95%.

We look at a batch of F-18 contaminated with one other isotope with a half-life of $\beta T_{18F}$. The contamination level is $\alpha$ at time 0. The recorded number of counts, $N(t)$, for a sample, that contains one other isotope, is described by

$$N(t) = \frac{N(0)}{1 + \alpha} \left( \frac{1}{2} \right)^{t/T_{18F}} + \alpha \left( \frac{1}{2} \right)^{t/\beta T_{18F}}$$

with $N(0)$ as the total number of counts at $t = 0$.

RNP is defined by the expression

$$RNP = \frac{A_{18F}}{A_{tot}} \Rightarrow RNP(0) = \frac{1}{1 + \alpha} \simeq 1 - \alpha, \quad \alpha = \frac{A_{18F}(0)}{A_{other}(0)}$$

If all measured impulses are converted to initial point values ($t = 0$ min.), the curve should give a straight line with constant value (the initial value of counts) for a pure F-18 sample. Due to the stochastic nature of the F-18 nuclide, the data points will deviate from this line. If the sample is contaminated the curve will increase rapidly. The condition for the pure and unpure curves to be separated is, the difference of the
measurements must be equal to (or larger than) the sum of 1.96 standard deviations for the two curves (confidence of 95%). An approximated expression for the limit of $\alpha$ is

$$\alpha \simeq \frac{3.92 \left(\frac{1}{2}\right)^{t/T_{18F}}}{\sqrt{N(0)} \left[\left(\frac{1}{2}\right)^{t/\beta T_{18F}} - \left(\frac{1}{2}\right)^{t/T_{18F}}\right]}$$

In the figure below a contour plot of $\text{RNP}(0)$ ($\simeq 1 - \alpha$) is plotted against $\beta$ and recording time for a total amount of initial counts of $10^6$ (the limit of the Liquid Scintillation Counter). We can readily see that after 6 hours, we cannot detect a contamination with $\alpha \leq 0.1\%$ ($\text{RNP}(0) \geq 99.9\%$), but after another 6 hours we should be able to detect a $\text{RNP}(0)$ of 99.95% or smaller (for $\beta = 20$). However at very low $\beta$ values there is a strong divergence in the time needed to detect these small RNP’s, which in practice sets a lower limit for a detectable $\beta$. In the case below this lower $\beta$ value is $\sim 3$.

![RNP−diagram for F18 with N0 = 1000000](image)

Figure 1: RNP plotted against $\beta$ and recording time. The confidence is 95%.

In the above method, the lower level of the recording time and $\beta$ is set by the inherent poisson noise. By using a series of recordings in a method that looks at the mean, rather than just two single points (start and stop), the statistical noise is lowered and consequently the lower limit of $\beta$ is reduced to approximately 1.5 (recording time of $\sim 800$ min). In conclusion we cannot find any contaminating isotope with half-lives shorter than 1.5 times 109.77 min. for $\text{RNP}(0) = 0.9990$ and a confidence of 95%.
18F as an example

Determining the RNP of a 18F batch with confidence is non-trivial...

Current accepted method uses half-life determined from decay over 6+6 hours...

We investigate the boundaries of validity for this method and introduce simple methods that both improve accuracy as well as optimize time consumption.

A possible byproduct from silver (Ag) is 107Cd.

107Cd has a half-life that is 3.6 times longer than 18F.

With 1% impurity at production time the pink and purple lines illustrate how the impure and pure samples behave.

It is clear that this method would not be able to distinguish the impurity from 18F before well after 800 minutes.

We can improve on that...

A possible byproduct from silver (Ag) is 107Cd.

107Cd has a half-life that is 3.6 times longer than 18F.

With 1% impurity at production time the pink and purple lines illustrate how the impure and pure samples behave.

We can improve on that...

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We can improve on that...

A possible byproduct from silver (Ag) is 107Cd.

107Cd has a half-life that is 3.6 times longer than 18F.
We compare a pure and an impure decay curve. Both are converted into initial point values (multiplied by \((\frac{1}{2}) \times (\frac{t}{T})\)).

First we identify the time where the separation of the two curves (pure and impure) becomes statistically significant. This is the minimum time our sample needs to decay.

Significance (95%) occurs when:

\[
\frac{d[N]}{d[t]} \times 3.2 \times (\frac{t}{T}) \times (0.96) \times (0.1) = RNp - 1
\]

If we consider only the Poisson noise in the system, we can write up the relation between RNP, \(t\) and \(p\). This is approximately given by:

\[
(1)^d N \times 0.96^d \times 1 + (1)^d N = (1)^d N \times 0.96^d 
\]

First we identify the time where the separation of the two curves (pure and impure) becomes statistically significant.
Simple method 1

From hereon it's a simple YES/NO answer e.g.

If the answer is YES – then we have a 95% confidence that our sample is not contaminated more than the limit set by RNP...

Some points to stress:

Simple method 1

Simple method 2

We can increase efficiency (lower detectable $\beta$ and $t_c$ at given $RNP$) by taking more data points in a time frame and use the mean and standard deviation of the mean.

This way statistical noise is lowered to:

$$\bar{x} \pm \frac{\sigma}{\sqrt{n}}$$

where $n$ is the number of data points.

For lower $RNP$ – impurity is detected earlier, so we find every impurity $\lt RNP$ (depending on $RNP$)...

Lower detection limit for $\beta$ (depending on $RNP$)...

$\beta$ dependence only at small $p$ (but strong here)...

Simple method 2

From hereon it's a simple YES/NO answer e.g.

\[
\left( \frac{1}{N} \right) N > (0) N + (0) N < (1) N
\]
Methods have been verified computationally but not yet experimentally.

<table>
<thead>
<tr>
<th>I</th>
<th>100min</th>
<th>1000min</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>50min</td>
<td>250min</td>
</tr>
<tr>
<td>Current</td>
<td>1000min</td>
<td>1500min</td>
</tr>
</tbody>
</table>

1. Example: 107Cd
   - Ag targets by-product
   - Different half-life, but impossible to distinguish before 800 mins

2. HPGe spectroscopy need
   - Requirement: 0.1% RNP: not trivial (if possible) using HPGe

13
PC-controlled radiochemistry system for preparation of NCA $^{64}\text{Cu}$

Adam Rebeles R., Van den Winkel P., De Vis L., Waegeneer R.
Cyclotron Laboratory, Vrije Universiteit Brussel (VUB), Brussels, Belgium

Due to the rapid increase of the use of nuclear medicine techniques in modern clinical diagnosis and in a selected series of therapies, researchers’ efforts are focusing on the standardization and optimization of different production routes for a series of emerging radioisotopes like $^{64}\text{Cu}$, $^{67}\text{Cu}$, $^{114m}\text{In}$, $^{211}\text{At}$.

In particular the EC/$\beta^+/\beta^-$ decay of $^{64}\text{Cu}$ makes it a promising candidate for both PET imaging and internal targeted radiotherapy. In the last decades several groups studied different production routes like for this radio nuclide, i.e. $^{64}\text{Ni}(p,n)$, $^{64}\text{Ni}(d,2n)$, $^{64}\text{Zn}(d,2p)$.

Taking into account the wider availability of the medium energy proton beam machines, the (p,n) reaction on $^{64}\text{Ni}$ seems to be the most attractive one, although $^{64}\text{Zn}(d,2p)$ may be considered as an alternative where lower activity is necessary, as it may require less investment in enriched material.

The production of large activities of $^{64}\text{Cu}$ on regular basis requires a fast and reliable chemistry system. Based on the experience gathered in the last decades in our laboratory we present here an efficient, remote controlled chemistry system for production of the non carrier added $^{64}\text{Cu}$ via $^{64}\text{Ni}(p,n)$ reaction.

To avoid excessive investment in a gold target carrier, a good practice is to coat the copper target carrier with a thin inert material, i.e. 5-6 $\mu$m of gold, followed by electrodeposition of the $^{64}\text{Ni}$ target layer. In that way, the cross contamination of the non carrier added $^{64}\text{Cu}$ with the copper present in the target carrier is excluded. In general the irradiations are performed with protons having incident energy of about 15 MeV, and, depending on irradiation condition, may lead to curie amount of induced activity of $^{64}\text{Cu}$.

To reduce the thickness of the $^{64}\text{Ni}$ target layer, and, as consequence, to minimize the problems related with the plating and dissolution of the target layer, a low beam/target angle geometry (6 degrees) is desired. Nevertheless, the separation of target / activation product is required. Upon irradiation, our chemistry system proposes the dissolution of the $^{64}\text{Ni}$ layer in a heated flow trough stripper by means of diluted nitric acid. Next, the non carrier added $^{64}\text{Cu}$ is selective extracted into benzene (containing 0.1 M benzoylecetone) at pH 4.5, leaving the enriched $^{64}\text{Ni}$ and possible Co induced isotopes in the inorganic phase. The back extraction of $^{64}\text{Cu}$ is done in a small volume of diluted hydrochloric acid (6 N). The final purification step is achieved using an anion exchange column Dowex 1X8. Finally, the NCA $^{64}\text{Cu}$ is eluted with a small volume (10 ml), diluted hydrochloric acid (1 N).

The overall yield of the chemistry is estimated as being higher than 95% with a short total chemistry time, less than 2 hours, while the gold plated target carriers can be reused as long as the thin gold layer remains intact, meaning that scratches and cracking by careless handling are avoided.
PC-controlled radiochemistry system for preparation of $^{64}$Cu

**Introduction**

- EC/β⁺/β⁻ decay of $^{64}$Cu: promising candidate for PET imaging
- Internal targeted radiotherapy

**Different production routes**

- $^{64}$Ni(p,n)$^{64}$Cu
- $^{64}$Ni(d,2n)$^{64}$Cu

**Chemistry – separation of NCA isotope**

**Target preparation**

- IBA Cyclone 30 solid target carrier
- Copper preplated with a thin Au layer (5 μm)

**Plating baths:**

- Watts (NiSO₄·6H₂O, NiCl₂·6H₂O, H₂BO₂)
- Chloride bath (NiCl₂·6H₂O, H₂BO₂)
- Sulfamate (Ni(NH₂SO₃)₂, H₃BO₃)
- Alkaline bath (NiSO₄·6H₂O, (NH₄)₂SO₄, NH₃, pH 9-11)

**Target preparation**

- Example of gold preplated target carrier
Chemistry – separation of NCA ⁶⁴Cu

- Dissolution of the ⁶⁴Ni layer in diluted nitric acid
- Selective extraction of ⁶⁴Cu into tert-Butyl Methyl Ether (containing 0.1 M benzoyl trifluoroacetone at pH 2.7-3)
- Enriched ⁶⁴Ni and possible Co induced isotopes remain in the inorganic phase (NH₄NO₃ - HNO₃)
- Other solvents like isooamyl acetate or ethyl acetate may be used.

Surface area granulometry (50x)

| Good | Poor |

Example of nickel plated target

Target preparation
Chemistry–separation of NCA 64Cu

- Back extraction of 64Cu is done in a small volume of diluted hydrochloric acid (6N).
- The NCA 64Cu is eluted with a small volume of diluted hydrochloric acid (0.05N).
- Final purification step – anion exchange column Dowex 1X8.
- The NCA 64Cu is eluted with a small volume of diluted hydrochloric acid.


Conclusions

Based on the experience gathered in our laboratory in developments on solid target chemistry systems, a robust modular system for the separation of NCA was developed.

Analytical separation techniques:
- solvent/solvent extraction
- ion exchange chromatography
- solvent extraction

High chemistry yield >95%
Total chemistry time <2 hours

The user friendly Visual Basic interface allows the full control over each step of the chemistry with a minimum risk of operator errors and of radiation exposure for the staff.

Acknowledgements

The authors would like to thank the IBA - Ion Beam Applications - Louvain-la-Neuve company for providing the enriched Ni.
1. Extracted in ion exchanger
2. Reuse of golden plated back
   - Reused 10x without big activation
   - Careful: Cu/Au dissolve in each other. Hotspots = activation
   - Worst: Cu dissemination = low specific activity

WITC XIII – Presentation Discussions
Iodine-124 (T_{1/2} = 4.18 d) and copper-64 (T_{1/2} = 12.7 h) are two very important radionuclides for radiopharmaceuticals production for preclinical research in a positron emission tomography (PET). The method for producing $^{124}$I was based on a dry distillation of $^{124}$I from a solid $[^{124}$Te]$TeO_2$ target technique. The platinum target disk was used as a base for TeO$_2$ melt and irradiated on COSTIS target station installed at the end of the external beam line of the IBA Cyclone 18/9 cyclotron. The target station was equipped with a 25 µm aluminum or 250 µm Nb window foil in front of the target, which results in a final beam energy of 17.7 or 13.5 MeV respective.

The $^{64}$Ni(p,n)$^{64}$Cu reaction route was used for $^{64}$Cu (T_{1/2} = 12.7 h) preparation because its entrance channel is accessible at low energies and yield of the reaction is quite high. Disadvantage of the reaction used is high price of enriched $^{64}$Ni. Gold and platinum targets were used for a thick $^{64}$Ni target preparation by electro deposition. Because the external beam line of the cyclotron has no beam diagnostic devices, several aluminum plates were irradiated in the COSTIS target station with a 5 µA proton beam for 5 min with different settings for the beam focusing quadrupole magnets. After 15 minutes decay time the plates were scanned by a TLC scanner along the horizontal and vertical central axes of the plates in order to visualize the beam shape. The settings providing the most homogeneous beam spot on the target were selected and used further for the actual target irradiations. The radionuclidic purity of the product was determined by γ-spectrometry.
Carbon-11 (T_{1/2} = 20.39 min) was prepared in the form of methane in aluminum target made by IBA. Total irradiated volume of the gas mixture (90% N₂ +10%H₂) was 50 cm³. Reaction used at irradiation was \(^{14}\text{N}(p,\alpha)^{11}\text{C}\). Aluminum and niobium windows were used during irradiation. The irradiations were performed first without and then with niobium foil inside the target with purpose to eliminate the surface influence of aluminum. During the optimization of irradiation, different pressures of gas were tested as well as the beam currents. Produced methane was sorbed on Carboxen 1000 column at the temperature of -150 °C on TracerLab FXC module made by GE Medical Systems.

Acknowledgement

The authors are indebted to IAEA Vienna for financial support during realization of TC Project SLR/4/010 Production of the Positron Emitting Radionuclides and the work connected with Cu-64 production was supported by the Slovak Research and Development Agency under the contract No. VMSP-P-0075-09
Production of \(^{124}\text{I} \) and \(^{64}\text{Cu} \) and \(^{[11]}\text{C} \)O\(_2\) in 1/8 MeV cyclotron.

Production of \(^{124}\text{I} \) and \(^{64}\text{Cu} \) and \(^{[11]}\text{C} \)O\(_2\) in 1/8 MeV cyclotron.

Preparation and characterization of nickel targets for cyclotron production of \(^{64}\text{Cu} \).

Preparation of \(^{64}\text{Cu} \) targets for cyclotron production of \(^{64}\text{Cu} \).

Preparation and characterization of nickel targets for cyclotron production of \(^{64}\text{Cu} \).

The aim of this study was development an electroplating method for preparation of nickel targets suitable for COSTIS assembly. The desired product is a thick layer of metallic nickel on a gold disc.

Production of \(^{64}\text{Cu} \) can be described in these steps: • Preparing of a target by electrodeposition of a galvanostatic or potentiostatic deposition of nickel on a thick gold or platinum target • Irradiating the target • Dissolving the target material and separation of \(^{64}\text{Ni} \) and \(^{64}\text{Cu} \) • Preparing of a \(^{64}\text{Cu}X \) solution

The bath, containing 0.5 g NiSO\(_4\)·6H\(_2\)O, 0.056 g H\(_3\)BO\(_3\) and 0.5 g NH\(_4\)Cl in 5 ml H\(_2\)O, was brought to pH 9. Simultaneously, NH\(_4\)Cl/NH\(_4\)OH buffer was added to keep pH at 9 during the whole electrodeposition process. As the electroplating process continued, the color of the electrolytic bath turned from dark blue to colorless. The full loss of color indicates that electrodeposition is finished. The efficiency of electroplating in this bath was 96%. Decrease of nickel in the bath during the electrodeposition process was as follows: 96%.
The yield of $^{64}\text{Cu}$ in the EOB time.

<table>
<thead>
<tr>
<th>Current [µA]</th>
<th>Yield EOB [mg]</th>
<th>Yield EOB [mCi/µAh]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3-4</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>2.6-4.2</td>
<td>60-110</td>
<td></td>
</tr>
<tr>
<td>2.77</td>
<td>5</td>
<td>100</td>
</tr>
</tbody>
</table>

Our results:

- $^{64}\text{Ni}$ plated, 64Ni plated, Current Yield EOB

Gamma spectrum of the $^{64}\text{Cu}$ target after irradiation.

PET scan of the $^{64}\text{Ni}$ target after irradiation.

PET scan on a mini-PET system.

Target Irradiation System (COSTIS) Compact Solid Target Irradiation System.

Preparation and characterization of nickel $^{64}\text{Cu}$ targets for cyclotron production of $^{64}\text{Cu}$.


60-110 15-30 2.6-4.2

PET scan on a mini-PET system.

Our results:

- $^{64}\text{Ni}$ plated, Current Yield EOB

Gamma spectrum of the $^{64}\text{Cu}$ target after irradiation.

PET scan of the $^{64}\text{Ni}$ target after irradiation.

PET scan on a mini-PET system.

Target Irradiation System (COSTIS) Compact Solid Target Irradiation System.
Production of 11C\[CH4\]

The target, which results in a final beam energy of 17.7 MeV, the target station was equipped with a 25 mm aluminium window foil in front of the target. The foil was installed on COSTIS target station installed at the end of the external beam line of the IBA Cyclone 18/9 cyclotron. The 124I target disk was used as a base for TeO2 target technique. The platinum target disk was used as a base for 124I target technique. The platinum target disk was used as a base for TeO2 target technique. The target station was equipped with a 25 µm aluminum window foil in front of the target, which results in a final beam energy of 17.7 MeV.

Production of 124I

The method for producing 124I was based on a dry distillation of 124Te from a solid [124Te]TeO2 target technique. The platinum target disk was used as a base for TeO2 melt and irradiated on COSTIS target station installed at the end of the external beam line of the IBA Cyclone 18/9 cyclotron. The target station was equipped with a 25 µm aluminum window foil in front of the target, which results in a final beam energy of 17.7 MeV.

Beam current (10-30 μA)

Input gas pressure (from 10–30 bar)

Modified parameters:

- With quartz glass and Nb foil inside (will be realized in near future)
- With Nb foil inside
- Without changes (Al-body)

We used standard aluminium-body target (50 cm²) made by IBA in these three modifications:

- Standard target (Al-body) for production of 11C from IBA
- Without changes (Al-body)
- With tube made from Nb foil inside
- With tube made from Nb foil inside
- With tube from quartz glass inside (will be realized in near future)

We used standard aluminium-body target (50 cm²) made by IBA in these three modifications:

- Standard target (Al-body) for production of 11C from IBA
- Without changes (Al-body)
- With tube made from Nb foil inside
- With tube made from Nb foil inside
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We used standard aluminium-body target (50 cm²) made by IBA in these three modifications:
### Production of 124I

<table>
<thead>
<tr>
<th>Peak Nuclide E, keV</th>
<th>Intensity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>123I</td>
<td></td>
</tr>
<tr>
<td>124I</td>
<td></td>
</tr>
</tbody>
</table>

- **1** 123I 158.97 83.3
- **2** 123I 247.96 0.071
- **3** 123I 281.03 0.079
- **4** 123I 346.35 0.126
- **5** 123I 440.02 0.428
- **6** 123I 505.33 0.316
- **7** 124I 511.0 46.0
- **8** 123I 528.96 1.39
- **9** 123I 538.54 0.382
- **10** 124I 602.72 62.9
- **11** 124I 624.57 0.083
- **12** 124I 645.82 0.988
- **13** 124I 662.4 0.056
- **14** 124I (annih.) 511.0 46.0
- **15** 123I 722.78 10.35
- **16** 123I 735.78 0.062
- **17** 123I 783.59 0.059
- **18** 124I 968.22 0.435
- **19** 124I 1045.0 0.441
- **20** 124I 1325.50 1.561
- **21** 124I 1376.0 1.75
- **22** 124I 1488.9 0.199
- **23** 124I 1509.49 3.13
- **24** 124I 1559.8 0.165
- **25** 124I 1691.02 10.88

### CONCLUSIONS

1. More than 95% efficiency of the electroplating deposition of $^{64}$Cu.
2. First irradiation with yield 2.8 mCi/microAh.
3. Future – radiochemical separation of $^{64}$Cu and $^{64}$Ni.
4. In the future continue with Quartz-tube.
5. Successful synthesis of $^{124}$I.
6. Works were stopped for stopping financial support.
7. Future – association separation of $^{64}$Cu and $^{64}$Ni.
8. More than 90% efficiency of the electroplating deposition of $^{64}$Cu.

### Acknowledgement
The authors are indebted to IAEA Vienna for financial support during realization of TC Project SLR/4/010 Production of the Positron Emitting Radionuclides and APVV Slovakia for financial support project VMSP P-0075-09.
A simple and flexible device for LabView applications
A. Hohn, E. Schaub, S. Ebers, R. Schibli

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LabView is the state of the art programming tool for measurement and control applications and the market offers a wide range of sophisticated data acquisition tools (DAQ). However, for radionuclide separation purposes a high sample rate and a high accuracy is often not necessary. Therefore, we were looking for a low-cost DAQ with a USB interface for maximum flexibility and sufficient I/O lines. Finally, we decided to use the USB-6008 by National Instruments. This small size, low-cost DAQ has 8 analog inputs, 2 analog outputs and 12 digital I/O lines. Mounted on a print together with a transistor for each digital line (Fig. 1) this DAQ is the base of our device.

Fig. 1   USB DAQ mounted on a print

For the portable version of our device (Fig.2) the USB DAQ module is mounted in a desktop rack together with a power supply module (24 V, 120 W) and a relay module containing 12 relays. Additional slots are available for other modules. Each single module can be replaced easily in case of a failure. If more slots are needed all modules can be mounted as well in a 19” rack.

Fig. 2   Portable device for LabView applications with a mounted PC
Several additionally modules like a temperature module and a pulse-width-modulator (PWM) are available. An amplifier for pH measurements and for activity measurements with photodiode radiation detectors (Fig.3) was developed. This amplifier with a variable gain is a modified version of the amplifier described by Zeisler et al. Another module is a mini PC including a hard drive. In combination with a touch screen the device can be used without an external PC or notebook.

Fig. 3   Amplifier with photodiode radiation detector

The described devices are used in our group for the routine production of radionuclides (\(^{89}\text{Zr}\) and \(^{64}\text{Cu}\)) for several years without any problems.

Literature:

A simple and flexible device for LabView applications

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WTTC XLI
A. Hohn, E. Schaub, S. Ebers, R. Schibli

Data Acquisition Tool (DAQ)

Amplifier for activity and pH measurements

Computer

- Alix3d single board PC
  - CPU: 500 MHz AMD Geode LX800
  - DRAM: 256 MB DDR DRAM
  - Storage: 8 GB CompactFlash
  - OS: Windows XP

Data Acquisition Tool (DAQ)

- USB-6008 by National Instruments
  - 8 analog inputs, 2 analog outputs and 12 digital I/O lines
  - USB-DAQ mounted on a print for plug and play
  - Digital I/O lines, 2 analog outputs and 12 analog inputs by National Instruments
89Zr-Separation with LabView
Three years experience in operation and maintenance of the $[^{18}\text{F}]\text{F}_2$ proton target at the Rossendorf Cyclone® 18/9 cyclotron

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Introduction
An increasing demand of radiopharmaceuticals based on electrophilic reaction with $[^{18}\text{F}]\text{F}_2$ gas (for instance $[^{18}\text{F}]\text{FDOPA}$) led to an upgrade of the IBA $[^{18}\text{F}]\text{F}_2$ gas target system in summer 2007. The more than 10 years operated $[^{18}\text{F}]\text{F}_2$ deuteron target $[^{20}\text{Ne}(p,\alpha)^{18}\text{F}]$ was not able to meet the increasing requirements in terms of activity anymore and was thus replaced by an IBA $[^{18}\text{F}]\text{F}_2$ proton gas target $[^{18}\text{O}(p,n)^{18}\text{F}]$ based on the so-called “double-shot” irradiation method by R.J. Nickles [1]. The upgrade itself was done by IBA.

We run the Cyclone® 18/9 cyclotron in routine operation for more than 14 years. One of the specific features of the Rossendorf PET Center is the Radionuclide transport system (RATS) [2], 500 m in length that bridges the distance from the cyclotron to the radiopharmaceutical laboratories. The activity at the end of bombardment (EOB) is calculated taking in account the transfer time and experimental data of activity losses (about 30%) in the transfer tube [2].

The target and its supply
The $[^{18}\text{F}]\text{F}_2$ proton gas target is connected directly to the vacuum chamber of the cyclotron inside the return yoke. Target body: aluminium; target volume: 35 cm$^3$ of conical shape; target window: aluminium, thickness 500 µm; vacuum window: titanium, thickness 12.5 µm.

As target gases are used for the first bombardment: $^{18}\text{O}$ (enrichment: > 97%; cartridge volume: 75 ml, gas volume: 5250 ml, pressure: 70 bar, manufacturer: Cambridge Isotopes Laboratories, Inc./USA, distributor: ABX/Germany) and for the second bombardment: (Ne/2% $^{18}\text{F}_2$), filled up with pure Ne (both: Air Liquide/Germany) to achieve (N$^2_2$/0.45% $^{18}\text{F}_2$).

Experience in operation and maintenance of the target
First bombardment: $^{18}\text{O}_2$: 20 - 22 bar, 40 or 60 or 80 minutes at 22 µA target current
Second bombardment: Ne/$^{18}\text{F}_2$: 20 - 22 bar, 15 minutes in each case at 22 µA

Hints for operation:
- Keep the target cavity in standby always under (Ne/$^{18}\text{F}_2$) atmosphere
- Prior to the first bombardment of the $[^{18}\text{F}]\text{F}_2$ production a pre-irradiation (5 minutes, 10 µA) with (Ne/$^{18}\text{F}_2$) of the irradiated gas to the radiopharmaceutical laboratory for the conditioning of the target cavity and the transfer tube is useful.
- After deposition of the irradiated $^{18}\text{O}$ gas into the liquid nitrogen cooled trap: A careful pump down of the target cavity for some minutes is mandatory before filling it for the second bombardment to prevent the formation of $[^{18}\text{F}]\text{F} – \text{O}$ species.
- One $^{18}\text{O}$ cartridge is sufficient for (100 – 120) irradiations. An average gas loss of less than 5% per bombardment has to be compensated by filling from the $^{18}\text{O}$ cartridge. It is possible to use the $^{18}\text{O}$ gas (from the cooling trap and the cartridge) until the residual pressure of the $^{18}\text{O}$ cartridge is around 10 bars.

A slight but permanent drop in the target yield is an indication for a target cleaning procedure to be necessary (see Fig. 1).

After target opening it is observed that the surface of the target cavity did not have a metallic sheen anymore. We added a grinding procedure of the cavity with very fine sand paper to the IBA cleaning procedure [3]. After the cleaning the surface of the cavity should look as metallic. We found this procedure necessary to be done after 100 to 120 runs and perform it once a year.

The handling of the target system is not easy because the results of any kind of changes are often not well reproducible. The highly-reactive $[^{18}\text{F}]\text{F}_2$ gas at the µmol level is difficult to handle due to the large surfaces of the target cavity, the transfer tube and the synthesis module.
Fig. 1: \([^{18}\text{F}]\text{F}_2\text{BOS}\) and \([^{18}\text{F}]\text{FDOPA}\) activity yields in 2007 – 2009, TC: target cleaning, line: \([^{18}\text{F}]\text{FDOPA}\) yield

Results
- Dependence of produced \([^{18}\text{F}]\text{F}_2\text{BOS}\) activity on the irradiation time of first bombardment:
  - 40 minutes - 16 ± 2 GBq, 60 minutes - 20 ± 3 GBq, 80 minutes - 20 ± 5 GBq — no increase of \([^{18}\text{F}]\text{F}_2\text{BOS}\) activity increasing the irradiation time of first bombardment from 60 to 80 minutes,
- Besides the produced absolute \([^{18}\text{F}]\text{F}_2\) activity, the reactivity of the \(\text{F}_2\) gas is important for the \([^{18}\text{F}]\text{FDOPA}\) activity yields.
- Target cleaning is recommended if:
  - The absolute \([^{18}\text{F}]\text{F}_2\text{BOS}\) activity yield drops down to about 15 GBq or
  - The \([^{18}\text{F}]\text{FDOPA}\) yield is near or below 15 %.

The advantages of the new \([^{18}\text{F}]\text{F}_2\) proton target are:
- Higher efficiency in terms of \([^{18}\text{F}]\text{F}_2\) activity and resulting \([^{18}\text{F}]\text{FDOPA}\) activity yields,
- Operating conditions far from limitations of the target current; that results in less wear of the cyclotron.

A comparison of the \([^{18}\text{F}]\text{F}_2\) deuteron and proton targets is given in the table.

<table>
<thead>
<tr>
<th></th>
<th>Deuteron target</th>
<th>Proton target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max. target current</td>
<td>18 µA</td>
<td>30 µA</td>
</tr>
<tr>
<td>Irradiating conditions</td>
<td>120 min</td>
<td>First bombardment: 60 min</td>
</tr>
<tr>
<td>average /common current</td>
<td>18 µA</td>
<td>Second bombardment: 15 min</td>
</tr>
<tr>
<td>(A^{\text{EOB}}), GBq</td>
<td>7 - 11</td>
<td>34 ± 5</td>
</tr>
</tbody>
</table>

References
[2] St. Preusche, F. Füchtner, J. Steinbach, J. Zessin, H. Krug, W. Neumann; Long-distance transport of radionuclides between PET cyclotron and PET radiochemistry,

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Cancer Research

Three years experience in operation and maintenance of the $^{18}\text{F}^2$/$^{18}\text{O}^2$-gas target at the Rossendorf Cyclone® cyclotron

1. Introduction

Why change from $^{18}\text{F}^2$-deuteron target to $^{18}\text{F}^2$-proton target?

• increasing demand of radiopharmaceuticals based on electrophilic reaction with $^{18}\text{F}^2$ gas (for instance $^{18}\text{F}$-FDOPA)

• Not enough $^{18}\text{F}^2$ activity with $^{18}\text{F}^2$-deuteron target $^{20}\text{Ne}(d,\alpha)^{18}\text{F}$

• Routine operation of Cyclone® 18/9 for 14 years

2. The target and its supply

$^{18}\text{F}^2$-gas target connected directly to vacuum chamber

- target window: aluminium, thickness 500 µm
- target volume: 35 cm³ of conical shape
- target body: aluminium
- vacuum window: titanium, thickness 12.5 µm

3. Experience in operation and maintenance of the target

5. References

6. Some more details

St. Preusche, F. Füchtner, J. Steinbach

Institute of Radiopharmacy

St. Preusche et al.

www.fzd.de

Member of the Leibniz Association
3. Experience in operation and maintenance of the target

Irradiating conditions

1st bombardment: 18O2: 20 - 22 bar, 40 or 60 or 80 minutes at IT = 22 µA

2nd bombardment: Ne/F2: 20 - 22 bar, 15 minutes at IT = 22 µA

Hints for operation

- Use of 18O gas (trap, cartridge) until residual pressure of 18O cartridge: 10 bars
- Avoiding gas loss by bombardment of primary target
- Switching off 100 - 120 minutes before 18O carbide to 18O gas
- Catching up of the target cavity for some minutes, incl. Ne-flush (20 sec)
- Releasing the primary target gas (F2, O2)
- Preparing the target cavity for bombardment
- Condition of the target cavity and the 500 m transfer tube prior to bombardment
- Keep the target cavity in standby always under (Ne/F2) atmosphere

Handling conditions

- 1st bombardment: Ne/F2: 20 - 22 bar, 15 minutes or 40 or 60 minutes at IT = 22 µA
- 2nd bombardment: 18O: 20 - 22 bar, 40 or 60 or 80 minutes at IT = 22 µA

Hints for maintenance

• Prevent formation of [18F]F – O species

- After deposition of the irradiated 18O gas into the trap:
  - Careful pump down of the target cavity for some minutes, incl. Ne-flush (20 sec)

- 18O cartridge
  - Sufficient for 100 - 120 irradiations
  - Average gas loss per bombardment: < 5%, compensated by filling from 18O cartridge
  - Use of 18O gas (trap, cartridge) until residual pressure of 18O cartridge: ~ 10 bars.

Conclusion of operation and maintenance

Handling of target system is not easy

- Results of any kind of changes are often not well reproducible
- Highly reactive [18F]F2 gas at the µmol level is difficult to handle

Maintenance

- A slight but permanent drop in the target yield
  - Indication for target cleaning

Before cleaning

- Target cavity: no metallic sheen anymore

After cleaning

- Target cavity: should look as metallic

Hints for operation

- Large surface of target cavity, transfer tube and synthesis module
- Slightly but permanent drop in the target yield
- Indication for target cleaning

Handling conditions

- 1st bombardment: Ne/F2: 20 - 22 bar, 15 minutes or 40 or 60 minutes at IT = 22 µA
- 2nd bombardment: 18O: 20 - 22 bar, 40 or 60 or 80 minutes at IT = 22 µA

Hints for maintenance

- Prevent formation of [18F]F – O species

- After deposition of the irradiated 18O gas into the trap:
  - Careful pump down of the target cavity for some minutes, incl. Ne-flush (20 sec)

- 18O cartridge
  - Sufficient for 100 - 120 irradiations
  - Average gas loss per bombardment: < 5%, compensated by filling from 18O cartridge
  - Use of 18O gas (trap, cartridge) until residual pressure of 18O cartridge: ~ 10 bars.
**Summary**

Comparison of \[^{18}F\]F2/deuterium target (old) and proton target (new)

- Higher efficiency in terms of \[^{18}F\]F2 activity and resulting FDOPA activity yields

Advantages of the new \[^{18}F\]F2/O2-gas target

### Results

- Irradiation conditions:
  - Max. target current: µA
  - Irradiating time: 18 minutes
- Target cleaning is recommended if:
  - Target yield drops down to an activity level where the FDOPA yield is not sufficient for the investigation of the target current, µA.
- Besides the produced absolute \[^{18}F\]F2-BOS activity, the reactivity of the F2 gas is important for the FDOPA activity.
  - FDOPA activity as function of the bombardment

<table>
<thead>
<tr>
<th>Date (yy.mm)</th>
<th>Deuteron target</th>
<th>Proton target</th>
</tr>
</thead>
<tbody>
<tr>
<td>34 ± 5</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>32 ± 5</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>30 ± 5</td>
<td>18</td>
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<td>12</td>
</tr>
<tr>
<td>26 ± 5</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>24 ± 5</td>
<td>18</td>
<td>12</td>
</tr>
</tbody>
</table>

The table shows the comparison of deuteron target and proton target for the production of \[^{18}F\]F2 activity yields over 2.5 years.
Cancer Research

5. References


6. Some more details

6.1 Target cleaning procedure

1. Dismount the target completely (rear plate too)
2. Grinding the target cavity with very fine sand paper
3. IBA cleaning procedure (solvents, water, dry) [3]
4. Pray for good results

Cleaning tools

Dose rate of grinding water after 500 S/h use:

> 500 µSv/h

Important

6.2 Further maintenance hints

4. PR:E: Production target; maintenance procedure, 2007
5. IBA: [18F]F2 proton target; maintenance procedure

6.3 Transfer lines

• Cu 15mm diameter used
• Careful with cleaning
• Valve poppets that can handle 18F (IBA has new ones)

1. Transient lines

[photo: Parker]

6.4 Problems with inserts (= poppets):

- Drop in target pressure: valves not leak-proof anymore

⇒ Keep poppets as spare parts
⇒ Change poppet during He-flush through target
⇒ Some pre-irradiations after changing poppet

[photo: Parker]

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Non-HPLC Methods for the Production of F-18, C-11 and Ga-68 PET Tracers

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The most popular PET radionuclides in routine clinical use are C-11 and F-18, although other radionuclides, such as Ga-68, continue to make headlines. This is due to their well established chemistry, their utility for labeling low molecular weight compounds, and their ease of production in modern PET cyclotrons or via commercially available generators. Their relatively short half-lives, along with the global trend toward Good Manufacturing Practice in PET drug production has necessitated the development of aseptic, robust and rapid labeling methodologies. This is achieved by the use of automated radiochemistry systems, which, in turn, has allowed radiosynthesis scale-up and multiple dose preparation.

Major impediments to routine production of a number of useful C-11, F-18 and Ga-68 PET tracers, and to new tracer development, remain: 1) the necessity of thorough system clean up in between consecutive runs; and 2) inconsistent yields and prolonged synthesis time when using HPLC methods for final product separation and purification. To address these issues, new radiochemistry applications have been developed for the radiochemistry modules:

a) for F-18: FLT Lite, F-MISO Lite, F-Choline Lite, and FET Lite;
b) for C-11: Acetate, Methyl Iodide, Methionine, Choline;
c) for Ga-68: DOTA-Peptides.

These methods utilize sterile disposable kits, and allow for the PET tracers to be purified and isolated with SPE cartridges only, thus eliminating the need for HPLC separation. The processes and the radiochemical yields obtained with these methods will be presented, and their utility discussed.
FET Scheme

C-11 Acetate

C-11 Methyl Iodide

C-11 Choline

C-11 Methionine
Non-HPLC Methods for the Production of F-18, C-11, Ga-68, Cu-64 and Sc-44 Radiopharmaceuticals

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H. Bagci, A. Soylu, Eczacibasi-Monrol, Ankara, Turkey
D. LeBars, CERMEP, Lyon, France

Disclaimer

This presentation is solely intended to provide and disseminate the authors' scientific results, interpretation and views in the nuclear medicine community. It does not constitute an endorsement of any Bioscan or other commercial manufacturer's products, brands, labels, or mentioned herein.
Is There Future for New Radionuclides in Imaging and Therapy?

Yes if (among other factors) the radionuclide:
• has a convenient half-life
• is available in commercial quantities
• is available in commercial quantities and at reasonable cost
• has optimal radio-labeling chemistry
• has established an optimal target–radionuclide match

Is There Future for New Radionuclides in Imaging and Therapy (cont.)?

• Yes if (among other factors) the imaging or therapeutic drug candidate:
  - is manufactured in a process easy to scale up
  - has demonstrated sufficient in vivo stability
  - has established an optimal target–radionuclide match
  - has optimal radio-labeling chemistry
  - is available in commercial quantities
  - has a convenient half-life

And last but not least:
• entrepreneurship (the right person doing the right thing)
• availability of funding for clinical trials
• it is a trial-and-error process (out of every 12 radiolabeled molecules only one will become a drug on the market)

Radionuclides Status from Industry Point of View

Existing or under construction manufacturing network:
- C-11, N-13, O-15, F-18, I-124, Cu-64, Zr-89, Tc-99m, I-123, I-131, Y-90

Manufacturing issues that are expected to be solved during the next few years:
- for Ga-68

Other radionuclides not mentioned here—may be available in large quantities in 10 years or more.
Standard Purification Tools for Pharmaceuticals

- Crystallization
- Sublimation
- Filtration
- Distillation
- Preparative HPLC purification

Pros and Cons of HPLC separation

Pros:
- Universal separation method
- Provides separation of complex mixtures

Cons:
- Column packing material is variable
- Column packing damage is possible
- Radiolytic damage to column packing
- Longens radiosynthesis time
- Lengthens radiosynthesis time
- Radiolytic damage to column packing

Ga-68, Cu-64 and Sc-44 Peptide Radiolabeling

1. Capture eluent in reactor that contains precursor
2. Heat Mixture
3. Elute with Ethanol into mixing vial
4. Rinse with Acetate Buffer
5. Collect product
Bu₄N⁺, PS-H:
4,4'-dimethoxytrityl alcohol
WAX:
Nosylate anion
HLB:
Later eluted with 10% aq. EtOH

<table>
<thead>
<tr>
<th>Date</th>
<th>Beam</th>
<th>Duration of Bombardment (Minutes)</th>
<th>Activity (mCi)</th>
<th>Corrected Yield Precursor (mCi)</th>
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<td>18</td>
<td>557</td>
<td>61</td>
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<tr>
<td>14.02.2009</td>
<td>Single</td>
<td>198</td>
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<td>90</td>
<td>2509</td>
<td>235</td>
</tr>
</tbody>
</table>

*The precursor was dissolved the previous day and kept in a fridge overnight*
More challenges ahead:

Clearly, there is a lot of work to be done.
Evaluation on metallic Sc as target for the production of $^{44}$Ti on high energy protons

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$^2$ Labor für Radio- und Umweltchemie Departement Chemie und Biochemie Universität Bern Switzerland

Radionuclide generators provide an alternative and often more convenient source of radionuclides compared to the direct production routes at accelerators and nuclear reactors. Especially generator produced positron emitters are of increased interest for development of novel PET-radiopharmaceuticals [1]. Thus $^{68}$Ge/$^{68}$Ga radionuclide generator is successfully introduced into the clinical PET for routine production of $^{68}$Ga-PET tracers. Due to rather short half-life ($T_{1/2}$ 68 min) $^{68}$Ga is useful, however, only for the investigations on fast in vivo processes.

With 3.97 h half-life and 94.27 % positron branching $^{44}$Sc is a very attractive alternative for applications in clinical PET. The major advantage is the production possibility of this radionuclide via $^{44}$Ti/$^{44}$Sc radionuclide generator ($^{44}$Ti $T_{1/2} = 60.0$ y). The limited availability of the long-lived mother nuclide $^{44}$Ti complicates further development in the radionuclide generator technique and $^{44}$Sc-radiolabelled compounds.

$^{44}$Ti can be produced by the $^{45}$Sc(p,2n) nuclear reaction. The long half-life of the accumulating nuclide and a low cross section (Fig. 1) result in a very low production rates and long-term high-current irradiations must be performed. The irradiation facility at Paul Scherrer Institute provides up to 72 MeV and 70 $\mu$A proton beam. For the production of $^{44}$Ti we are evaluating massive metallic $^{45}$Sc targets for the long-term irradiation with protons up to 40 MeV. Up to 10 mm thick scandium blocks are encapsulated in an electron-beam welded thin Al-foil. For the possible routine production the water-cooled target system is supposed to withstand up to 7000 $\mu$Ah resulting in 50 – 100 MBq of $^{44}$Ti. In this respect, the preliminary results on the irradiation yields and optimizations as well as stability of the system are presented.


Figure 1. Excitation function of $^{45}$Sc(p,2n)$^{44}$Ti reaction [2]
Operating RbCl Targets Beyond the Boiling Point? – Work in progress

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²John W. Lenz & Associates, Waxahachie, Texas, USA

The 100 MeV Isotope Production Facility (IPF) at Los Alamos National Laboratory produces the medical isotope Sr-82 on a large-scale. For routine production runs, RbCl salt targets are encapsulated in electron beam welded Inconel® 625 capsules and irradiated in a typical target stack consisting of two RbCl targets for Sr-82 production and one gallium target for Ge-68 production [1] (see Fig. 1). These two-inch diameter targets are cooled on their faces with water flowing through 5 mm wide cooling channels that separate the targets. Systematic target performance studies of similar encapsulated targets under extended bombardment with intense proton beams are not available in the literature. Routine production experience at LANL shows that while the unexpected failure of a gallium target after an extended irradiation is often associated with radiation damage and other cumulative effects in the niobium capsule material [2], the abrupt early failure of a RbCl target is usually associated with the thermal effects occurring in the encapsulated target material. Numerous Sr-82 production runs were performed at IPF over a period of six years. Almost one hundred RbCl targets were irradiated with production beam currents of up to the facility administrative limit of 250 µA. Target performance statistics indicate that these targets can reliably accept production beam currents of between 230 µA and 240 µA. At higher beam currents, occasional early target failures are likely to occur. Excessive bulging of the two adjacent RbCl target capsules interrupts the water flow in the cooling channel between the targets and leads to sudden loss of cooling, causing the two target capsules to fuse together (see Fig. 2).

In a recent development, the administrative limit of the IPF facility was increased from 250 µA to 450 µA, increasing the production capacity of the facility by almost a factor of two. In December of 2009 a preliminary high current test was conducted using a test stack consisting of three aluminium targets. During this test, the IPF demonstrated that the facility can safely operate at 360 µA. A follow-up high current test is now planned for the 2010 run cycle in order to demonstrate facility operation at the authorized current limit of 450 µA. Since most of the facility beam time is consumed by the large scale production of Sr-82, this new development sparked the desire to...
better understand the RbCl target failure mechanisms in order to push the in-beam performance of the targets beyond their present beam current limit.

The existing failure theory assumes that the observed target bulging results from internal pressure driven by localized boiling of the RbCl salt, which has a boiling point of 1390 °C. In one controlled experimental irradiation, a set of RbCl targets were driven to the point of failure by systematically increasing the beam current. The targets were inspected before each beam current increase. During this experiment, a thermal performance limit for the RbCl targets was established at 275 µA. It should be noted that occasional thermal failure under production conditions could occur at beam currents as low as 245 µA. In a separate, more theoretical effort, a detailed thermal analysis (see Fig. 3) predicted localized RbCl boiling at a beam current of 250 µA, suggesting that the thermal performance limit should be at 250 µA. The analysis took into account the major coupled thermal processes outside and inside the target, such as the water cooling of the target faces by means of forced convection, heat conduction through the solid and molten materials, and natural convection in the molten part of the salt. These results, together with data gained from the few target failures experienced during production runs, tend to support the theory that failure occurs when the maximum temperature reaches the boiling point of RbCl.

However, some evidence also suggests that the maximum temperature must be much higher than the boiling point at the time of failure. For example, it is known that bulging is observed in most of the production targets but that abrupt target failure occurs only when the cooling channel is sufficiently disturbed. This suggests that failure occurs when the bulging windows of the two adjacent RbCl targets touch, meaning the deflection of a single window reaches 2.5 mm. Based upon hydraulic deflection tests of capsule windows, a deflection of 2.5 mm corresponds to an internal capsule pressure in excess of 30 bar. Assuming that the internal pressure is caused by RbCl vapour, the high pressure value suggests a maximum internal target temperature in excess of 2100 °C, which does not correlate with the thermal analysis results.

Considering the growing demand for Sr-82 and the recent increase in the IPF administrative beam current limit, there is renewed interest in increasing the existing beam current limit imposed on our RbCl targets. Efforts to gain a still better understanding of the failure mechanisms occurring in these high-power targets through improved analysis and capsule design changes are in progress.


Operating RbCl Targets Beyond the Boiling Point? A work in progress

FM

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Operated by Los Alamos National Security, LLC for the U.S. Department of Energy’s NNSA

Improving RbCl Salt Target Performance

What to do?

Understand what is going on
Learn how to control each individual parameter in order of decreasing significance
Understand what is going on

Success!!!

Routine productions use beam currents between 230 and 360 µA – available beam time is limited by the availability of this facility, so more than 90% of Sr-82 production consumes more than 90% of available beam time. RbCl targets are encapsulated in niobium and generally targets are irradiated with 100 MeV protons up to 250 µA.

Operated by Los Alamos National Security, LLC for the U.S. Department of Energy’s NNSA
Six years of production experience

- >100 production targets irradiated at beam currents up to 250 µA
- Occasional failures at currents >240 µA
- Excessive bulging due to internal pressure
- Targets fuse together due to obstruction of the cooling water channel
- Thermal performance limit assumed to be 240 µA

Targets fail when internal pressure cause 2.5 mm window deflection

- Structural analysis predicts an internal pressure of ~25 bar

Exhibit D – Thermal analysis results

Parallel, more theoretical effort

- Takes into account major thermal processes
  - Forced convection cooling with turbulent water
  - Conduction through solid- and molten materials
  - Natural convection in the molten part of the RbCl salt

Results predict local boiling of the RbCl at beam currents beyond 250 µA

- Thermal performance limit assumed to be 240 µA
- Tend to support Exhibits A&B

Thermal performance limit assumed to be 240 µA

Exhibit D – Controlled experiment

Building at 270 µA

- Targets fail at >275 µA
- Thermal performance limit assumed to be 240 µA
- Targets were inspected for bulging after each incremental incrementing the beam current
- Set of RbCl targets driven to failure by the cooling water channel

Occasional failures at currents >250 µA

Exhibit C – Thermal analysis results

- The cooling water channel targets froze together due to obstruction of excessive building due to internal pressure
- >100 production targets irradiated at beam currents up to 250 µA

Exhibit B – Controlled experiment

Targets failed at 275 µA

Thermal performance limit assumed to be 240 µA

Supports production experience to 270 µA

Parallel more theoretical effort

- Takes into account major thermal processes

Thermal performance limit assumed to be 240 µA

Exhibit B – Controlled experiment

- The cooling water channel targets fused together due to obstruction of excessive building due to internal pressure
- Occasional failures at currents >250 µA

Exhibit A – Routine Production experience

Six years of production experience

- Thermal performance limit assumed to be 240 µA
- Tend to support Exhibits A&B

Thermal performance limit assumed to be 240 µA

Exhibit A – Routine Production experience

- The cooling water channel targets fused together due to obstruction of excessive building due to internal pressure
- Occasional failures at currents >250 µA

Exhibit C – Thermal analysis results

- The cooling water channel targets fused together due to obstruction of excessive building due to internal pressure
Are we the first to routinely operate a solid-liquid-gas target?

Much higher than suggested by Exhibits A, B & C (~1400 °C)

RbCl Vapour Pressure reaches 25 bar at 2200 °C.

Much higher than suggested by Exhibits A, B & C (~1400 °C)

To be continued...

Conclusions

1) Production experience anticipates occasional target failure beyond 240 µA.
2) A controlled experiment confirms target failure at 275 µA.
3) A thermal analysis expects the maximum local internal temperature in the RbCl to exceed boiling point at 250 µA. This may be interpreted as supporting evidence for the results in 1 & 2.
4) A structural analysis of the target capsule expects target failure to occur at local internal temperatures far beyond the boiling point of RbCl, this does not correlate with the thermal analysis results.

Which is more realistic? Why discrepant results from the thermal and structural analysis results? How do these targets fail exactly? Are we operating our RbCl targets beyond the boiling point?

To be continued....

WTTC XIII – Presentation Discussions

1. RbCl vs metallic Rb
   - “Burocracy” favours RbCl
   - Why not RbF?

2. Gas sealing
   - Electron beam welding
   - Beam shape
   - Gas sealing
   - Why not Rf?

3. Beam shape
   - Focused to 12mm
   - Rotated 5 kHz

4. RbCl changes in density
   - Solid to liquid : 30% change
   - Heat of vaporization : 7.8 kJ/mol
Abstract 051

[\textsuperscript{18}O]Water Target Design for Production of [\textsuperscript{18}F]Fluoride at High Irradiation Currents

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Abstract

The current standard for [\textsuperscript{18}F]fluoride production is proton irradiation on a [\textsuperscript{18}O]water target. Heat removal is the main obstacle to achieve a higher production. The 16.5\,MeV proton cyclotron at Ris\o{} has a maximum [\textsuperscript{18}F]fluoride production rate at an irradiation current of 55 \,\mu\text{A}. The aim of this target design is to irradiate at a proton current not below 100 \,\mu\text{A} while maintaining a [\textsuperscript{18}O]water volume close to 5 \,mL and a yield better than 80\% compared with theoretical. The theoretical yield is calculated by cross section data [1] and using SRIM [2] \textit{H\textsubscript{2}O} stopping power calculation. At 55 \,\mu\text{A} the production yields 84\% $\pm$ 4\% of theoretical yield. This corresponds to an average of 140 \,GBq [\textsuperscript{18}F]fluoride for 1 hour of irradiation. A higher intensity beam will further reduce the efficiency of the [\textsuperscript{18}F]fluoride production. Still much remains in understanding the physics inside the currently used water target. However it is claimed that current water targets operating at maximum yield contain saturated steam vapor phase region(s) which are not constant in volume over time [3]. We propose a new target design which is a deep narrow cylindrical/cone shaped silver\textsuperscript{1} target, see figure 1. The target has a depth of over 80 \,mm and width of about 10 \,mm near the target front. The width decreases as the target deepens. Its chosen shape is based on our model, which simulate the extent of the claimed steam/water matrix. This target is designed to operate at 30 \,bar of helium pressure and it is cooled by water at the sides and back and not by helium at the front. Introducing fins inside the target cavity will increase the [\textsuperscript{18}O]water-target wall surface and the heat transfer over this boundary is assumed to be the limiting factor in transferring heat from the [\textsuperscript{18}O]target water. Possible nucleate boiling heat transfer by conduction via convection may increase the heat conduction of up by a factor 10\textsuperscript{2}.

References


\textsuperscript{1}Silver is chosen as target chamber material during this stage og modelling and prototype development, because of the good mechanical and thermal characteristics, its reasonable low price and universal availability. Once cavity design is optimized other target chamber materials will be used, i.e. noble metal plated silver.
Figure 1: The target cavity of the $^{18}$O water target design is illustrated in the figure. The typical dimension of the target is 80 mm deep and 10 mm wide. A schematic extent of an assumed steam/water matrix (Steam/Water) is also shown. In the rest of the cavity is water.
The Targets

**Present and new design**

**The Aim:**
- Increase the beam current from 55 µA to 100+ µA and maintaining high saturation/µA (presently 8.3 GBq/µA)

**The New Target Design**:
- Deep narrow cylindrical/cone shaped target
- 30 bar (unchanged) He pressure ($T_b = 234^\circ C$)
- Water density ($T_b$) = 0.8219 g/cm$^3$
- No helium cooling in front
- Max 5 mL of [18O]water when filled
- What regions have steam/water matrix?
- Constraints of the steam/water matrix:
  - Determines where is water and what is steam/water matrix
  - We set a value for heat removal for the entire water cavity
  - Else - Phase transition

Consider a volume element in the target cavity:

**A Theoretical Phase State: Steam/Water Matrix**

*Fitting with Experimental Data*

We set a value for heat removal for the entire water cavity:

- Heat is transported away
- Heat is transported away
- If total heat load is transported away:
- We irradiate: deposit heat to the water
- Initial: Water

At $T_b$:
- If total heat load is transported away:
- Stays water
- Else - Phase transition

We set a value for heat removal for the entire water cavity!

- Determines what is water and what is steam/water matrix

**Constraints of the Steam/Water Matrix**:
- Worst case density ($T_b$): close to saturated steam vapor at 30 bar ($0.0150$ g/cm$^3$), i.e. mostly steam vapor
- The heat load must be transferred to the surrounding water
- Water density ($T_b$) close to saturated steam vapor at 30 bar
- $T_b = 234^\circ C$
- $P_b = 30$ bars
- $\rho_{water} = 1.0$ g/cm$^3$
- $\rho_{steam} = 0.0150$ g/cm$^3$
- Most likely:
- A liquid phase and a phase of steam with water droplets (steam/water matrix)

Where we go for a new target design?*

- Simulation!
- Finite element analysis?
- Or can we do with less?
- Where do we go for a new target design?

**A Liquid phase:**
- Most likely:
- We lose production rate as increase beam current
- Target cavity must contain steam vapor
- Target cavity highly governed by dynamics
- Liquid volume in target cavity is not constant over time

**We know:**
- So far...
Steam/Water Matrix

A Static Scenario

Mostly in the center of the impinging beam!

Initial guess of the extent of the steam/water matrix for different irradiation currents for Risø’s present target (~55 µA and below)

White with blue droplets: Steam/Water Matrix

Blue: Water

Conditions for the Steam/Water Matrix:

• The target cavity is assumed only radially cooled
• We simulate a static target performance (the dynamics is there, but we do not calculate it!)
• A constant value for heat removal is set
• Regions heated above threshold are considered steam/water matrix
• The threshold level: Calculated to match yields of Risø’s present targets but scaled to higher irradiation currents

Risø DTU, Technical University of Denmark

Simulation of the Steam/Water Matrix

Simulation Tools and Data Used

Protons are simulated in ROOT using SRIM and cross section data

SRIM + Cross Section Data:

• SRIM H2O stopping power calculation → Ionization, range and lateral range.
• We use density reduction for water (\(\rho_{\text{water}} = 0.8219 \text{ g/cm}^3\)) and a steam/water matrix (\(\rho_{\text{steam/water matrix}} = 0.0150 \text{ g/cm}^3\))
• Cross section data from E. Hess et al. Radiochim. Acta 89, 357, 2001

Cern ROOT Simulation:

• Used to simulate the extent of SRIM simulation of 16.5 MeV protons impinging on a 25 µA Havar, steam/water matrix.
• Average proton range is 195 mm.

Simulation of Heat Transfer Out of the Steam/Water Matrix

Direction of Heat Transfer:

• Hottest in the center of the proton beam.
• Heat is transferred radially from the beam center and longitudinally in the steam/water matrix until it reaches the water / steam/water matrix boundary (left picture).
• Heat is transferred radially from the beam center.
• Hottest in the center of the proton beam.

Simulated Results

Risø’s Present Standard Target(s)

Beam current 55 µA, Depth 10 mm, 2D axial symmetric view

This matches our day in and day out yields

Water

Steam/Water Matrix

Transferred heat to the imminent boundary

Transferred heat from the imminent boundary to nearby water

Risø DTU, Technical University of Denmark
Simulated Results

The New Target

Beam current 100 µA, Depth 80 mm
~80% of theoretical sat yield

Water

Steam/Water

Matrix

Left:
Energy deposited due to ionization from the water/steam/water matrix boundary

Right:
Extent of the steam/water matrix (red) in the water (blue)

Why not a water mixer inside target?

Conventional mixer experience

Steam observed close to the target window

Simulation results

1. Simulation

The New Design

A sketch

Very thin, very efficiently cooled metal surface

Typical 80 mm

Typical 10 mm

Beam

Thank you!

We still wait for experiments...

WTTC XIII – Presentation Discussions

1. Simulation results

• Steam observed close to the target window

• Coincident with experience

• Why not a water mixer inside target?

10-06-2011
Direct production of Ga-68 from proton bombardment of concentrated aqueous solutions of [Zn-68] Zinc Chloride.

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Expecting a drastic increase in use of Ga-68 in the coming years, we have reconsidered the possibilities for direct production by small cyclotrons. Although the Ge-68 generator is widely available and easily used, it often does suffer problems from limited lifetime (shorter than the physical T½ of Ge-68), high price and limited activity output. It is also our concern that a global creep from Tc-99m examinations towards Ga-68 PET-CT counterparts could rapidly exhaust the present global supply of Ge-68.

The direct production by electroplated, solid, highly enriched Zn-68(p,n)Ga-68 is well known and closely mimics the production of the blockbuster isotope Ga-67. Same target, same chemistry, just a little more energy to give the (p,2n) reaction. However the prospect of doing an enriched electroplated solid target, bombardment, etching, ion exchange separation and target material recovery chemistry for a single patient dose of Ga-68 does not seem feasible for routine use.

For this reason we have tested a “solution target”, where we bombard ZnCl2 in high concentration in water. Of course, the water does “eat up” some useful cross section and gives more stopping, but for a high yield “easy” (p,n) reaction and with a short lifetime product, this is certainly possible.

From the outset, we only had four concerns:
1. Can highly concentrated zinc chloride solutions be contained in a metal target and behind a target foil during bombardment? It is, after all, strongly acidic, and popularly used as strong soldering flux, dissolving many metal oxides.
2. Can the yield be predicted and is it high enough for routine application?
3. Will zinc remain as zinc chloride during the rather unusual conditions during proton bombardment? And will Ga-68 come out in solution from the target?
4. Can the Ga-68 be extracted rapidly from the target solution and will it be possible to reuse the enriched zinc chloride solutions directly?

We have addressed all four problems experimentally, and will report the very satisfying outcome. As target we used a slightly modified Niobium target body (designed for F-18 production), kindly provided with very few questions by Tomas Eriksson of GE Medical Systems in Uppsala. As target foil we chose 100 micrometer thick Niobium foil, partly to degrade 16.5 MeV proton beam of our PETtrace down to more optimal (p,n) energies, partly because we wanted to lower the risk of getting foil breaks and loss of the brine solution into a routinely used cyclotron.

We have kept a piece of this Nb foil in a concentrated ZnCl2 solution for 6 months without any signs of attack, loss of luster or change of weight. The target has survived many bombardments at 5, 10 uA and a single 20 uA run. We have not yet pressurised the target beyond atmospheric, and we thus did get boiling through the target filling line at 20 uA. But pressurisation should allow higher currents. After bombardments, the target body chamber and the foil look completely untouched.
Clear ZnCl2 solutions at room temperature can be prepared with more than 3 grams of ZnCl2 to 1 gram of water. We did the early target testing with 2 grams of ZnCl2 to 1 gram of water. When testing with enriched Zn-68, we used 1 gram ZnCl2 to 1 gram water.

The cross section for Zn-68(p,n)Ga-68 is well known (F. Szelecsneyi et al. JARI, 49, 1005 (1998). Using this and a straight forward stopping power calculation made by SRIM (version 2008.04, J.F. Ziegler et al. 2008 WWW.SRIM.ORG) we predicted a saturation yield for 1µA of 1500 MBq for a one-to-one ZnCl2 solution. This again corresponds to 1500 MBq at EOB after 20 minutes bombardment at 5 µA.

Experimentally we found values at little higher than this (1800 MBq Ga-68 @ EOS), measured by both dose calibrator after 1 hour and by gamma spectroscopy and thus corrected for influence of other positron emitters. With pressurisation of target, higher current on target and a higher Zn concentration, yields above 10 Gbq EOS should be obtainable.

We have used a batch of Zn-68 from Campro with 99% enrichment for our target solution. The only observed radionuclic impurity (after chemical separation of the Gallium, see below) was Ga-67 (probably from the (p,2n) process), and this accounted for less than 0.1% of total activity EOB.

To extract the Ga-68 from the target solution (still having a pH around 2 after bombardment) we passed it through a preconditioned Waters C-18 sep-pak. From old literature, it is known that Gallium chloride complexes behave “lipophilic”, - but the success of this was still a pleasant surprise to us. Zinc chloride passes through while more than 90% of Ga-68 sticks on the seppak. The seppak was washed by 2 fractions of 10 ml water to remove effectively the remaining Zinc. The primary eluate and the water washings were collected and concentrated by simple boiling up the original ZnCl2 concentration. Another successful production with same yield was done on this solution. The Ga-68 could be eluted from the seppak in a small volume of 0.1 Molar HCl. Thus, both activity extraction and target material recovery can be done rapidly and simple.

Ga-68 activity will be of limited use, if it cannot be reclaimed in more or less metal free form. The large initial load of Zinc on the column is however effectively washed out by the water fractions. Using Zn-63 and Zn-65 as indicators, the Zinc “decontamination” factor of this process is better than 5000. Other metals, like for example Iron impurities in target solution, can be more difficult to separate out by this method and should thus be avoided.

We believe that this method with some more development can be of value for local production of large activities of Ga-68 for subsequent radiopharmaceutical production. It also looks like the “solution target” with Niobium body and Niobium foil is a viable approach to a broader class of metal radioisotopes, bypassing the need for electroplating and solid targets.
Direct production of Ga-68 from proton bombardment of concentrated aqueous solutions of [Zn-68] Zinc Chloride.

4 gram of 99% enriched Zn-68 Cl2 dissolved in 4 ml of water

SRIM and EXFOR gives a saturation yield 1500 MBq/1µA
dE/dx = 0.025 MeV/mg/cm²
Target nuclides/mg = 9E18
SRIM and EXFOR gives

Yield nuclear reaction

Zn68(p,n)Ga-68 is an excellent high

Target:

Why?

n

For many purposes
You could imagine Ga-68 replacing Tc-99m.
It gives low doses.
It has excellent imaging.
It labels nicely (Ga+++).
It is easy to get.
It is easy to make.

It can work the "bifunctional chelator game".

Ga-68 is the PET radionuclide of the future.

"Instant Ga-68"
Target provided kindly and without questions by Tomas Erikksson of GE, Uppsala.

Target chamber and foil unchanged.

We had problems with Iron-68 from the Zn-68 by boiling. Zinc salts out in water wash, but can be reclaimer.

Experiment yield 1800 MBq /14A.

Ga-68 eluted by 2 ml 0.1 M HCl.

More washing should be possible.

Reduction by factor 5000.

Zn-68 reduced by factor 5000.

Target solution was pushed through C-18 Seppack Traps Ga-68.

52% of Ga-68 next to Ga-68.

Our DOTA-Octreotate turned purple!

(our DOTA-Octreotate turned purple!)

Corresponds to 1500 MBq at EOB after 20 minutes bombardment at 5 µA.

•Target solution was pushed through C-18 Seppack Traps Ga-68.

Ga-68 eluted by 2 ml 0.1 M HCl.
1. Irradiation conditions and yields

- 10uA OK; 20uA = boiling
- 10GBq in saturation
Using the Neutron Flux from p,n Reactions for n,p Reactions on Medical Cyclotrons

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The formation of the isomeric pair \(^{58}\text{Co}^{m,g}\) can be reached via the \(^{58}\text{Ni}(n,p), \(^{59}\text{Co}(n,2n), \(^{59}\text{Co}(p,pn),\)
\(^{58}\text{Fe}(p,n),\) \(^{57}\text{Fe}(d,n),\) \(^{55}\text{Mn}(a,n),\) and \(^{61}\text{Ni}(p,a)\) reactions. Natural nickel (68.1\% \(^{58}\text{Ni}\)) foils were placed
behind a \(^{18}\text{F}\)Flouride water target to produce \(^{58}\text{Co}^{[1]}\) (\(T_{1/2}=70.86\) d, \(\beta^+=14.9\%\), \(E_\gamma=811\) keV, 99.4\%) through the
\(^{58}\text{Ni}(n,p)\)\(^{58}\text{Co}\) reaction. The water target is mounted on a MC 17 Scanditronix cyclotron
(15.5 MeV protons on water). To quantify the \(^{58}\text{Co}\) activity the irradiated foils were measured after
four days (after EOB) for a full conversion of the co-produced metastable state \(^{58m}\text{Co}\) (\(T_{1/2}=9\) h).

Nickel foils (~20x20 mm) with different thicknesses were placed between the water cooling tubes on
the backside of the water target according to figure 3. The foils were irradiated with ejected neutrons
from the \(^{18}\text{O}(p,n)^{18}\text{F}\) reaction for different accumulated proton charges (\(\mu\text{Ah}\)) in the water target.

So far, \(^{58}\text{Co}\)-activities of about 0.1-0.15 kBq/\(\mu\text{Ah}\) have been produced in 0.25 mm thick foils and
approximately 1 kBq/\(\mu\text{Ah}\) in a 2 mm thick foil. The \(^{58}\text{Co}\) activities were quantified with an HPGe
detector against a known 511 keV peak in same geometry. More results will be presented at the
conference.

References:
Introduction

We were asked if we could produce $^{58}\text{Co}$ activity.

- Can be used for labeling of organo metallic compounds for biomedical studies.
- Available is a MC 17 Scanditronix cyclotron.

Background

Curiosity about the ejected neutrons from p,n reactions:

- Natural Ni (68.08% $^{57}\text{Ni}$) $(n,p)$ $^{58}\text{Co}$ was...
- Requires enriched $^{57}\text{Fe}$ (only 2.2% abundance) and a dedicated target.
- The preferred way may be d,n on 57Fe.

Reactions

Routes to $^{58}\text{Co}$ production:

- $^{58}\text{Fe}$ $(0.28\%)(p,n)$, $^{59}\text{Co}$ $(100\%)(n,2n)$, $^{59}\text{Co}$ $(100\%)(p,pn)$.
- $^{55}\text{Mn}$ $(1.14\%)(a,n)$, $^{57}\text{Fe}$ $(2.2\%)(d,n)$.
- $^{59}\text{Co}$ $(1\%)(u,\gamma)$, $^{61}\text{Ni}$ $(1.14\%)(p,a)$.
- $^{58}\text{Ni}$ $(68.08\%)(n,p)$ $^{58}\text{Co}$, $^{58}\text{Co}$ $(T_{1/2} = 70.86\,d)$.
- $^{58}\text{Co}$ $(T_{1/2} = 9.04\,h)$.
- $^{58}\text{Fe}$ $(\text{Stable})$ EC $\beta^+ (14.9\%)$, $^{58}\text{Co}$ $(T_{1/2} = 70.86\,d)$.
- $^{58}\text{Co}$ $(T_{1/2} = 9.04\,h)$.

Using the Neutron Flux from p,n Reactions for n,p Reactions
Neutron Source: Homemade [18F]Flouride Target

Target Design

Estimation: Neutron Flux on 20x20 mm² nickel plate

- Advantage: The short distance to target material (Ni)
- \( A = \frac{4}{3} \pi r^2 \) covers 8-14% of sphere area
- p+n-reactions at \( r = 1.5-2 \) cm away from Ni-foil

- \( 45 \) µA at 3.5 bars (50 psi)
- A target with 45 µA at 3.5 MeV
- No pressure
- No dedicated target
- No cooling
- No heat deposition problems

\[ \text{Neutron Flux} \]

\[ \text{Estimation of the total neutron flux} \]

\[ \text{At 45 µA the total flux is } < 3 \times 10^{11} \text{ S}^{-1} \]

\[ \text{Typical for a water target (~8)} \]

\[ \text{A = 4 cm² covers 8-14% of sphere area} \]

\[ \text{p,n-reactions at } r = 1.5-2 \text{ cm away from Ni-foil} \]
Results

- Single Foils
  - 0.25 mm foils give ~0.12 Kbg/µAh
  - 2 mm foils give ~1.13 Kbg/µAh
  - 2 mm foils give ~1.3 Kbg/µAh

- Two Separated Foils
  - Front foil ~1.3 Kbg/µAh
  - Back foil ~0.4 Kbg/µAh

Experiments

- Irradiated with neutrons from F-18 target (about 50 µAh)
- Two 20x20x2 Ni foils separated by 20 mm
- Nickel foils (~20x20 mm) different thicknesses and set-ups

L. R. Carroll, 9th WTTC Turku Finland, 2002
1. Irradiation conditions

- Ni foils and a usual F18 target
- Neutron flux > 3.6 x 10^11 Sr^-1 (from p,n alone)

2. Other isotopes?

- Co58, Co57, Co60
- Would produce Ni59, Ni60
- 10^10 neutrons: too little

3. Thermalisation?

- Co55, Co57, Co60
- Other isotopes?
Repairing water leaks in the TR-19 cyclotron: A case study in what not to do. MJ Schueller, DJ Schlyer. Medical Department, Brookhaven National Laboratory, Upton, NY 11973, USA.

In early September, 2009, a water leak opened up in one of the dees of BNL's ACSI TR-19/9 cyclotron. Attempts to patch the leak in place failed, so the dee was removed, repaired and replaced. After a week of operation, a nearly identical leak opened in the other dee. This began a chain of failures in the cyclotron, leading to approximately 8 months of down time in the human PET program at BNL. Multiple water leaks, burned internal components, and two new dees later, the machine is back to running stably.

A time sequence of events will be presented, with cascading problems, and a discussion of what steps were taken and why, with a particular focus on in house repairs that "seemed like a good idea at the time."

Some highlights:

The first leak, in an elbow near the dee stem.

Fingerstock shouldn't look like this. When we opened the vacuum tank and smelled burned flux we knew we had a problem.

This issue was finally resolved with ACSI providing a replacement part with factory-soldered fingerstock.

An attempt by BNL to replace burned fingerstock in situ failed. The cold solder joint held for a few weeks.

The new lower dee was installed and aligned, then removed to replace the burned fingerstock. At some point, it became bent ~2mm at the dee tip. Made of 7mm copper, it did not bend back easily. The cause is unknown.
Improved High Current Liquid and Gas Targets for Cyclotron Produced Radioisotopes


Coordinated Research Project, International Atomic Energy Agency
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Radiopharmaceuticals utilizing cyclotron produced radionuclides have already been shown to be extremely valuable in basic medical research, disease diagnosis and radiotherapy. IAEA Member States world-wide have acquired more than 600 cyclotrons employed for nuclear medicine applications and the number is growing every year. In the past, cyclotrons and the related targetry systems were mainly operated by dedicated professionals situated either within academic physics research institutions, large university hospitals or industrial scale radionuclide manufacturers. However, because of the rapidly spreading use of PET and PET/CT, the number of cyclotron installations is rapidly growing and target technology needs to be appreciated by a much larger group of professionals. Although many of the new cyclotrons are primarily erected for the production of a single isotope (F-18) in the form of a single, well defined radiopharmaceutical (FDG) a sizeable fraction of these new installations have declared and started active research programs in C-11 and other non-traditional positron emitting radiotracers. As part of International Atomic Energy Agency (IAEA) activities to disseminate knowledge for member states, a three year Coordinated Research Project (CRP) was organized. The overall goal of this CRP was the development of new and reliable cyclotron targetry technology for the production of high specific radioactivity for the most widely used radionuclides.

Significant advances have been made under this CRP in the development and standardization of high power gas and liquid targets. The primary focus of this CRP was to develop targets and methods to increase specific activity, radionuclidic purity and production reliability for several radionuclides including F-18, C-11, I-123, and Rb-81/Kr-81m. These advances applied in several facilities have minimized the unnecessarily operator exposure to radiation. A particular area of interest for this group was the recovery and characterization of enriched H$_2^{18}$O focusing on the reuse of the water and several important conclusions were reached. It was determined that the tritium introduced by the inevitable nuclear reactions does not pose any health physics problems either during the tracer manufacturer or during potential water reclamation. It was further determined that radionuclides produced in the metal foil during irradiation are found in the target water at very low concentrations. These impurities can be essentially eliminated by using noble metal plated foils and by the separation used for fluorine extraction from the O-18 water. In no case were the radionuclides produced in the foil found in the final product. Moreover, a survey of target maintenance procedures has been carried out and the results of this survey are reported in this CRP. In spite of these findings, the knowledge that has been gained needs to be transferred to the countries and facilities where it will help to optimize the production of radionuclides used for PET and SPECT. In this regard, a book will be published focusing on two of the most widely used target systems (F-18 and C-11) and including both fundamental knowledge and practical advice on the operation of these target systems. In addition to this book, lectures have been planned to convey both the knowledge gained in this CRP and the problems identified by the expert panel to the wider radionuclide production community with the idea that further research on these problems will benefit all the member states and the community in general.
120+ µA Single $^{18}$F Target and Beam Port Upgrade for the RDS/Eclipse

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A high power (>1.3 kW) target platform has been developed for the RDS-111/Eclipse and RDS-112 cyclotrons. This fully engineered solution includes upgrades to four subsystems: target, beam port, target support unit and deionized water cooling system. This platform has been in service 6 days per week since August 2009. The target is operated within an intensity range of 100 to 120 µA with a mean $^{18}$F saturation yield of 121 mCi/µA. Only 2300 µL of $^{18}$O-enriched water is consumed each irradiation, resulting in one of the highest aqueous $^{18}$F target power densities to date (570 W/cc). In addition to offering unprecedented performance, the single target platform greatly simplifies operation and improves the overall robustness of the cyclotron system.

The water target model CF-1000 is a conventionally pressurized cousin to the highly optimized, bottom pressurized Thermosyphon target. Due to the small volume of the target and the simplicity of using the OEM target support unit software, bottom pressurization was not viable. The target insert is constructed of either EB melted or arc cast tantalum or niobium, and is housed in a 6061 aluminum body. The conduction layer between cooling water and target medium is less than 0.030” for all chamber surfaces except the target window, and the flow regime is fully developed turbulent in all cooling water passages. To achieve turbulent conditions a conservative minimum flow rate of 2.5 GPM is required for this specific geometry. Window cooling is provided by nucleate boiling in the target medium.

The single target port replaces the rotating “turret” target changer on the 111/Eclipse cyclotron. The port includes a beam tube, vacuum isolation valve, water cooled graphite collimator, and vacuum roughing line. The assembly is constructed primarily of hard anodized 6061 aluminum for ruggedness and electrical isolation. Some PEEK is used sparingly in high wear areas and critical insulating layers. The ring collimator is made of very low porosity ATJ grade graphite to mitigate water absorption during target changes. This greatly shortens subsequent pump down time. The graphite is baked out at 150°C under 10 microns partial vacuum prior to installation. The assembly mounts to the cyclotron steel via the carrier plate which allows for independent adjustment in x and y via small lead screws. The collimator, port and beam tube section interface with the carrier plate via a spherical bearing, which is clamped in place after alignment.

Figure 1: CF-1000 Installed on RDS-111 Cyclotron
adjustments are made. This ensures that the collimator and target are coaxial at all times and provides an extremely rigid yet easily adjustable mount.

A larger recirculation pump is installed in the water system to accommodate the additional flow requirements. To ensure that proper flow balance is maintained, adjustable distribution manifolds are installed at the recirculation pump inlet and outlet. The supply manifold has a back-pressure regulating valve to allow bypass flow. This prevents both dead heading and overpressure conditions when the cyclotron is shut down. The upgrades to the water system are a small fraction of the total system fabrication cost and critical to high performance operation.

The target support unit (TSU) geometry was redesigned to mitigate the pressure rise from elevated vapour fraction at high intensity and to improve liquid recovery. The OEM software is used to operate the TSU so the functionality remained the same. Significant improvement is made from a maintenance perspective as a much more suitable pressure transducer is used resulting in smaller hysteresis, increased robustness and a reduction in replacement cost of more than a factor of five.

The performance history of the target system is shown in figure 2. The product was used exclusively for clinical $^{18}$FDG, and showed radiochemical yields consistently within specifications for both synthesis modules used. Note that the discontinuity at run number 65 is due to change in the Capintec CRC-15PET dose calibrator settings. This is the result of a technical bulletin issued by Capintec in 2009.

![Figure 2: Operational Performance from DV3](image-url)
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