Optimized microbial cells for production of melatonin and other compounds

Described herein are recombinant microbial host cells comprising biosynthetic pathways and their use in producing oxidation products and downstream products, e.g., melatonin and related compounds, as well as enzyme variants, nucleic acids, vectors and methods useful for preparing and using such cells. In specific aspects, the present invention relates to monooxygenases, e.g., amino acid hydroxylases, with a modified cofactor-dependency, and to enzyme variants and microbial cells providing for an improved supply of cofactors.

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Organisations: Novo Nordisk Foundation Center for Biosustainability, iLoop, Department of Systems Biology
Authors: Luo, H. (Intern), Förster, J. (Intern)
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A family of microbial lysine transporter polypeptides

The present invention provides a genetically modified microbial cell for production of lysine, comprising a transgene encoding a polypeptide capable of exporting lysine from the cell. The genetically modified microbial cell for production of lysine may be further characterized by genetic modifications that confer reduced lysine metabolism and/or enhanced lysine synthesis as compared to the parent cell from which said genetically modified cell was derived. The invention further provides a method for producing lysine using the genetically modified microbial cell. The invention further provides a novel family of lysine transporter polypeptides; and the use of said polypeptide to enhance production of extracellular lysine in a microbial cell.

Anionic Extraction for Efficient Recovery of Biobased 2,3-Butanediol - A Platform for Bulk and Fine Chemicals

2,3-Butanediol (BDO) presents a promising platform molecule for the synthesis of basic and fine chemicals. Biotechnological production of BDO from renewable resources with living microbes enables high concentrations in the fermentation broth. The recovery of high-boiling BDO from an aqueous fermentation broth presents a subsequent challenge. A method is proposed for BDO isolation based on reversible complexation with phenylboronate in an anionic complex. BDO can be recovered by back-extraction into an acidic solution. The composition of the extracted species was determined by NMR spectroscopy, MS, and GC-MS methods. The conditions of extraction and back-extraction were optimized by using commercial BDO and finally applied to different fermentation broths. Up to 72-93% BDO can be extracted and up to 80-90% can be back-extracted under the optimized conditions. Purified bio-BDO was used in the presence of sulfuric acid for the synthesis of methyl ethyl ketone, an established organic solvent and discussed tailor-made biofuel.
BacHBerry:: BACterial Hosts for production of Bioactive phenolics from bERRY fruits

BACterial Hosts for production of Bioactive phenolics from bERRY fruits (BacHBerry) was a 3-year project funded by the Seventh Framework Programme (FP7) of the European Union that ran between November 2013 and October 2016. The overall aim of the project was to establish a sustainable and economically-feasible strategy for the production of novel high-value phenolic compounds isolated from berry fruits using bacterial platforms. The project aimed at covering all stages of the discovery and pre-commercialization process, including berry collection, screening and characterization of their bioactive components, identification and functional characterization of the corresponding biosynthetic pathways, and construction of Gram-positive bacterial cell factories producing phenolic compounds. Further activities included optimization of polyphenol extraction methods from bacterial cultures, scale-up of production by fermentation up to pilot scale, as well as societal and economic analyses of the processes. This review article summarizes some of the key findings obtained throughout the duration of the project.

General information
Fermentation and purification strategies for the production of betulinic acid and its lupane-type precursors in Saccharomyces cerevisiae

Microbial production of plant derived, biologically active compounds has the potential to provide economic and ecologic alternatives to existing low productive, plant-based processes. Current production of the pharmacologically active cyclic triterpenoid betulinic acid is realized by extraction from the bark of plane tree or birch. Here, we reengineered the reported betulinic acid pathway into S. cerevisiae and used this novel strain to develop efficient fermentation and product purification methods. Fed-batch cultivations with ethanol excess, using either an ethanol-pulse feed or controlling a constant ethanol concentration in the fermentation medium, significantly enhanced production of betulinic acid and its triterpenoid precursors. The beneficial effect of excess ethanol was further exploited in nitrogen-limited resting cell fermentations, yielding betulinic acid concentrations of 182 mg/L and total triterpenoid concentrations of 854 mg/L, the highest concentrations reported so far. Purification of lupane-type triterpenoids with high selectivity and yield was achieved by solid-liquid extraction without prior cell disruption using polar aprotic solvents such as acetone or ethyl acetate and subsequent precipitation with strong acids. This study highlights the potential of microbial production of plant derived triterpenoids in S. cerevisiae by combining metabolic and process engineering. This article is protected by copyright. All rights reserved.

General information
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Organisations: Novo Nordisk Foundation Center for Biosustainability, iLoop, Research Groups, Applied Metabolic Engineering, RWTH Aachen University, Technische Universität Dortmund
Authors: Czarnotta, E. (Ekstern), Dianat, M. (Ekstern), Korf, M. (Ekstern), Granica, F. (Ekstern), Merz, J. (Ekstern), Maury, J. (Intern), Baallal Jacobsen, S. A. (Intern), Förster, J. (Intern), Ebert, B. E. (Ekstern), Blank, L. M. (Ekstern)
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Web of Science (2014): Indexed yes
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ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
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Scopus rating (2012): SJR 1.639 SNIP 1.366 CiteScore 4.04
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
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This review discusses opportunities and bottlenecks for cell factory development of Lactic Acid Bacteria (LAB), with an emphasis on lactobacilli and pediococci, their metabolism and genetic tools. In order to enable economically feasible bio-based production of chemicals and fuels in a biorefinery, the choice of product, substrate and production organism is important. Currently, the most frequently used production hosts include Escherichia coli and Saccharomyces cerevisiae, but promising examples are available of alternative hosts such as LAB. Particularly lactobacilli and pediococci can offer benefits such as thermodurability, an extended substrate range and increased tolerance to stresses such as low pH or high alcohol concentrations. This review will evaluate the properties and metabolism of these organisms, and provide an overview of their current biotechnological applications and metabolic engineering. We substantiate the review by including experimental results from screening various lactobacilli and pediococci for transformability, growth temperature range and ability to grow under biotechnologically relevant stress conditions. Since availability of efficient genetic engineering tools is a crucial prerequisite for industrial strain development, genetic tool development is extensively discussed. A range of genetic tools exist for Lactococcus lactis, but for other species of LAB like lactobacilli and pediococci such tools are less well developed. Whereas lactobacilli and pediococci have a long history of use in food and beverage fermentation, their use as platform organisms for production purposes is rather new. By harnessing their properties such as thermodurability and stress resistance, and by using emerging high-throughput genetic tools, these organisms are very promising as versatile cell factories for biorefinery applications.
Metabolic engineering of yeast for fermentative production of flavonoids

Yeast Saccharomyces cerevisiae was engineered for de novo production of six different flavonoids (naringenin, liquiritigenin, kaempferol, resokaempferol, quercetin, and fisetin) directly from glucose, without supplementation of expensive intermediates. This required reconstruction of long biosynthetic pathways, comprising up to eight heterologous genes from plants. The obtained titers of kaempferol 26.57±2.66mgL⁻¹ and quercetin 20.38±2.57mgL⁻¹ exceed the previously reported titers in yeast. This is also the first report of de novo biosynthesis of resokaempferol and fisetin in yeast. The work demonstrates the potential of flavonoid-producing yeast cell factories.
Quantifying the Metabolome of Pseudomonas taiwanensis VLB120: Evaluation of Hot and Cold Combined Quenching/Extraction Approaches

Absolute quantification of free intracellular metabolites is a valuable tool in both pathway discovery and metabolic engineering. In this study, we conducted a comprehensive examination of different hot and cold combined quenching/extraction approaches to extract and quantify intracellular metabolites of Pseudomonas taiwanensis (P. taiwanensis) VLB120 to provide a useful reference data set of absolute intracellular metabolite concentrations. The suitability of commonly used metabolomics tools including a pressure driven fast filtration system followed by combined quenching/extraction techniques (such as cold methanol/acetonitrile/water, hot water, and boiling ethanol/water, as well as cold ethanol/water) were tested and evaluated for P. taiwanensis VLB120 metabolome analysis. In total 94 out of 107 detected intracellular metabolites were quantified using an isotope-ratio-based approach. The quantified metabolites include amino acids, nucleotides, central carbon metabolism intermediates, redox cofactors, and others. The acquired data demonstrate that the pressure driven fast filtration approach followed by boiling ethanol quenching/extraction is the most adequate technique for P. taiwanensis VLB120 metabolome analysis based on quenching efficiency, extraction yields of metabolites, and experimental reproducibility.

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Organisations: Novo Nordisk Foundation Center for Biosustainability, Research Groups, iLoop, Applied Metabolic Engineering, University of California, San Diego
Authors: Wordofa, G. G. (Intern), Kristensen, M. (Intern), Schrübbers, L. (Intern), McCloskey, D. (Ekstern), Förster, J. (Intern), Schneider, K. (Intern)
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Microbial production of the flavonoids garbanzol, resokaempferol and fisetin

The invention provides a genetically modified micro-organism comprising one or more transgene for the production of one or more of the flavonoids garbanzol, resokaempferol and fisetin. The micro-organism may be a bacterial or yeast cell engineered to express a metabolic pathway for garbanzol, resokaempferol and/or fisetin biosynthesis. The invention further provides a method for producing garbanzol, resokaempferol and/or fisetin employing the genetically modified micro-organism of the invention. The genetically modified micro-organism may be used to convert a number of substrates and/or co-substrates into fisetin via a fisetin biosynthetic pathway.

General information

State: Published

Organisations: Novo Nordisk Foundation Center for Biosustainability, Research Groups, Bacterial Synthetic Biology, iLoop, Applied Metabolic Engineering, Membrane Synthetic Biology Group, Yeast Metabolic Engineering, Yeast Cell Factories, Department of Systems Biology

Bio-based chemicals - green, but also sustainable?

For almost two decades, the chemical industry has put great effort into developing bio-chemicals, among others to fight global warming caused by greenhouse gas emissions, one of the biggest threats that are faced by our society today. To facilitate a growing and versatile bio-based chemical production, the US Department of Energy proposed in 2004 a list of 12 building block chemicals which can either be converged through biological or chemical conversions. Moving toward more bio-based chemicals, the chemical industry does not only claim to reduce climate change impacts, but also that they are increasing overall sustainability in chemical production. Whether such claims are justifiable is unclear. When sustainability of bio-based polymer production is assessed, various environmental trade-offs occur that need to be considered. It is not enough to claim that a bio-chemical is sustainable by exclusively looking at reduced global warming impacts related to avoiding oil refining and related greenhouse gas emissions. However, there is big variation of which impacts are assessed and which life cycle stages are included between existing published studies focusing on assessing environmental sustainability of bio-based polymers.

Cell Factory Stability and Genetic Circuits for Improved Strain Development

Development of new chemical—producing microbial cell factories is an iterative trial-and-error process, and to screen candidate cells at high throughput, genetic biosensor systems are appealing. Each biosensor has distinct biological parameters, making modular tuning networks attractive. However, all synthetic gene systems—including the target metabolic pathways themselves—represent a possible fitness burden to the cell and thus constitute a threat to strain stability.

In this thesis, several studies served to develop genetic systems for optimizing cell factory development and understanding the common error modes leading to loss of stable metabolic productivity during long-term microbial fermentation.

A molecular buffer system in Saccharomyces cerevisiae was designed and engineered to tune the signals of a known tetracycline-responsive RNA switch (riboswitch). Generalizable and based on split transcription factors, the system e.g. allowed shift of ligand sensitivity and inversion of the output signal from OFF to ON—without changing the riboswitch or output gene. The system was i.a. characterized by green fluorescent protein (GFP), for which a recombination-stabilized multimeric GFP was developed. Overcoming cellular autofluorescence, this multimer enabled detection of weak promoter signals in S. cerevisiae. The concept of split transcription factors was further applied in S. cerevisiae as a tool to enable selection for three DNA fragments under a single selectable phenotype. This enabled quick introduction of a three-step polyketide pathway and may also serve to challenge the current paradigm of “one selectable trait – one selection gene”, as was demonstrated in plasmid and chromosomal gene introduction. Despite of genetic selection, the load of all synthetic systems can challenge the
stability of strain designs. A metabolite-producing Escherichia coli strain was long-term cultured to study production stability and the dynamic effects of mutations within the cell population. A genetic error landscape of pathway disruptions was identified including particular, recurring error modes. Driven by a gain in fitness, these errors within 70 generations led to a transformation of the strain to a population of genetic non-producer cells. Knowledge about these mechanisms and the applied simple mathematical model may likely serve to realize more stable microbial cell factories in future.

**General information**
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Organisations: Novo Nordisk Foundation Center for Biosustainability, Bacterial Synthetic Biology, Research Groups, Applied Metabolic Engineering
Authors: Rugbjerg, P. (Intern), Sommer, M. O. A. (Intern), Förster, J. (Intern)
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**EasyCloneMulti: A Set of Vectors for Simultaneous and Multiple Genomic Integrations in *Saccharomyces cerevisiae***
*Saccharomyces cerevisiae* is widely used in the biotechnology industry for production of ethanol, recombinant proteins, food ingredients and other chemicals. In order to generate highly producing and stable strains, genome integration of genes encoding metabolic pathway enzymes is the preferred option. However, integration of pathway genes in single or few copies, especially those encoding rate-controlling steps, is often not sufficient to sustain high metabolic fluxes. By exploiting the sequence diversity in the long terminal repeats (LTR) of Ty retrotransposons, we developed a new set of integrative vectors, EasyCloneMulti, that enables multiple and simultaneous integration of genes in *S. cerevisiae*. By creating vector backbones that combine consensus sequences that aim at targeting subsets of Ty sequences and a quickly degrading selective marker, integrations at multiple genomic loci and a range of expression levels were obtained, as assessed with the green fluorescent protein (GFP) reporter system. The EasyCloneMulti vector set was applied to balance the expression of the rate-controlling step in the β-alanine pathway for biosynthesis of 3-hydroxypropionic acid (3HP). The best 3HP producing clone, with 5.45 g L⁻¹ of 3HP, produced 11 times more 3HP than the lowest producing clone, which demonstrates the capability of EasyCloneMulti vectors to impact metabolic pathway enzyme activity.

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Web of Science (2015): Indexed yes
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Web of Science (2012): Indexed yes
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Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 2.473 SNIP 0.985
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
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Engineering and systems level analysis of *Saccharomyces cerevisiae* for production of 3 hydroxypropionic acid via malonyl CoA reductase dependent pathway

In the future, oil- and gas-derived polymers may be replaced with bio-based polymers, produced from renewable feedstocks using engineered cell factories. Acrylic acid and acrylic esters with an estimated world annual production of approximately 6 million tons by 2017 can be derived from 3-hydroxypropionic acid (3HP), which can be produced by microbial fermentation. For an economically viable process 3HP must be produced at high titer, rate and yield and preferably at low pH to minimize downstream processing costs.

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- Web of Science (2015): Indexed yes
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- ISI indexed (2013): ISI indexed yes
- Web of Science (2013): Indexed yes
- BFI (2012): BFI-level 1
- Scopus rating (2012): SJR 1.392 SNIP 1.312 CiteScore 3.69
- ISI indexed (2012): ISI indexed yes
- Web of Science (2012): Indexed yes
- BFI (2011): BFI-level 1
- Scopus rating (2011): SJR 1.417 SNIP 1.38 CiteScore 3.91
- ISI indexed (2011): ISI indexed yes
- Web of Science (2011): Indexed yes
- BFI (2010): BFI-level 1
- Scopus rating (2010): SJR 1.609 SNIP 1.463
- Web of Science (2010): Indexed yes
- BFI (2009): BFI-level 1
- Scopus rating (2009): SJR 1.276 SNIP 1.206
- Web of Science (2009): Indexed yes
- BFI (2008): BFI-level 1
- Scopus rating (2008): SJR 1.325 SNIP 1.335
- Scopus rating (2007): SJR 1.13 SNIP 1.293
- Web of Science (2007): Indexed yes
- Scopus rating (2006): SJR 0.973 SNIP 0.906
- Web of Science (2006): Indexed yes
- Scopus rating (2005): SJR 0.99 SNIP 1.056
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This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium,
Engineering Lactococcus lactis for stilbene production

General information
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Organisations: Novo Nordisk Foundation Center for Biosustainability, Research Groups, Microbial Evolution and Synthetic Biology
Authors: Gaspar, P. (Intern), Dudnik, A. (Intern), Neves, A. R. (Intern), Förster, J. (Intern)
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Main Research Area: Technical/natural sciences
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Bibliographical note
Satellite Workshop: Bacterial Hosts for Production of Bioactive Phenolics from Berry Fruits

Genome-Scale Models
An introduction to genome-scale models, how to build and use them, will be given in this chapter. Genome-scale models have become an important part of systems biology and metabolic engineering, and are increasingly used in research, both in academia and in industry, both for modeling chemical production and for fundamental studies aiming at describing and explaining phenotypic behavior of microbial and mammalian cells.

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Organisations: Novo Nordisk Foundation Center for Biosustainability, Research Groups, Applied Metabolic Engineering, University of Minho
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Glucose-based microbial production of the hormone melatonin in yeast *Saccharomyces cerevisiae*

Melatonin is a natural mammalian hormone that plays an important role in regulating the circadian cycle in humans. It is a clinically effective drug exhibiting positive effects as a sleep aid and a powerful antioxidant used as a dietary supplement. Commercial melatonin production is predominantly performed by complex chemical synthesis. In this study, we demonstrate microbial production of melatonin and related compounds, such as serotonin and N-acetylserotonin. We generated *Saccharomyces cerevisiae* strains that comprise heterologous genes encoding one or more variants of an L-tryptophan hydroxylase, a 5-hydroxy-L-tryptophan decarboxylase, a serotonin acetyltransferase, an acetylserotonin O-methyltransferase, and means for providing the cofactor tetrahydrobiopterin via heterologous biosynthesis and recycling pathways. We thereby achieved de novo melatonin biosynthesis from glucose. We furthermore accomplished increased product titers by altering expression levels of selected pathway enzymes and boosting co-factor supply. The final yeast strain produced melatonin at a titer of 14.50 ± 0.57 mg L−1 in a 76h fermentation using simulated fed-batch medium with glucose as sole carbon source. Our study lays the basis for further developing a yeast cell factory for biological production of melatonin.
Physiology of *Saccharomyces cerevisiae* strains isolated from Brazilian biomes: new insights into biodiversity and industrial applications

Fourteen indigenous *Saccharomyces cerevisiae* strains isolated from the barks of three tree species located in the Atlantic Rain Forest and Cerrado biomes in Brazil were genetically and physiologically compared to laboratory strains and to strains from the Brazilian fuel ethanol industry. Although no clear correlation could be found either between phenotype and isolation spot or between phenotype and genomic lineage, a set of indigenous strains with superior industrially relevant traits over commonly known industrial and laboratory strains was identified: strain UFMG-CM-Y257 has a very high specific growth rate on sucrose (0.57 ± 0.02 h⁻¹), high ethanol yield (1.65 ± 0.02 mol ethanol mol hexose equivalent⁻¹), high ethanol productivity (0.19 ± 0.00 mol L⁻¹ h⁻¹), high tolerance to acetic acid (10 g L⁻¹) and to high temperature (40°C). Strain UFMG-CM-Y260 displayed high ethanol yield (1.67 ± 0.13 mol ethanol mol hexose equivalent⁻¹), high tolerance to ethanol and to low pH, a trait which is important for non-aseptic industrial processes. Strain UFMG-CM-Y267 showed high tolerance to acetic acid and to high temperature (40°C), which is of particular interest to second generation industrial processes.

**General information**

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Organisations: Novo Nordisk Foundation Center for Biosustainability, Research Groups, Applied Metabolic Engineering, Technical University of Denmark, Federal University of Minas Gerais, State University of Campinas
Authors: Beato, F. B. (Ekstern), Bergdahl, B. (Intern), Rosa, C. A. (Ekstern), Förster, J. (Intern), Gombert, A. K. (Ekstern)
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Rational and Evolutionary Engineering of Industrial Saccharomyces Cerevisiae Strains for Production of Chemicals from Xylose-Rich Feedstocks

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Organisations: Novo Nordisk Foundation Center for Biosustainability, Research Groups, Yeast Metabolic Engineering, Department of Chemical and Biochemical Engineering, CAPEC-PROCESS
Authors: Stovicek, V. (Intern), Lis, A. V. (Intern), Borodina, I. (Intern), Förster, J. (Intern)
Number of pages: 1
Publication date: 2016

Host publication information
Saccharomyces cerevisiae is one of the key cell factories for production of chemicals and active pharmaceuticals. For large-scale fermentations, particularly in biorefinery applications, it is desirable to use stress-tolerant industrial strains. However, such strains are less amenable for metabolic engineering than the standard laboratory strains. To enable easy delivery and overexpression of genes in a wide range of industrial S. cerevisiae strains, we constructed a set of integrative vectors with long homology arms and dominant selection markers. The vectors integrate into previously validated chromosomal locations via double cross-over and result in homogenous stable expression of the integrated genes, as shown for several unrelated industrial strains. Cre-mediated marker rescue is possible for removing markers positioned on different chromosomes. To demonstrate the applicability of the presented vector set for metabolic engineering of industrial yeast, we constructed xylose-utilizing strains overexpressing xylose isomerase, xylose transporter and five genes of the pentose phosphate pathway.
Microorganisms for efficient production of melatonin and related compounds.
Recombinant microbial cells and methods for producing 5HTP, melatonin and related compounds using such cells are described. More specifically, the recombinant microbial cell may comprise exogenous genes encoding one or more of an L-tryptophan hydroxylase, a 5-hydroxy-L-tryptophan decarboxylase, a serotonin acetyltransferase, an acetylserotonin O-methyltransferase; and means for providing tetrahydrobiopterin (THB), and can be further genetically modified to enrich one or more of tryptophan, S-adenosyl-L-methionine and acetyl coenzyme A. Related sequences and vectors for use in preparing such recombinant microbial cells are also described.

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Organisations: Bacterial Cell Factories, Novo Nordisk Foundation Center for Biosustainability, Department of Systems Biology, Research Groups, Yeast Metabolic Engineering
Authors: Zhu, J. (Intern), Jensen, N. B. (Intern), Chen, X. (Intern), Förster, J. (Intern), Borodina, I. (Intern)
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Priority number: EP20130183120
Assembly of a novel biosynthetic pathway for production of the plant flavonoid fisetin in *Escherichia coli*

Plant secondary metabolites are an underutilized pool of bioactive molecules for applications in the food, pharma and nutritional industries. One such molecule is fisetin, which is present in many fruits and vegetables and has several potential health benefits, including anti-cancer, anti-viral and anti-aging activity. Moreover, fisetin has recently been shown to prevent Alzheimer’s disease in mice and to prevent complications associated with diabetes type I. Thus far the biosynthetic pathway of fisetin in plants remains elusive. Here, we present the heterologous assembly of a novel fisetin pathway in *Escherichia coli*. We propose a novel biosynthetic pathway from the amino acid, tyrosine, utilizing nine heterologous enzymes. The pathway proceeds via the synthesis of two flavanones never produced in microorganisms before – garbanzol and resokaempferol. We show for the first time a functional biosynthetic pathway and establish *E. coli* as a microbial platform strain for the production of fisetin and related flavonols.

**General information**

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Authors: Stahlhut, S. G. (Intern), Siedler, S. (Intern), Malla, S. (Intern), Harrison, S. J. (Intern), Maury, J. (Intern), Neves, A. R. (Intern), Förster, J. (Intern)
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BFI (2014): BFI-level 2
Scopus rating (2014): SJR 3.381 SNIP 2.034 CiteScore 7.23
Web of Science (2014): Indexed yes
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Scopus rating (2013): SJR 4.004 SNIP 2.185 CiteScore 8.43
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Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 3.032 SNIP 1.858 CiteScore 6.72
ISI indexed (2012): ISI indexed yes
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Scopus rating (2011): SJR 3.124 SNIP 2.144 CiteScore 6.75
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
CRISPR–Cas system enables fast and simple genome editing of industrial Saccharomyces cerevisiae strains

There is a demand to develop 3rd generation biorefineries that integrate energy production with the production of higher value chemicals from renewable feedstocks. Here, robust and stress-tolerant industrial strains of *Saccharomyces cerevisiae* will be suitable production organisms. However, their genetic manipulation is challenging, as they are usually diploid or polyploid. Therefore, there is a need to develop more efficient genetic engineering tools. We applied a CRISPR–Cas9 system for genome editing of different industrial strains, and show simultaneous disruption of two alleles of a gene in several unrelated strains with the efficiency ranging between 65% and 78%. We also achieved simultaneous disruption and knock-in of a reporter gene, and demonstrate the applicability of the method by designing lactic acid-producing strains in a single transformation event, where insertion of a heterologous gene and disruption of two endogenous genes occurred simultaneously. Our study provides a foundation for efficient engineering of industrial yeast cell factories.

General information

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Organisations: Novo Nordisk Foundation Center for Biosustainability, Applied Metabolic Engineering, Yeast Metabolic Engineering
Authors: Stovicek, V. (Intern), Borodina, I. (Intern), Förster, J. (Intern)
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Main Research Area: Technical/natural sciences
Development Of An Efficient Glycerol Utilizing Saccharomyces Cerevisiae Strain Via Adaptive Laboratory Evolution

With increasing interest in biosustainable technologies, the need for converting available non-saccharide carbon sources most efficiently is emerging. Highly abundant crude glycerol, a major waste residue in biodiesel production, has attracted attention as a cheap carbon source for microbial fermentation processes. The most commonly known microbial cell factory, the yeast Saccharomyces cerevisiae, has been extensively applied for the production of a wide range of scientifically and industrially relevant products using saccharides (mainly glucose) as carbon source. However, it was shown that popular wild-type laboratory yeast strains, commonly applied in metabolic engineering studies, did not grow or grew very slowly in glycerol medium. In this work, an adaptive laboratory evolution approach to obtain S. cerevisiae strains with an improved ability to grow on glycerol was applied. A broad array of evolved strains, which exhibited a significant increase in the specific growth rate and a higher glycerol consumption rate, were isolated. The best performing strains were further analyzed by classical genetics and whole genome re-sequencing in order to understand the molecular basis of glycerol catabolism in yeast. The knowledge acquired in this study may be further applied for rational S. cerevisiae strain improvement for using glycerol as a carbon source in industrial biotechnology processes. This work is a part of the DeYeastLibrary consortium financed by ERA-IB DeYeastLibrary - Designer yeast strain library optimized for metabolic engineering applications http://www.era-ib.net/deyeast-library
Development of a yeast cell factory for production of aromatic compounds: test case flavonoids production

General information
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Organisations: Novo Nordisk Foundation Center for Biosustainability, Yeast Cell Factories, Research Groups, Applied Metabolic Engineering
Authors: Rodriguez Prado, E. A. (Intern), Kildegaard, K. R. (Intern), Li, M. (Intern), Borodina, I. (Intern), Stahlhut, S. G. (Intern), Förster, J. (Intern), Nielsen, J. (Intern)
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BFI (2016): BFI-level 1
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Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.962 SNIP 0.745 CiteScore 2.01
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.875 SNIP 0.792 CiteScore 1.67
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.232 SNIP 0.72 CiteScore 2.09
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
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ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.063 SNIP 0.701 CiteScore 1.77
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.049 SNIP 0.835
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Establishing a synthetic pathway for high-level production of 3-hydroxypropionic acid in *Saccharomyces cerevisiae* via β-alanine

Microbial fermentation of renewable feedstocks into plastic monomers can decrease our fossil dependence and reduce global CO2 emissions. 3-Hydroxypropionic acid (3HP) is a potential chemical building block for sustainable production of superabsorbent polymers and acrylic plastics. With the objective of developing *Saccharomyces cerevisiae* as an efficient cell factory for high-level production of 3HP, we identified the β-alanine biosynthetic route as the most economically attractive according to the metabolic modeling. We engineered and optimized a synthetic pathway for de novo biosynthesis of β-alanine and its subsequent conversion into 3HP using a novel β-alanine-pyruvate aminotransferase discovered in *Bacillus cereus*. The final strain produced 3HP at a titer of 13.7±0.3 g・L⁻¹ with a 0.14±0.0 C-mol・C-mol⁻¹ yield on glucose in 80 hours in controlled fed-batch fermentation in mineral medium at pH 5, and this work therefore lays the basis for developing a process for biological 3HP production.
Highly Active and Specific Tyrosine Ammonia-Lyases from Diverse Origins Enable Enhanced Production of Aromatic Compounds in Bacteria and Saccharomyces cerevisiae

Phenylalanine and tyrosine ammonia-lyases form cinnamic acid and p-coumaric acid, which are precursors of a wide range of aromatic compounds of biotechnological interest. Lack of highly active and specific tyrosine ammonia-lyases has previously been a limitation in metabolic engineering approaches. We therefore identified 22 sequences in silico using synteny information and aiming for sequence divergence. We performed a comparative in vivo study, expressing the genes intracellularly in bacteria and yeast. When produced heterologously, some enzymes resulted in significantly higher production of p-coumaric acid in several different industrially important production organisms. Three novel enzymes were found to have activity exclusively for phenylalanine, including an enzyme from the low-GC Gram-positive bacterium *Brevibacillus laterosporus*, a bacterial-type enzyme from the amoeba *Dictyostelium discoideum*, and a phenylalanine ammonia-lyase from the moss *Physcomitrella patens* (producing 230 μM cinnamic acid per unit of optical density at 600 nm [OD600]) in the medium using *Escherichia coli* as the heterologous host. Novel tyrosine ammonia-lyases having higher reported substrate specificity than previously characterized enzymes were also identified. Enzymes from *Herpetosiphon aurantiacus* and *Flavobacterium johnsoniae* resulted in high production of p-coumaric acid in *Escherichia coli* (producing 440 μM p-coumaric acid OD600 unit−1 in the medium) and in *Lactococcus lactis*. The enzymes were also efficient in *Saccharomyces cerevisiae*, where p-coumaric acid accumulation was improved 5-fold over that in strains expressing previously characterized tyrosine ammonia-lyases.

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Organisations: Novo Nordisk Foundation Center for Biosustainability, Bacterial Cell Factories, Research Groups, Applied Metabolic Engineering, Yeast Metabolic Engineering, Yeast Cell Factories, Bacterial Cell Factory Optimization
Authors: Jendresen, C. B. (Intern), Stahlhut, S. G. (Intern), Li, M. (Intern), Gaspar, P. (Intern), Siedler, S. (Intern), Förster, J. (Intern), Maury, J. (Intern), Borodina, I. (Intern), Nielsen, A. T. (Intern)
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Scopus rating (2016): CiteScore 4.08
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.891 SNIP 1.308 CiteScore 4.14
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.857 SNIP 1.384 CiteScore 4.02
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.899 SNIP 1.414 CiteScore 4.25
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.975 SNIP 1.429 CiteScore 4.29
ISI indexed (2012): ISI indexed yes
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Scopus rating (2011): SJR 1.914 SNIP 1.455 CiteScore 4.12
Molecular toolbox for efficient engineering of industrial yeast cell factories

General information
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Organisations: Novo Nordisk Foundation Center for Biosustainability, Research Groups
Authors: Stovicek, V. (Intern), Borodina, I. (Intern), Förster, J. (Intern)
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Recombination-stable multimeric green fluorescent protein for characterization of weak promoter outputs in *Saccharomyces cerevisiae*

Green fluorescent proteins (GFPs) are widely used for visualization of proteins to track localization and expression dynamics. However, phenotypically important processes can operate at too low expression levels for routine detection, i.e. be overshadowed by autofluorescence noise. While GFP functions well in translational fusions, the use of tandem GFPs to amplify fluorescence signals is currently avoided in *Saccharomyces cerevisiae* and many other microorganisms due to the risk of loop-out by direct-repeat recombination. We increased GFP fluorescence by translationally fusing three different GFP variants, yeast-enhanced GFP, GFP+ and superfolder GFP to yield a sequence-diverged triple GFP molecule 3vGFP with 74–84% internal repeat identity. Unlike a single GFP, the brightness of 3vGFP allowed characterization of a weak promoter in *S. cerevisiae*. Utilizing 3vGFP, we further engineered a less leaky Cu²⁺-inducible promoter based on *CUP1*. The basal expression level of the new promoter was approx. 61% below the wild-type *CUP1* promoter, thus expanding the absolute range of Cu²⁺-based gene control. The stability of 3vGFP towards direct-repeat recombination was assayed in *S. cerevisiae* cultured for 25 generations under strong and slightly toxic expression after which only limited reduction in fluorescence was detectable. Such non-recombinogenic GFPs can help quantify intracellular responses operating a low copy number in recombination-prone organisms.
3HP tolerance

Cells and cell cultures are provided that have improved tolerance to 3-hydroxypropionic acid (3HP). Genetic modifications to provide a mutated or overexpressed SFA1 gene or other enhancement of 3HP detoxification via a glutathione-dependent dehydrogenase reaction, including medium supplementation with glutathione, may be combined with a 3HP producing metabolic pathway.

General information

State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, Research Groups, Fungal Cell Factories
Authors: Kildegaard, K. R. (Intern), Borodina, I. (Intern), Förster, J. (Intern), Nielsen, J. (Intern)
Publication date: 2014

Publication information

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Main Research Area: Technical/natural sciences
Publication: Research - Patent – Annual report year: 2014
BioREFINE-2G project – Engineering of industrial yeast strains for production of dicarboxylic acids from side and waste streams

For our future we need to assure that fuels as well as chemicals will be produced environmentally friendly from renewable resources. There must be a major move away from the use of food biomass towards the use of renewable non-food feedstocks, such as wood, stover, straw etc. The existing 2nd generation biorefineries utilize less than 20% of the biomass feedstock for ethanol production. Major side-streams are produced such as pentose and lignin waste streams that are used for biogas and energy production. Converting the carbon from these waste streams into added-value products would improve the environmental benefits of the biorefineries. The BioREFINE-2G project aims at the development of genetically modified industrial *Saccharomyces cerevisiae* strains suitable for the production of the selected dicarboxylic acids from side and waste streams rich in C5 sugar and mixtures of C5/C6 sugars. The target compounds can be polymerised to biodegradable polymer that can find application as plastics, coatings or adhesives. To reach the goals, the identification of relevant metabolic routes, strain engineering and the development of a toolbox for manipulation of industrial *S. cerevisiae* strains are required. Here, we present advanced genetic engineering tools applicable for generally hardly amenable strains with industrial background. This involves tools for stable heterologous gene (over-)expression and a strategy for fast performance of gene disruption in multiple ploidy strains. The use of the developed toolbox in metabolic engineering of various industrial yeast strains will be demonstrated.

Development of Industrial Yeast Platform Strains

Most of the current metabolic engineering projects are carried out using laboratory strains as the starting host. Although such strains are easily manipulated genetically, their robustness does not always meet the requirements set by industrial fermentation conditions. In such conditions, the cells frequently encounter high substrate concentrations, low pH, high temperatures and various inhibitory compounds originating either from the raw material used or from cellular metabolism. The aim of this research project is to develop robust platform strains of *Saccharomyces cerevisiae* based on industrial and environmental isolates. The project is expected to relate the genetic diversity among a group of 36 natural and domesticated isolates of *S. cerevisiae* strains to the observed phenotypes, with special focus on extreme phenotypes characterized by high robustness and specific metabolic traits. The genetic diversity will further be harnessed to generate completely new strains with selected, desirable traits. These new platform strains will be a preferable choice as starting hosts in which to implement existing and new metabolic engineering designs for the production of specific classes of compounds. The project has four main tasks that are interconnected to reach the final goal (Fig. 1). It is highly multidisciplinary and involves several research fields. In this communication, we will present selected results from ongoing activities, such as the whole genomes sequencing, intracellular metabolite profiling and tolerance screening of the 36 industrial and laboratory yeast strains. In addition, progress in the development of molecular biology methods for generating the new strains will be presented.
EasyClone: method for iterative chromosomal integration of multiple genes in *Saccharomyces cerevisiae*

Development of strains for efficient production of chemicals and pharmaceuticals requires multiple rounds of genetic engineering. In this study, we describe construction and characterization of EasyClone vector set for baker's yeast *Saccharomyces cerevisiae*, which enables simultaneous expression of multiple genes with an option of recycling selection markers. The vectors combine the advantage of efficient uracil excision reaction-based cloning and Cre-LoxP-mediated marker recycling system. The episomal and integrative vector sets were tested by inserting genes encoding cyan, yellow, and red fluorescent proteins into separate vectors and analyzing for co-expression of proteins by flow cytometry. Cells expressing genes encoding for the three fluorescent proteins from three integrations exhibited a much higher level of simultaneous expression than cells producing fluorescent proteins encoded on episomal plasmids, where correspondingly 95% and 6% of the cells were within a fluorescence interval of $\log_{10}$ mean $\pm$ 15% for all three colors. We demonstrate that selective markers can be simultaneously removed using Cre-mediated recombination and all the integrated heterologous genes remain in the chromosome and show unchanged expression levels. Hence, this system is suitable for metabolic engineering in yeast where multiple rounds of gene introduction and marker recycling can be carried out.

General information

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Organisations: Novo Nordisk Foundation Center for Biosustainability, CFB - Core Flow, Department of Systems Biology, Eucaryotic Molecular Cell Biology, Bacterial Cell Factories, Research Groups, Fungal Cell Factories, Chalmers University of Technology
Authors: Jensen, N. B. (Intern), Strucko, T. (Intern), Kildegaard, K. R. (Intern), David, F. (Ekstern), Maury, J. (Intern), Mortensen, U. H. (Intern), Förster, J. (Intern), Nielsen, J. (Intern), Borodina, I. (Intern)
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Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.076 SNIP 0.838 CiteScore 2.37
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.225 SNIP 0.863 CiteScore 2.5
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.187 SNIP 0.844 CiteScore 2.56
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.217 SNIP 1.015 CiteScore 2.54
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.036 SNIP 0.921
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.973 SNIP 0.817
BFI (2008): BFI-level 1
Evolution Reveals a Glutathione-dependent Mechanism Of 3-hydroxypropionic Acid Detoxification

Biologically produced 3-hydroxypropionic acid (3HP) is a potential source for sustainable acrylates and can also find direct use as monomer in the production of biodegradable polymers. For industrial-scale production, high titer, rate and yield are essential; thus there is a need for robust cell factories tolerant to high concentration of 3HP, preferably at low pH. Through adaptive laboratory evolution we selected S. cerevisiae strains with improved tolerance to 3HP at pH 3.5. Genome sequencing followed by functional analysis identified the causal mutation in SFA1 gene encoding S-(hydroxymethyl)glutathione dehydrogenase. Based on our findings, we propose that 3HP toxicity is mediated by 3-hydroxypropionic aldehyde (reuterin) and that glutathione-dependent route for detoxification of 3-hydroxypropionic aldehyde (reuterin). The identified molecular response to 3HP and reuterin may well be a general mechanism for handling resistance to organic acids and aldehydes by living cells.

General information
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Organisations: Novo Nordisk Foundation Center for Biosustainability, Research Groups, iLoop, CFB - Core Flow, Bacterial Cell Factories, Metagenomics, Fungal Cell Factories, KTH - Royal Institute of Technology, University of Copenhagen
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Main Research Area: Technical/natural sciences
Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2015

Evolution reveals a glutathione-dependent mechanism of 3-hydroxypropionic acid tolerance

Biologically produced 3-hydroxypropionic acid (3HP) is a potential source for sustainable acrylates and can also find direct use as monomer in the production of biodegradable polymers. For industrial-scale production there is a need for robust cell factories tolerant to high concentration of 3HP, preferably at low pH. Through adaptive laboratory evolution we selected S. cerevisiae strains with improved tolerance to 3HP at pH 3.5. Genome sequencing followed by functional analysis identified the causal mutation in SFA1 gene encoding S-(hydroxymethyl)glutathione dehydrogenase. Based on our findings, we propose that 3HP toxicity is mediated by 3-hydroxypropionic aldehyde (reuterin) and that glutathione-
dependent reactions are used for reuterin detoxification. The identified molecular response to 3HP and reuterin may well be a general mechanism for handling resistance to organic acid and aldehydes by living cells.

**General information**

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**Organisations:** Novo Nordisk Foundation Center for Biosustainability, Research Groups, iLoop, CFB - Core Flow, Bacterial Cell Factories, Metagenomics, Fungal Cell Factories, KTH - Royal Institute of Technology, University of Copenhagen

**Authors:** Kildegaard, K. R. (Intern), Hallström, B. M. (Ekstern), Blicher, T. H. (Ekstern), Sonnenschein, N. (Intern), Jensen, N. B. (Intern), Sherstyk, S. (Intern), Harrison, S. J. (Intern), Maury, J. (Intern), Herrgard, M. (Intern), Juncker, A. (Intern), Förster, J. (Intern), Nielsen, J. (Intern), Borodina, I. (Intern)

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Scopus rating (2004): SJR 1.657 SNIP 1.261
Scopus rating (2003): SJR 1.168 SNIP 0.884
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 1.182 SNIP 1.028
Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 0.921 SNIP 0.766
Scopus rating (2000): SJR 0.724 SNIP 0.896
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10.1016/j.ymben.2014.09.004
Source: PublicationPreSubmission
Source-ID: 100811114
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**Genetically engineered yeast**

A genetically modified Saccharomyces cerevisiae comprising an active fermentation pathway producing 3-HP expresses an exogenous gene expressing the aminotransferase YhxA from Bacillus cereus AH1272 catalysing a transamination reaction between beta-alanine and pyruvate to produce malonate semialdehyde. The yeast may also express a 3-hydroxyisobutyrate dehydrogenase (HiBADH) and a 3-hydroxypropanoate dehydrogenase (3-HPDH) and aspartate 1-decarboxylase. Additionally the yeast may express pyruvate carboxylase and aspartate aminotransferase.

**General information**

State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, Research Groups
Authors: Borodina, I. (Intern), Kildegaard, K. R. (Intern), Förster, J. (Intern), Öberg, F. (Intern)
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Priority number: EP20120188198
Original language: English

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Main Research Area: Technical/natural sciences
Publication: Research › Patent – Annual report year: 2014

**Microbial bioreaction process**

A cis- or trans-stilbenoid of the general formula (1): in which each of R1, R2, R3, R4 and R5 is hydrogen or hydroxy, or a glycosylated or oligomeric form thereof, is produced by cultivating a micro-organism producing said stilbenoid, in a multi-phase system comprising at least an aqueous first phase containing said micro-organism and a second phase immiscible with said aqueous phase in which (e.g. as which) said stilbenoid accumulates. The second phase may be said stilbenoid or a free or encapsulated solvent compatible with the growth of the micro-organism, for instance an ester.

**General information**

State: Published
Organisations: Department of Systems Biology
Authors: Schmidt, H. P. (Ekstern), Katz, M. (Ekstern), Stenhuus, B. (Ekstern), Förster, J. (Intern)
Publication date: 2014

**Publication information**

Microbial production of 3-hydroxypropionic acid

A yeast cell having a reduced level of activity of NAD dependent glyceraldehyde-3-phosphate dehydrogenase (GAPDH) has at least one exogenous gene encoding NADP dependent GAPDH and/or has up-regulation of at least one endogenous gene expressing NADP dependent GAPDH, wherein combined expression of the enzymes NADP dependent GAPDH, PDC, ALD, ACS, ACC* and MCR in said host cell increases metabolic flux towards 3-HP via malonyl-CoA compared to an otherwise similar yeast cell lacking said genetic modification.

Development of new USER-based cloning vectors for multiple genes expression in Saccharomyces cerevisiae

Saccharomyces cerevisiae is one of the most widely used cell factory in industrial biotechnology and it is used for the production of fuels, chemicals, food ingredients, food and beverages, and pharmaceuticals. Such bioprocesses frequently require multiple rounds of metabolic engineering to obtain the production strain with the proper phenotype and product yield. However, the sequential number of metabolic engineering is time-consuming. Furthermore, the number of available selectable markers is also limiting the number of genetic modifications. To overcome these limitations, we have developed a new set of shuttle vectors for convenience of use for high-throughput cloning and selectable marker recycling. The new USER-based cloning vectors consist of a unique USER site and a CRE-loxP-mediated marker recycling system. The USER site allows insertion of genes of interest along with a bidirectional promoter of choice into the vector backbone with time- and cost-effective. The selectable marker cassette is flanked by loxP recognition sites for the CreA recombinase to allow reutilization of the same selectable marker. Furthermore, our USER vector set provides a choice of different selectable markers both auxotrophic and dominant markers for convenience of use. Our vector set also contains both integrating and multicopy vectors for stability of protein expression and high expression level. We will make the new vector system available to the yeast community and provide a comprehensive protocol for cloning in these vectors using USER cloning strategy.
Genomic landscapes of Chinese hamster ovary cell lines as revealed by the Cricetulus griseus draft genome.

Chinese hamster ovary (CHO) cells, first isolated in 1957, are the preferred production host for many therapeutic proteins. Although genetic heterogeneity among CHO cell lines has been well documented, a systematic, nucleotide-resolution characterization of their genotypic differences has been stymied by the lack of a unifying genomic resource for CHO cells. Here we report a 2.4-Gb draft genome sequence of a female Chinese hamster, Cricetulus griseus, harboring 24,044 genes. We also resequenced and analyzed the genomes of six CHO cell lines from the CHO-K1, DG44 and CHO-S lineages. This analysis identified hamster genes missing in different CHO cell lines, and detected >3.7 million single-nucleotide polymorphisms (SNPs), 551,240 indels and 7,063 copy number variations. Many mutations are located in genes with functions relevant to bioprocessing, such as apoptosis. The details of this genetic diversity highlight the value of the hamster genome as the reference upon which CHO cells can be studied and engineered for protein production.
Microorganisms for the production of 5-hydroxytryptophan

Recombinant microbial cells and methods for producing 5-hydroxytryptophan (5HTP) using such cells are described. More specifically, the recombinant microbial cell comprises an exogenous gene encoding an L-tryptophan hydroxylase, and means for providing tetrahydrobiopterin (THB). Related sequences and vectors for use in preparing such recombinant microbial cells are also described.

General information
State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, CFB - Core Flow, Bacterial Cell Factories
Authors: Knight, E. M. (Intern), Zhu, J. (Intern), Förster, J. (Intern), Luo, H. (Intern)
Publication date: 2013

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Patent number: WO2013127914
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Priority date: 29/02/2012
Priority number: EP20120157540
Original language: English
Microorganisms for the production of melatonin

Recombinant microbial cells and methods for producing melatonin and related compounds using such cells are described. More specifically, the recombinant microbial cell may comprise exogenous genes encoding one or more of an L-tryptophan hydroxylase, a 5-hydroxy-L-tryptophan decarboxylase, a serotonin acetyltransferase, an acetylserotonin O-methyltransferase; an L-tryptophan decarboxylase, and a tryptamine-5-hydroxylase, and means for providing tetrahydrobiopterin (THB). Related sequences and vectors for use in preparing such recombinant microbial cells are also described.

Understanding the 3-hydroxypropionic acid tolerance mechanism in Saccharomyces cerevisiae

3-Hydroxypropionic acid (3HP) is an important platform chemical that can be converted into other valuable chemicals such as acrylic acid and its derivatives that are used in baby diapers, various plastics, and paints. With the oil and gas resources becoming limiting, biotechnology offers a sustainable alternative for production of acrylic acid from renewable feedstocks. We are establishing Saccharomyces cerevisiae as an alternative host for 3HP production. However, 3HP also inhibits yeast growth at levels well below what is desired for commercial applications. Therefore, we are aiming to improve 3HP tolerance in S. cerevisiae by applying adaptive evolution approach. We have generated yeast strains with significantly improved capacity for tolerating 3HP when compared to the wild-type. We will present physiological characterization, genome re-sequencing, and transcriptome analysis of the evolved strains. Consequently, mechanism underlying 3HP tolerance will be investigated.
Compositions and methods for modeling Saccharomyces cerevisiae metabolism

The invention provides an in silico model for determining a S. cerevisiae physiological function. The model includes a data structure relating a plurality of S. cerevisiae reactants to a plurality of S. cerevisiae reactions, a constraint set for the plurality of S. cerevisiae reactions, and commands for determining a distribution of flux through the reactions that is predictive of a S. cerevisiae physiological function. A model of the invention can further include a gene database containing information characterizing the associated gene or genes. The invention further provides methods for making an in silico S. cerevisiae model and methods for determining a S. cerevisiae physiological function using a model of the invention.

General information
State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, Research Groups
Authors: Palsson, B. (Ekstern), Famili, I. (Ekstern), Fu, P. (Ekstern), Nielsen, J. B. (Ekstern), Förster, J. (Intern)
Publication date: 2012

Publication information
IPC: G01N33/48; G06F17/30; G06F19/00
Patent number: WO03036296
Date: 13/06/2012
Priority date: 26/10/2001
Priority number: US20010344447P
Original language: English
Electronic versions:

Bibliographical note
Also published as: WO03036296 (A1); WO03036296 (A9); US2010280803 (A1); US8170852 (B2); US2003228567 (A1); US7751981 (B2); JP2012164338 (A); JP2009187562 (A); JP5081187 (B2); JP2005507108 (A); EP2434421 (A2); EP2434421 (A3); EP1438580 (A1); EP1438580 (A4); CA2462099 (A1); CA2462099 (C); AU2002348089 (B2)
Main Research Area: Technical/natural sciences
Source: PublicationPreSubmission
Source-ID: 103122147
Publication: Research › Patent – Annual report year: 2012

Genome-scale metabolic representation of Amycolatopsis balhimycina
Infection caused by methicillin-resistant Staphylococcus aureus (MRSA) is an increasing societal problem. Typically, glycopeptide antibiotics are used in the treatment of these infections. The most comprehensively studied glycopeptide antibiotic biosynthetic pathway is that of balhimycin biosynthesis in Amycolatopsis balhimycina. The balhimycin yield obtained by A. balhimycina is, however, low and there is therefore a need to improve balhimycin production. In this study, we performed genome sequencing, assembly and annotation analysis of A. balhimycina and further used these annotated data to reconstruct a genome-scale metabolic model for the organism. Here we generated an almost complete A. balhimycina genome sequence comprising 10,562,587 base pairs assembled into 2,153 contigs. The high GC-genome (~69%) includes 8,585 open reading frames (ORFs). We used our integrative toolbox called SEQTOR for functional annotation and then integrated annotated data with biochemical and physiological information available for this organism to reconstruct a genome-scale metabolic model of A. balhimycina. The resulting metabolic model contains 583 ORFs as protein encoding genes (7% of the predicted 8,585 ORFs), 407 EC numbers, 647 metabolites and 1,363 metabolic reactions. During the analysis of the metabolic model, linear, quadratic and evolutionary programming algorithms using flux balance analysis (FBA), minimization of metabolic adjustment (MOMA), and OptGene, respectively were applied as well as phenotypic behavior and improved balhimycin production were simulated. The A. balhimycina model shows a good agreement between in silico data and experimental data and also identifies key reactions associated with increased balhimycin production. The reconstruction of the genome-scale metabolic model of A. balhimycina serves as a basis for physiological characterization. The model allows a rational design of engineering strategies for increasing balhimycin production in A. balhimycina and glycopeptide production in general. Biotechnol. Bioeng. 2012; 109:1798–1807. © 2012 Wiley Periodicals, Inc.

General information
USER-based vector set for high-throughput cloning and metabolic engineering in *Saccharomyces cerevisiae*

**General information**

State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, Research Groups, Yeast Metabolic Engineering, CFB - Core Flow, Applied Metabolic Engineering, Department of Systems Biology, Eucaryotic Molecular Cell Biology, iLoop
Number of pages: 1
Publication date: 2012
Event: Abstract from The 13th International Congress on Yeasts, Madison, Wisconsin, United States.
Main Research Area: Technical/natural sciences
Source: PublicationPreSubmission
Source-ID: 118363831
Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2012

**Production of Metabolites**

A recombinant micro-organism such as *Saccharomyces cerevisiae* which produces and excretes into culture medium a stilbenoid metabolite product when grown under stilbenoid production conditions, which expresses in above native levels a ABC transporter which transports said stilbenoid out of said micro-organism cells to the culture medium. The genome of the *Saccharomyces cerevisiae* produces an auxotrophic phenotype which is compensated by a plasmid which also expresses one or more of said enzymes constituting said metabolic pathway producing said stilbenoid, an expression product of the plasmid is genetically modified to include a ubiquitination tag sequence. Expression of an enzyme participating in catabolism of phenylalanine by the Ehrlich pathway is optionally reduced compared to its native expression level.

**General information**

State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, CFB - Core Flow
Authors: Katz, M. (Ekstern), Durhuus, T. (Ekstern), Smits, H. P. (Intern), Förster, J. (Intern)
Publication date: 2011

**Publication information**

Patent number: WO2011147818
Date: 01/12/2011
Priority date: 26/05/2010
Priority number: 1008826.8
Original language: English
Electronic versions:
19B5Cd01.pdf
Resveratol - sundhedsfremmende effekter, produktionsmuligheder og forventninger
Populært kaldet rødvinsmedicin

**General information**
State: Published
Organisations: Roskilde University, Fluxome A/S
Authors: Sassi, S. (Ekstern), Vang, O. (Forskerdatabase), Förster, J. (Intern)
Pages: 18-21
Publication date: 2010
Main Research Area: Technical/natural sciences

**Publication information**
Journal: Dansk Kemi
Volume: 91
Issue number: 8
ISSN (Print): 0011-6335
Ratings:
ISI indexed (2013): ISI indexed no
ISI indexed (2012): ISI indexed no
ISI indexed (2011): ISI indexed no
Web of Science (2007): Indexed yes
Web of Science (2004): Indexed yes
Original language: Danish
Source: dtu
Source-ID: n::oai:DTIC-ART:dkart/277261643::19512
Publication: Research - peer-review › Journal article – Annual report year: 2010

Recovery of stilbenoids
A cis- or trans- stilbenoid of the general formula (1) in which each of R1, R2, R3, R4 and R5 is hydrogen or hydroxy, or a glycosylated or oligomeric form thereof, such as resveratrol or pinosylvin is produced by cultivating a microorganism such as a genetically engineered yeast to produce said stilbenoid in a culture medium in solid form, and is separated by filtration or settling.

**General information**
State: Published
Organisations: Department of Systems Biology
Authors: Smits, H. P. (Intern), David, H. S. M. (Intern), Förster, J. (Intern), Stenhuus, B. (Ekstern)
Publication date: 2009

**Publication information**
Patent number: WO2009124967
Date: 15/10/2009
Priority date: 11/04/2009
Priority number: GB20080006595
Original language: English
Electronic versions:
WO2009124967A2_1.pdf

**Bibliographical note**
Also published as:WO2009124967 (A3); US2011086399 (A1); EP2265722 (A2); AU2009235411 (A1); AU2009235411 (B2)
Main Research Area: Technical/natural sciences
Source: PublicationPreSubmission
Source-ID: 103122638
Publication: Research › Patent – Annual report year: 2009

**Securing the supply of functional ingredients.**
This article discusses the health benefits of trans resveratrol and PUFA as functional food ingredients, together with their production by fermentation of microorganisms such as Saccharomyces cerevisiae.
Design and Application of Genome-Scale Reconstructed Metabolic Models

In this chapter, the process for the reconstruction of genome-scale metabolic networks is described, and some of the main applications of such models are illustrated. The reconstruction process can be viewed as an iterative process where information obtained from several sources is combined to construct a preliminary set of reactions and constraints. This involves steps such as genome annotation; identification of the reactions from the annotated genome sequence and available literature; determination of the reaction stoichiometry; definition of compartmentation and assignment of localization; determination of the biomass composition; measurement, calculation, or fitting of energy requirements; and definition of additional constraints. The reaction and constraint sets, after debugging, may be integrated into a stoichiometric model that can be used for simulation using tools such as Flux Balance Analysis (Section 3.8). From the flux distributions obtained, physiologic parameters such as growth yields or minimal medium components can be calculated, and their distance from similar experimental data provides a basis from where the model may need to be improved.

Metabolically engineered cells for the production of pinostravin

A genetically engineered micro-organism having an operative metabolic pathway producing cinnamoyl-CoA and producing pinostravin therefrom by the action of a stilbene synthase is used for pinostravin production. Said cinnamic acid may be formed from L-phenylalanine by a L-phenylalanine ammonia lyase (PAL) which is one accepting phenylalanine as a substrate and producing cinnamic acid therefrom, preferably such that if the PAL also accepts tyrosine as a substrate and forms coumaric acid therefrom, the ratio Km(phenylalanine)/Km(tryptophane) for said PAL is less than 1:1 and if said micro-organism produces a cinammatate-4-hydroxylase enzyme (C4H), the ratio Kcat(PAL)/Kcat(C4H) is at least 2:1.
Metabolically Engineered Fungal Cells With Increased Content Of Polyunsaturated Fatty Acids

This invention relates to the production of fatty acids and particularly to the production of the polyunsaturated fatty acids (PUFAs) arachidonic acid (ARA) and eicosapentaenoic acid (EPA) in genetically engineered fungal cells, in particular, to metabolically engineered Saccharomyces cerevisiae cells with increased content of ARA and EPA. The invention especially involves improvement of the PUFA content in the host organism through various over-expression of e.g. cytochrome b5 and cytochrome b5 reductase involved in fatty acid desaturation, and heterologous expression of cytochrome b5 and cytochrome b5 reductase and expression of heterologous fatty acid synthases.

General information
State: Published
Organisations: Department of Systems Biology
Authors: Förster, J. (Intern), Gunnarsson, N. K. (Ekstern), Svensson, E. M. (Ekstern), David, H. S. M. (Intern), Plate, I. (Intern), de Andrade, P. T. S. (Ekstern), Mouillion, J. (Ekstern), Petersen Bjørn, S. (Intern), Møller, P. (Intern)
Publication date: 2008

Characterization of a cyanobacterial-like uptake [NiFe] hydrogenase: EPR and FTIR spectroscopic studies of the enzyme from Acidithiobacillus ferrooxidans

Electron paramagnetic resonance (EPR) and Fourier transform IR studies on the soluble hydrogenase from Acidithiobacillus ferrooxidans are presented. In addition, detailed sequence analyses of the two subunits of the enzyme have been performed. They show that the enzyme belongs to a group of uptake [NiFe] hydrogenases typical for cyanobacteria. The sequences have also a close relationship to those of the H2-sensor proteins, but clearly differ from those of standard [NiFe] hydrogenases. It is concluded that the structure of the catalytic centre is similar, but not identical, to that of known [NiFe] hydrogenases. The active site in the majority of oxidized enzyme molecules, 97% in cells and more than 50% in the purified enzyme, is EPR-silent. Upon contact with H2 these sites remain EPR-silent and show only a limited IR response. Oxidized enzyme molecules with an EPR-detectable active site show a Nir*-like EPR signal which is light-sensitive at cryogenic temperatures. This is a novelty in the field of [NiFe] hydrogenases. Reaction with H2 converts these active sites to the well-known Nia-C* state. Illumination below 160 K transforms this state into the Nia-L* state. The reversal, in the dark at 200 K, proceeds via an intermediate Ni EPR signal only observed with the H2-sensor protein from Ralstonia eutropha. The EPR-silent active sites in as-isolated and H2-treated enzyme are also light-sensitive as observed by IR spectra at cryogenic temperatures. The possible origin of the light sensitivity is discussed. This study represents the first spectral characterization of an enzyme of the group of cyanobacterial uptake hydrogenases.

General information
State: Published
In silico aided metabolic engineering of \textit{Saccharomyces cerevisiae} for improved bioethanol production.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Microbial Biotechnology, Fluxome Sciences A/S
Authors: Bro, C. (Intern), Regenberg, B. (Intern), Förster, J. (Intern), Nielsen, J. (Intern)
Pages: 102-111
Publication date: 2006
Main Research Area: Technical/natural sciences

**Publication information**

Journal: Metabolic Engineering
Volume: 8
Original language: English
DOIs:
10.1016/j.ymben.2005.09.007
Source: orbit
Source-ID: 190412
Publication: Research - peer-review › Journal article – Annual report year: 2007

Metabolically engineered cells for the production of resveratrol or an oligomeric or glycosidically-bound derivative thereof

A recombinant micro-organism producing resveratrol by a pathway in which phenylalanine ammonia lyase (PAL) produces trans-cinnamic acid from phenylalanine, cinnamate 4- hydroxylase (C4H) produces 4-coumaric acid from said trans-cinnamic acid, 4-coumarate-CoA ligase (4CL) produces 4-coumaroyl CoA from said 4-coumaric acid, and resveratrol synthase (VST) produces resveratrol from said 4-coumaroyl CoA, or in which L-phenylalanine- or tyrosine- ammonia lyase (PAL/TAL) produces 4-coumaric acid, 4-coumarate-CoA ligase (4CL) produces 4-coumaroyl CoA from said 4-coumaric acid, and resveratrol synthase (VST) produces resveratrol from said 4-coumaroyl CoA. The micro-organism may be a yeast, fungus or bacterium including \textit{Saccharomyces cerevisiae}, \textit{E. coli}, \textit{Lactococcus lactis}, \textit{Aspergillus niger}, or \textit{Aspergillus oryzae}.

**General information**

State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, Research Groups
Authors: Katz, M. (Ekstern), Smits, H. P. (Intern), Förster, J. (Intern), Bredal Nielsen, J. (Ekstern)
Publication date: 2006

**Publication information**

Patent number: WO2006089898
Date: 31/08/2006
Priority date: 22/02/2005
Priority number: GB20050003657
Original language: English
Electronic versions:
WO2006089898A1.pdf
Main Research Area: Technical/natural sciences
Source: PublicationPreSubmission
Source-ID: 103122416
Publication: Research › Patent – Annual report year: 2006

Evolutionary programming as a platform for in silico metabolic engineering

Background Through genetic engineering it is possible to introduce targeted genetic changes and hereby engineer the metabolism of microbial cells with the objective to obtain desirable phenotypes. However, owing to the complexity of metabolic networks, both in terms of structure and regulation, it is often difficult to predict the effects of genetic modifications on the resulting phenotype. Recently genome-scale metabolic models have been compiled for several different microorganisms where structural and stoichiometric complexity is inherently accounted for. New algorithms are being developed by using genome-scale metabolic models that enable identification of gene knockout strategies for obtaining improved phenotypes. However, the problem of finding optimal gene deletion strategy is combinatorial and consequently the computational time increases exponentially with the size of the problem, and it is therefore interesting to develop new faster algorithms. Results In this study we report an evolutionary programming based method to rapidly identify gene deletion strategies for optimization of a desired phenotypic objective function. We illustrate the proposed method for two important design parameters in industrial fermentations, one linear and other non-linear, by using a

Evolutionary programming as a platform for in silico metabolic engineering

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genome-scale model of the yeast Saccharomyces cerevisiae. Potential metabolic engineering targets for improved production of succinic acid, glycerol and vanillin are identified and underlying flux changes for the predicted mutants are discussed. Conclusion We show that evolutionary programming enables solving large gene knockout problems in relatively short computational time. The proposed algorithm also allows the optimization of non-linear objective functions or incorporation of non-linear constraints and additionally provides a family of close to optimal solutions. The identified metabolic engineering strategies suggest that non-intuitive genetic modifications span several different pathways and may be necessary for solving challenging metabolic engineering problems.

General information
State: Published
Organisations: Center for Microbial Biotechnology, Department of Systems Biology, University of Minho
Authors: Patil, K. R. (Intern), Rocha, I. (Ekstern), Förster, J. (Intern), Nielsen, J. (Intern)
Pages: 308
Publication date: 2005
Main Research Area: Technical/natural sciences

Publication information
Journal: BMC Bioinformatics
Volume: 6
ISSN (Print): 1471-2105
Ratings:
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.54 SJR 1.467 SNIP 0.946
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.656 SNIP 1.077 CiteScore 2.77
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.836 SNIP 1.202 CiteScore 2.91
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.932 SNIP 1.335 CiteScore 3.38
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.857 SNIP 1.155 CiteScore 3.24
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.655 SNIP 1.215 CiteScore 3.34
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.756 SNIP 1.15
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.89 SNIP 1.32
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.945 SNIP 1.146
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 1.971 SNIP 1.129
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 1.885 SNIP 1.207
Scopus rating (2005): SJR 2.49 SNIP 1.568
Metabolically engineered cells for the production of polyunsaturated fatty acids

The present invention relates to the construction and engineering of cells, more particularly microorganisms for producing PUFAs with four or more double bonds from non-fatty acid substrates through heterologous expression of an oxygen requiring pathway. The invention especially involves improvement of the PUFA content in the host organism through fermentation optimization, e.g. decreasing the temperature and/or designing an optimal medium, or through improving the flux towards fatty acids by metabolic engineering, e.g. through over-expression of fatty acid synthases, over-expression of other enzymes involved in biosynthesis of the precursor for PUFAs, or codon optimization of the heterologous genes, or expression of heterologous enzymes involved in the biosynthesis of the precursor for PUFAs.

Modeling Lactococcus lactis using a genome-scale flux model

General information
State: Published
Organisations: Department of Systems Biology
Authors: Soberano de Oliveira, A. P. (Intern), Nielsen, J. (Intern), Förster, J. (Intern)
Publication: Research - peer-review › Journal article – Annual report year: 2005
Reconstruction of the Mus musculus metabolic network (2005).
The reconstructed cellular metabolic network of Mus musculus, based on annotated genomic data, pathway databases, and currently available biochemical and physiological information, is presented. Although incomplete, it represents the first attempt to collect and characterize the metabolic network of a mammalian cell on the basis of genomic data. The reaction network is generic in nature and attempts to capture the carbon, energy, and nitrogen metabolism of the cell. The metabolic reactions were compartmentalized between the cytosol and the mitochondria, including transport reactions between the compartments and the extracellular medium. The reaction list consists of 872 internal metabolites involved in a total of 1220 reactions, whereof 473 relate to known open reading frames. Initial in silico analysis of the reconstructed model is presented.

General information
State: Published
Organisations: Technical University of Denmark, University of Queensland
Authors: Förster, J. (Intern), Sheikh, K. (Ekstern), Nielsen, L. K. (Ekstern)
Pages: 112-121
Publication date: 2005
Main Research Area: Technical/natural sciences

Publication information
Journal: Biotechnology progress
Volume: 21
Issue number: 1
ISSN (Print): 8756-7938
Ratings:
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.12 SJR 0.668 SNIP 0.762
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.727 SNIP 0.825 CiteScore 2.07
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.808 SNIP 0.931 CiteScore 2.2
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.764 SNIP 0.847 CiteScore 2.16
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.84 SNIP 0.868 CiteScore 2.35
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.918 SNIP 0.956 CiteScore 2.4
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.988 SNIP 0.947
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.965 SNIP 1.047
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.887 SNIP 0.992
Scopus rating (2007): SJR 1.011 SNIP 1.093
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 0.973 SNIP 1.108
Web of Science (2006): Indexed yes
En route for Systems Biology: In silico pathway analysis and metabolite profiling.

**General information**

State: Published
Organisations: Technical University of Denmark
Authors: Förster, J. (Intern), Åkesson, M. F. (Ekstern), Nielsen, J. (Ekstern)
Pages: 47-60
Publication date: 2004

**Host publication information**

Title of host publication: Function and regulation of cellular systems
Publisher: Birkhäuser Verlag GmbH
ISBN (Print): 3-7643-6925-6
Main Research Area: Technical/natural sciences

**Bibliographical note**

Source: dtu
Source-ID: u::5028
Publication: Research - peer-review › Book chapter – Annual report year: 2004

**Integration of gene expression data into genome-scale metabolic models**

A framework for integration of transcriptome data into stoichiometric metabolic models to obtain improved flux predictions is presented. The key idea is to exploit the regulatory information in the expression data to give additional constraints on the metabolic fluxes in the model. Measurements of gene expression from chemostat and batch cultures of Saccharomyces cerevisiae were combined with a recently developed genome-scale model, and the computed metabolic flux distributions were compared to experimental values from carbon labeling experiments and metabolic network analysis. The integration of expression data resulted in improved predictions of metabolic behavior in batch cultures, enabling quantitative predictions of exchange fluxes as well as qualitative estimations of changes in intracellular fluxes. A critical discussion of correlation between gene expression and metabolic fluxes is given.

**General information**

State: Published
Organisations: Center for Microbial Biotechnology, Department of Systems Biology
Authors: Åkesson, M. (Ekstern), Förster, J. (Intern), Nielsen, J. (Intern)
Pages: 285-273
Publication date: 2004
Main Research Area: Technical/natural sciences

**Publication information**

Journal: Metabolic Engineering
Volume: 6
Genome-scale reconstruction of the Saccharomyces cerevisiae metabolic network

The metabolic network in the yeast Saccharomyces cerevisiae was reconstructed using currently available genomic, biochemical, and physiological information. The metabolic reactions were compartmentalized between the cytosol and the mitochondria, and transport steps between the compartments and the environment were included. A total of 708 structural open reading frames (ORFs) were accounted for in the reconstructed network, corresponding to 1035 metabolic reactions. Further, 140 reactions were included on the basis of biochemical evidence resulting in a genome-scale reconstructed metabolic network containing 1175 metabolic reactions and 584 metabolites. The number of gene functions included in the reconstructed network corresponds to similar to 16% of all characterized ORFs in S. cerevisiae. Using the reconstructed network, the metabolic capabilities of S. cerevisiae were calculated and compared with Escherichia coli. The reconstructed metabolic network is the first comprehensive network for a eukaryotic organism, and it may be used as the basis for in silico analysis of phenotypic functions.
Large-scale evaluation of in silico gene deletions in Saccharomyces cerevisiae

A large-scale in silico evaluation of gene deletions in Saccharomyces cerevisiae was conducted using a genome-scale reconstructed metabolic model. The effect of 599 single gene deletions on cell viability was simulated in silico and compared to published experimental results. In 526 cases (87.8%), the in silico results were in agreement with experimental observations when growth on synthetic complete medium was simulated. Viable phenotypes were correctly predicted in 89.4% (496 out of 555) and lethal phenotypes were correctly predicted in 68.2% (30 out of 44) of the cases considered. The in silico evaluation was solely based on the topological properties of the metabolic network which is based on well-established reaction stoichiometry. No interaction or regulatory information was accounted for in the in silico model. False predictions were analyzed on a case-by-case basis for four possible inadequacies of the in silico model: (1) incomplete media composition, (2) substitutable biomass components, (3) incomplete biochemical information, and (4) missing regulation. This analysis eliminated a number of false predictions and suggested a number of experimentally testable hypotheses. A genome-scale in silico model can thus be used to systematically reconcile existing data and fill in our knowledge gaps about an organism.
Metabolic engineering in *Saccharomyces cerevisiae* through the use of a reconstructed genome-scale metabolic network leads to improved ethanol production

**General information**

State: Published
Organisations: Center for Microbial Biotechnology, Department of Systems Biology
Authors: Bro, C. (Intern), Regenberg, B. (Intern), Förster, J. (Intern), Nielsen, J. (Intern)
Pages: S284-S284
Publication date: 2003
Main Research Area: Technical/natural sciences

**Publication information**

Journal: Yeast
Volume: 20
Issue number: 1
ISSN (Print): 0749-503X

**Ratings:**

BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
Scopus rating (2017): SJR 0.816 SNIP 0.811 CiteScore 1.87
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.962 SNIP 0.745 CiteScore 2.01
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.875 SNIP 0.792 CiteScore 1.67
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.232 SNIP 0.72 CiteScore 2.09
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.197 SNIP 0.762 CiteScore 2.05
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.063 SNIP 0.701 CiteScore 1.77
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.049 SNIP 0.835
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.584 SNIP 0.81
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Pathway Analysis of the Metabolic Network of Saccharomyces Cerevisiae

General information
State: Published
Organisations: Center for Microbial Biotechnology, Department of Systems Biology
Authors: Förster, J. (Intern)
Publication date: 2003

Publication information
Original language: English
Main Research Area: Technical/natural sciences
Source: orbit
Source-ID: 155219
Publication: Research › Ph.D. thesis – Annual report year: 2003

Saccharomyces cerevisiae phenotypes can be predicted using constraint based analysis of a genome-scale reconstructed metabolic network

General information
State: Published
Organisations: Department of Systems Biology
Authors: Famili, I. (Ekstern), Förster, J. (Intern), Nielsen, J. (Intern), Palsson, B. (Ekstern)
Pages: 13134-13139
Publication date: 2003
Main Research Area: Technical/natural sciences

Publication information
Journal: Proceedings of the National Academy of Sciences of the USA
Volume: 100
Original language: English
Source: orbit
Source-ID: 46129
Publication: Research - peer-review › Journal article – Annual report year: 2003

Aerobic glucose metabolism of Saccharomyces kluyveri: Growth, metabolite production, and quantification of metabolic fluxes
The growth and product formation of Saccharomyces kluyveri was characterized in aerobic batch cultivation on glucose. At these conditions it was found that ethyl acetate was a major overflow metabolite in S. kluyveri. During the exponential-
growth phase on glucose ethyl acetate was produced at a constant specific rate of 0.12 g ethyl acetate per g dry weight per hour. The aerobic glucose metabolism in S. kluyveri was found to be less fermentative than in S. cerevisiae, as illustrated by the comparably low yield of ethanol on glucose (0.08 +/- 0.02 g/g), and high yield of biomass on glucose (0.29 +/- 0.01 g/g). The glucose metabolism of S. kluyveri was further characterized by the new and powerful techniques of metabolic network analysis. Flux distributions in the central carbon metabolism were estimated for respiro-fermentative growth in aerobic batch cultivation on glucose and respiratory growth in aerobic glucose-limited continuous cultivation. It was found that in S. kluyveri the flux into the pentose phosphate pathway was 18.8 mmole per 100 mmole glucose consumed during respiratory growth in aerobic glucose-limited continuous cultivation. Such a low flux into the pentose phosphate pathway cannot provide the cell with enough NADPH for biomass formation which is why the remaining NADPH will have to be provided by another pathway. During batch cultivation of S. kluyveri the tricarboxylic acid cycle was working as a cycle with a considerable flux, that is in sharp contrast to what has previously been observed in S. cerevisiae at the same growth conditions, where the tricarboxylic acid cycle operates as two branches. This indicates that the respiratory system was not significantly repressed in S. kluyveri during batch cultivation on glucose.
A functional genomics approach using metabolomics and in silico pathway analysis

In the field of functional genomics increasing effort is being undertaken to analyze the function of orphan genes using metabolome data. Improved analytical equipment allows screening simultaneously for a high number of metabolites. Such metabolite profiles are analyzed using multivariate data analysis techniques and changes in the genotype will in many cases lead to different metabolite profiles. Here, a theoretical framework that may be applied to identify the function of orphan genes is presented. The approach is based on a combination of metabolome analysis combined with in silico pathway analysis. Pathway analysis may be carried out using convex analysis and a change in the active pathway structure of deletion mutants expressed in a different metabolite profile may disclose the function or the functional class of an orphan gene. The concept is illustrated using a simplified model for growth of Saccharomyces cerevisiae.

General information
State: Published
Organisations: Center for Microbial Biotechnology
Authors: Förster, J. (Intern), Gombert, A. K. (Intern), Nielsen, J. (Intern)
Pages: 703-712
Publication date: 2002
Main Research Area: Technical/natural sciences

Publication information
Journal: Biotechnology and Bioengineering (Print)
Volume: 79
Issue number: 7
ISSN (Print): 0006-3592
Ratings:
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.14 SJR 1.411 SNIP 1.163
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.613 SNIP 1.37 CiteScore 4.44
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.589 SNIP 1.401 CiteScore 4.16
Production of activated charcoal beads or green moldings useful in stationary or fluidized bed uses rotary stirrer(s) for mixing carbonaceous powder with binder

In the production of activated charcoal beads or green moldings by mixing carbonaceous powder with a binder, mixing is carried out in a stirred vessel with rotary stirrer(s).

General information
State: Published
Organisations: Department of Systems Biology
Authors: Förster, J. (Intern), Feseker, M. (Ekstern), Guderian, J. (Ekstern)
Projects:

Flavor Tailoring for Future Brewing: Unleashing the Yeast Diversity Potential
National Food Institute
Period: 01/09/2016 → 31/08/2019
Number of participants: 4
Phd Student:
Colomer, Marc Serra (Ekstern)
Supervisor:
Förster, Jochen (Intern)
Mortensen, Uffe Hasbro (Intern)
Main Supervisor:
Hobley, Timothy John (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Industrial PhD
Project: PhD

ThermoFactories - Thermophilic cell factories for efficient conversion of brown algae biomass to high-value chemicals
Novo Nordisk Foundation Center for Biosustainability
Applied Metabolic Engineering
Period: 01/02/2016 → 31/01/2019
Number of participants: 1
Acronym: ThermoFactories
Project participant:
Förster, Jochen (Intern)

Development of tools for precise genome engineering in lactic acid bacteria and their implementation in construction of bacterial cell factories
Novo Nordisk Foundation Center for Biosustainability
Applied Metabolic Engineering
Period: 01/11/2015 → 30/11/2017
Number of participants: 2
Project participant:
Förster, Jochen (Intern)
Dudnik, Alexey (Intern)
Assessing Life Cycle Impacts of Bio-plastics from Dicarboxylic Acids
Novo Nordisk Foundation Center for Biosustainability
Applied Metabolic Engineering
Quantitative Sustainability Assessment
Department of Management Engineering
Period: 01/11/2015 → 30/11/2018
Number of participants: 4
Phd Student:
Ögmundarson, Ólafur (Intern)
Supervisor:
Fantke, Peter (Intern)
Förster, Jochen (Intern)
Olsen, Stig Irving (Intern)

Engineered yeast strains for the production of bulk chemicals from algae biomass
Novo Nordisk Foundation Center for Biosustainability
Applied Metabolic Engineering
Department of Chemical and Biochemical Engineering
CAPEC-PROCESS
Period: 15/10/2015 → 14/10/2018
Number of participants: 3
Project participant:
Förster, Jochen (Intern)
Gernaey, Krist V. (Intern)
Phd Student:
Porcayo Loza, Javier (Intern)

Synthetic biochemical pathways for efficient production of novel biofuels
ERA-SynbBio Project
Novo Nordisk Foundation Center for Biosustainability
Applied Metabolic Engineering
iLoop
Period: 01/12/2014 → 30/11/2017
Number of participants: 3
Acronym: SynPath
Phd Student:
Wordofa, Gossa Garedew (Intern)
Supervisor:
Kristensen, Mette (Intern)
Main Supervisor:
Förster, Jochen (Intern)

Designer yeast strain library optimized for metabolic engineering applications
ERA-IB Project
Novo Nordisk Foundation Center for Biosustainability
Applied Metabolic Engineering
Period: 01/03/2014 → 29/02/2016
Number of participants: 2
Acronym: DeYeastLibrary
Project participant:
**Industrial Yeast Platform Development**

Novo Nordisk Foundation Center for Biosustainability

*Applied Metabolic Engineering*

**Period:** 01/02/2014 → 31/12/2015  
**Number of participants:** 3  
**Acronym:** IndY

**Project participant:**  
Förster, Jochen (Intern)  
Dato, Laura (Intern)  
Bergdahl, Basti (Intern)

**From BACterial Hosts for production of Bioactive phenolics from bERRY fruits to products**

In the era of increased environmental and health awareness new ways are being explored how to fully exploit to this day unrivalled natural resources with renewable bio-production. These new production methods will generate a sustainable pipeline of environmentally-friendly methods to enable production of pharma and agrochemical products with bioactive properties from berry fruits.

This project stands out in bringing together the most recent technologies within the framework of systems metabolic engineering to develop the next-generation bacterial cell factories for the production of plant phenolics, and in applying it to phenolic compounds from cultivated, wild and underutilized species of berries - recognized for their antioxidant, health-promoting and functional properties and applied across applications as diverse as aromas, colours, nutraceuticals and medicines.

BacHBERRY (From BACterial Hosts for production of Bioactive phenolics from bERRY fruits to products) sets out over a three year period to develop a portfolio of sustainable methodologies to mine the potential of the untapped biodiversity of the bioactive phenolic compounds in an extensive collection of berry species. Full exploitation of this unrivalled natural resource requires an integrated and comprehensive effort from bioprospecting in berries using SMART high-throughput screens for the valorisation of phenolic bioactivities aligned with their identification using cutting edge analytics and subsequent elucidation of their biosynthetic pathways. This knowledge will facilitate metabolic engineering of suitable bacterial hosts for high-value phenolics production in scalable fermentation bioprocesses, ultimately serving as commercial production platforms.

Novo Nordisk Foundation Center for Biosustainability

*Research Groups*

- **Quantitative Sustainability Assessment**
  - **Period:** 01/11/2013 → 31/10/2016  
  - **Number of participants:** 7  
  - **Acronym:**  
  - **Project participant:**  
    Gaspar, Paula (Intern)  
    Stahlhut, Steen Gustav (Intern)  
    Ögmundarson, Ólafur (Intern)  
    Project Manager, organisational:  
    Rasmussen, Birte Kastrup (Intern)  
    Lohmann, Ricarda (Intern)  
    Project Manager, academic:  
    Dudnik, Alexey (Intern)  
    Förster, Jochen (Intern)  
  - **Project Coordinator:**
Development of 2nd Generation Biorefineries Production of Dicarboxylic Acids and Bio-based Polymers Derived Thereof

The existing 2nd generation biorefineries utilize less than 20% of the biomass feedstock for ethanol production, and major side-streams are produced such as pentose and lignin waste streams, that are respectively used for biogas and energy production. Converting the carbon from these waste streams into added-value products would increase the otherwise low profitability and improve the environmental benefits of the biorefineries. The suggested project BioREFINE-2G aims at developing commercially attractive processes for efficient conversion of pentose-rich side-streams from biorefineries into dicarboxylic acids, which can be used as precursors for bio-based polymers including biodegradable polymers. The project covers the whole value chain, from characterization of side streams from forest and other non-food feedstock, development of novel robust industrial yeast cell factories, fermentation and downstream process development, to polymerization methods development for the production of biodegradable polymers applicable as plastics, coatings or adhesives, scale-up and demonstration and to life cycle and economic viability analyses.

Novo Nordisk Foundation Center for Biosustainability
Applied Metabolic Engineering
Yeast Metabolic Engineering
Quantitative Sustainability Assessment
Department of Management Engineering
Department of Chemical and Biochemical Engineering

CAPEC-PROCESS
Period: 01/10/2013 → 30/09/2017
Number of participants: 7
Acronym: BioREFINE-2G
Project participant:
Stovicek, Vratislav (Intern)
Rasmussen, Birte Kastrup (Intern)
Lis, Alicia Viktoria (Intern)
Lohmann, Ricarda (Intern)
Phd Student:
Ögmundarson, Ólafur (Intern)
Project Coordinator:
Förster, Jochen (Intern)
Borodina, Irina (Intern)

Financing sources
Source: EU research programme (public)
Name of research programme: EU FP7 KBBE

Relations
Activities:
Strain Development for Diacid Production
Publications:
EasyClone 2.0
CRISPR–Cas system enables fast and simple genome editing of industrial Saccharomyces cerevisiae strains
Project
Production of Human Insulin Precursor using multiple chromosomal integrations & Investigations of strain physiology and secretion bottlenecks

Department of Systems Biology
Period: 01/05/2013 → 13/11/2017
Number of participants: 6
Phd Student:
Jensen, Malene Møller (Intern)
Supervisor:
Gunnarsson, Nina (Intern)
Main Supervisor:
Mortensen, Uffe Hasbro (Intern)
Examiner:
Frandsen, Rasmus John Normand (Intern)
Daran-Lapujade, Pascale (Ekstern)
Förster, Jochen (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Industrial PhD
Project: PhD

Utilize Gasified Biomass and Waste Products (Synthesis Gas) for the Production of Biochemicals

Department of Systems Biology
Period: 01/05/2013 → 29/09/2016
Number of participants: 6
Phd Student:
Redl, Stephanie Maria Anna (Intern)
Supervisor:
Förster, Jochen (Intern)
Main Supervisor:
Nielsen, Alex Toftgaard (Intern)
Examiner:
Herrgard, Markus (Intern)
Simpson, Sean D. (Ekstern)
Soucaille, Philippe (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Marie Curie (EU-stipendium)

Relations
Publications:
Gas Fermentation using Thermophilic Moorella Species for production of Biochemicals
Project: PhD

Enhancing the production of the commercially important feed ingredient L-lysine

Novo Nordisk Foundation Center for Biosustainability

Research Groups
Period: 01/02/2013 → 31/01/2015
Number of participants: 2
Project participant:
Förster, Jochen (Intern)
Wieschalka, Stefan (Intern)

Production of Human Metabolites in E.coli

Novo Nordisk Foundation Center for Biosustainability
CFB - Core Flow

iLoop

Bacterial Cell Factories
Period: 01/01/2013 → 30/09/2014
Number of participants: 3
Project participant:
Förster, Jochen (Intern)
Luo, Hao (Intern)
Zhu, Jiangfeng (Intern)

Biiosensors and genetic circuits for improved cell factory development

Department of Systems Biology
Period: 15/12/2012 → 30/06/2016
Number of participants: 6
Phd Student:
Rugbjerg, Peter (Intern)
Supervisor:
Förster, Jochen (Intern)
Main Supervisor:
Sommer, Morten Otto Alexander (Intern)
Examiner:
Jensen, Michael Krogh (Intern)
Jensen, Niels Bjerg (Intern)
Suess, Beatrix (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU)

Relations
Publications:
Cell Factory Stability and Genetic Circuits for Improved Strain Development
Project: PhD

Sustainable Production of Triterpenes in specialised baker's yeast

Novo Nordisk Foundation Center for Biosustainability

Research Groups
Period: 01/09/2012 → 31/08/2015
Number of participants: 2
Acronym: TRITERP
Project participant:
Förster, Jochen (Intern)
Knuf, Christoph (Intern)

Development of new metabolic engineering technologies for the production of biochemicals

Department of Systems Biology
Period: 01/06/2012 → 25/11/2015
Number of participants: 6
Phd Student:
Ronda, Carlotta (Intern)
Supervisor:
Molin, Søren (Intern)
Main Supervisor:
Nielsen, Alex Toftgaard (Intern)
Examiner:
Förster, Jochen (Intern)
Ingmer, Hanne (Ekstern)
de Gier, Jan-Willem (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU) Samf.

Relations
Publications:
Acceleration of cell factories engineering using CRISPR-based technologies
Project: PhD

**Inbicon sidestrømme**
Identification of production hosts useful in the valorization of streams from application of the Inbicon and REnescience technologies for chemical production
Novo Nordisk Foundation Center for Biosustainability
Period: 01/02/2012 → 01/10/2012
Number of participants: 3
DONG
Acronym: DONG
Project participant:
Stahlhut, Steen Gustav (Intern)
Project Manager, organisational:
Grunnet-Jepsen, Helle Lynnerup (Intern)
Project Manager, academic:
Förster, Jochen (Intern)
Project

**GC-MS based fluxomics using 13C and 15N labelled substrates**
Department of Systems Biology
Period: 01/03/2011 → 03/06/2015
Number of participants: 7
Phd Student:
Knudsen, Peter Boldsen (Intern)
Supervisor:
Nielsen, Kristian Fog (Intern)
Thykær, Jette (Intern)
Main Supervisor:
Workman, Mhairi (Intern)
Examiner:
Förster, Jochen (Intern)
Karaffa, Levente (Ekstern)
von Gulik, Walter M. (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU)
Project: PhD

**Establishment of Yeast Platform for Production of Libraries of Isoprenoids**
Department of Systems Biology
Period: 01/02/2004 → 25/09/2008
Number of participants: 6
Phd Student:
Asadollahi, Mohammadali (Intern)
Identification of Pathway Structures in *Saccharomyces cerevisiae*

Department of Systems Biology  
Period: 01/02/1999 → 21/02/2003  
Number of participants: 5  
PhD Student:  
Förster, Jochen (Intern)  
Main Supervisor:  
Nielsen, Jens (Intern)  
Examiner:  
Kielland-Brandt, Morten (Intern)  
Förster, Jochen (Intern)  
Pronk, Jack (Ekstern)  

**Financing sources**  
Source: Internal funding (public)  
Name of research programme: Stipendie fra udlandet  
Project: PhD

Identification of pathway structures in *Saccharomyces cerevisiae*

Based on a stoichiometric model for *S. cerevisiae* the metabolism of this organism will be analysed. The model will be applied both for optimisation of fluxes towards specific products and for analysis of metabolic phenotypes.

Department of Biotechnology  
Period: 01/02/1999 → 01/02/2002  
Number of participants: 2  
Project participant:  
Förster, Jochen (Intern)  
Project Manager, organisational:  
Nielsen, Jens (Intern)  

**Activities:**

**11th Danish Conference on Biotechnology and Molecular Biology**  
Period: 26 May 2016 → 27 May 2016  
Jochen Förster (Organizer)  
Novo Nordisk Foundation Center for Biosustainability  
Research Groups  
Applied Metabolic Engineering  

**Description**  
11th Danish Conference on Biotechnology and Molecular Biology  
Links:
Related event

11th Danish Conference on Biotechnology and Molecular Biology
26/05/2016 → 27/05/2016
Vejle, Denmark
Activity: Attending an event › Participating in or organising a conference

DTU Sustain Conference 2015
Period: 17 Dec 2015
Jochen Förster (Organizer)
Novo Nordisk Foundation Center for Biosustainability
Research Groups
Applied Metabolic Engineering

Description
DTU Sustain 2015 - Bioprocess & Cell factory engineering

Related event

Development of 2nd Generation Biorefineries for the Production of Dicarboxylic Acids and Bio-based Polymers
Period: 1 Sep 2015 → 4 Sep 2015
Jochen Förster (Keynote speaker)
Novo Nordisk Foundation Center for Biosustainability
Research Groups
Applied Metabolic Engineering

Related event

Brazilian National Congress on Bioprocesses (SINAFERM 2015)
01/09/2015 → 04/09/2015
Fortaleza, Brazil
Activity: Talks and presentations › Conference presentations

Microbial Polyphenol Production
Period: 27 Jul 2015 → 29 Jul 2015
Jochen Förster (Keynote speaker)
Novo Nordisk Foundation Center for Biosustainability
Research Groups
Applied Metabolic Engineering
Links:
http://www.cas.uni-muenchen.de/veranstaltungen/archiv_veranstaltung/tagungen/tag_synth_bio_2015/index.html

Related event

CAS Conference Synthetic Biology II
27/07/2015 → 29/07/2015
Martinsried, Germany
Activity: Talks and presentations › Conference presentations
**Polyphenol Production in Lactic Acid Bacteria**
Period: 19 Jul 2015 → 22 Jul 2015
Jochen Förster (Invited speaker)
Novo Nordisk Foundation Center for Biosustainability
Research Groups
Applied Metabolic Engineering

**Related event**

**12th Annual Congress on Industrial Biotechnology**
19/07/2015 → 22/07/2015
Montreal, Canada
Activity: Talks and presentations › Conference presentations

**Towards Integrated Biorefineries for Fuel and Chemical Production**
Jochen Förster (Keynote speaker)
Novo Nordisk Foundation Center for Biosustainability
Research Groups
Applied Metabolic Engineering
Links:
http://www.fuelcenter.rwth-aachen.de/index.php?id=602

**Related event**

**3rd International Conference of the Cluster of Excellence “Tailor-Made Fuels from Biomass”**
23/06/2015 → 25/06/2015
Aachen, Germany
Activity: Talks and presentations › Conference presentations

**BioREFINE-2G workshop on “Bioplastics from 2nd Generation Biorefineries” at RRB11**
Period: 5 Jun 2015
Jochen Förster (Lecturer)
Novo Nordisk Foundation Center for Biosustainability
Research Groups
Applied Metabolic Engineering
Links:
http://www.biorefine2g.eu

**Related event**

**Bioplastics from 2nd Generation Biorefineries**
05/06/2015 → 05/06/2015
York, United Kingdom
Activity: Talks and presentations › Conference presentations

**10th Danish Conference on Biotechnology and Molecular Biology**
Period: 4 Jun 2015 → 5 Jun 2015
Jochen Förster (Organizer)
Novo Nordisk Foundation Center for Biosustainability
Research Groups

**Description**
Stem cells are responsible for tissues to regenerate, remodel and function in a normal physiological milieu and thus offer a highly attractive approach for cell replacement therapy. Embryonic stem cells (ESC) and induced pluripotent stem cells (iPSC) hold the potential to generate virtually every cell type of our body, and within the last decade the regenerative
capacity of adult stem cells have been widely exploited, e.g. to generate tissues like blood vessels, bone, cartilage and more complex organs such as liver, intestine and heart. Particularly in the field of tissue engineering, research into developing the correct biomaterials and tissue-specific scaffolds have been given a tremendous push forward and with our increased understanding of fundamental stem cell biology, stem cell-based treatments and drug screening of patients is within reach. These translational stem cell activities are key to realizing the promise of stem cells for future clinical treatments and research groups and companies around the world are already pursuing clinical trials based on stem cells.

Links:
http://danishbiotechsociety.org/upcoming/

Related event

10th Danish Conference on Biotechnology and Molecular Biology: Stem Cells and Tissue Engineering Conference
04/06/2015 → 05/06/2015
Vejle, Denmark
Activity: Attending an event › Participating in or organising a conference

Cell Factories and Biosustainability 2015
Jochen Förster (Organizer)
Novo Nordisk Foundation Center for Biosustainability
Research Groups
Description
Rapid development of novel cell factories is currently a main barrier for advancing towards sustainable production of chemicals, materials, and pharmaceuticals. Advancement in computational and experimental methods for detailed phenotypic characterization of cell factories offer the opportunity to significantly reduce the cost and development time for establishment of novel bioprocesses. At this conference there will presentation of state-of-the-art technologies that can accelerate cell factory development, including tools for rapid genome editing, computational identification of metabolic engineering targets, and detailed phenotypic characterization.
Links:
http://www.cph-bioscience.com/conferences/cell-factories-biosustainability

Related event

Cell Factories and Biosustainability 2015
17/05/2015 → 21/05/2015
Hillerød, Denmark
Activity: Attending an event › Participating in or organising a conference

Cell Factories in Fermentation
Period: 15 Apr 2015
Jochen Förster (Lecturer)
Novo Nordisk Foundation Center for Biosustainability
Research Groups
Applied Metabolic Engineering

Related external organisation

Unknown external organisation
Activity: Talks and presentations › Conference presentations

DTU Sustain Conference 2014
Period: 17 Dec 2014
Jochen Förster (Organizer)
Novo Nordisk Foundation Center for Biosustainability
Research Groups
Applied Metabolic Engineering
Description
DTU Sustain Conference 2014
Links:
http://www.sustain.dtu.dk/

Related event
DTU Sustain Conference 2014
17/12/2014 → 17/12/2014
Lyngby, Denmark
Activity: Attending an event › Participating in or organising a conference

Genome-Scale Metabolic Models
Period: 8 Dec 2014
Jochen Förster (Lecturer)
Novo Nordisk Foundation Center for Biosustainability
Research Groups
Applied Metabolic Engineering

Related external organisation
Unknown external organisation
Activity: Talks and presentations › Conference presentations

BioREFINE-2G Project
Jochen Förster (Invited speaker)
Novo Nordisk Foundation Center for Biosustainability
Research Groups

Related event
Nordic Yeast Research Community Meeting 2014
Copenhagen, Denmark
Activity: Talks and presentations › Conference presentations

Genome-Scale Modelling of Metabolism
Period: 10 Nov 2014
Jochen Förster (Invited speaker)
Novo Nordisk Foundation Center for Biosustainability
Research Groups

Related event
The Danish Microbiological Society Annual Congress 2014
10/11/2014 → …
Copenhagen, Denmark
Activity: Talks and presentations › Conference presentations

2nd Danish-Brazilian Workshop on Biorefineries
Period: 22 Sep 2014 → 23 Sep 2014
Jochen Förster (Organizer)
Novo Nordisk Foundation Center for Biosustainability
Research Groups
The development of a biobased economy needs new biotechnologies for biorefining and conversion of biomass into fuels and chemicals. Denmark and Brazil are each major players within biomass research and biomass industries. Together our infrastructures, research, technologies and industry have what it takes to make the biobased economy become a reality!

This workshop will provide you with state of the art biorefinery research and technology within biomass production, logistics, conversion technologies and microbiology in Denmark and Brazil. The presentations will be given by key players from academia and industry. The Workshop on Biorefineries will explore how we together can meet challenges, build research and develop new innovative technologies promoting the biorefinery concept to help build our vision for a bio-based economy.

Links:
http://b21st.ku.dk/workshoponbiorefineries/

Related event

2nd Danish-Brazilian Workshop on Biorefineries
22/09/2014 → 23/09/2014
Copenhagen, Denmark
Activity: Attending an event › Participating in or organising workshops, courses, seminars etc.

Polyphenol Production in Lactic Acid Bacteria
Period: 15 Sep 2014 → 18 Sep 2014
Jochen Förster (Invited speaker)
Novo Nordisk Foundation Center for Biosustainability

Description
Polyphenols are plant secondary metabolites that are derived from the polypropanoid pathway. They are ubiquitous in nature and it is estimated that there exist more than 100,000 different polyphenols. In plants polyphenols serve various protective function i.e. antimicrobial functions, preventing damage by UV radiation, chelation of toxic heavy metals, and many more. They have been subject to intense research with respect to health benefits and application in pharma. Besides this, various polyphenols can find applications as pigments, preservatives, monomers for bioplastics, and composites, and they can directly be applied as food, feed, nutraceutical or cosmeceutical ingredients. The aim of the present project is the design of platform strains for production of polyphenols. Lactic acid bacteria have been chosen as production organism as they are generally regarded as save. First results will be presented on trans-resveratrol production in Lactococcus lactis. Trans-reveratrol is a promising polyphenol that may find application in treating obesity and diabetes Type II. The activities are part of a larger EU project, BacHBERRY (www.bachberry.eu) aiming at the development of BACterial Hosts for the production of Bioactive phenolics from bERRY fruits.

Polyphenol Production in Lactic Acid Bacteria

Related event

6th ÖGMBT Meeting : Life Sciences Meet Entrepreneurship
15/09/2014 → 18/09/2014
Vienna, Austria
Activity: Talks and presentations › Conference presentations

New Trends in Biotechnology for Bioeconomy
Period: 12 Jun 2014
Jochen Förster (Lecturer)
Novo Nordisk Foundation Center for Biosustainability

Related event

IBC Seminar: Industrial Biotechnology in Bioeconomy
12/06/2014 → …
Helsinki, Finland
Activity: Talks and presentations › Conference presentations
Model driven cell factory design for application in biorefineries
Period: 10 Jun 2014
Jochen Förster (Speaker)
Novo Nordisk Foundation Center for Biosustainability
Research Groups
Activity: Other

Yeast as Platform for Biopolymer Production
Period: 4 Jun 2014
Jochen Förster (Invited speaker)
Novo Nordisk Foundation Center for Biosustainability
Research Groups

Related event
10th International Conference on Renewable Resources and Biorefineries
04/06/2014 → 06/06/2014
Valladolid, Spain
Activity: Talks and presentations › Conference presentations

9th Danish Conference on Biotechnology and Molecular Biology
Period: 21 May 2014 → 22 May 2014
Jochen Förster (Organizer)
Novo Nordisk Foundation Center for Biosustainability
Research Groups

Description
Over the last fifty years research in cell biotechnology has revealed substantial potentials for the production of bioactive proteins and use of the cells themselves particularly in medical applications. The development of efficient and safe processes for production of novel pharmaceuticals is of significant industrial importance and subject to extensive research efforts. The increasing availability of genome editing tools and genome sequences of mammalian cell factories, such as the Chinese hamster ovary cell, and other animal cell cultures enables for the first time a systems biotechnology driven approach to cell factory design.

The conference will focus on
- Perspectives in Animal Cell Factory Research
- Expression and production systems
- Technology platforms
- Systems biology
- Post translational modifications
- Mammalian Cell Factories
- Insect Cell Factories
- Commercial perspectives and regulatory issues

The conference includes a poster session covering a broad range of topics on biotechnology as well as a commercial exhibition of equipment, consumables and services to Danish biotechnology.

Links:
http://danishbiotechsociety.org/previous-conferences-events/abstract-book-dcb9/

Related event
9th Danish Conference on Biotechnology and Molecular Biology: Symposium on Animal Cell Cultures
22/05/2014 → 23/05/2014
Denmark
Activity: Attending an event › Participating in or organising a conference
1st Danish-Brazilian Workshop on Biorefineries
Period: 2 Dec 2013 → 3 Dec 2013
Jochen Förster (Organizer)
Novo Nordisk Foundation Center for Biosustainability

Research Groups

Description
On December 2-3 2013 the first Brazilian-Danish workshop on biorefineries was held in Campinas, Sao Paulo, Brazil. The workshop was an initiative between University of Copenhagen, the Technical University of Denmark and The Brazilian Bioethanol Science and Technology Laboratory (CTBE). The purpose of the workshop was to explore the opportunities for further collaboration between Denmark and Brazil in the biorefining area.

More than 100 participants from Denmark and Brazil attended the workshop with presentations on biomass, conversion and microbiology within biorefineries from both Danish and Brazilian universities and industry.

Following the workshop a visit to the sugar/ethanol company Raizen and their 1G sugar mill in Costa Pinto was organized. The visit included a trip to the sugar cane fields, which showed the enormous capacity for biomass production in Brazil.

The impressions from the workshop were good and many. A large number of participants said they found potential partners for future collaboration and for sending students abroad.

The 2nd Brazilian-Danish workshop on biorefineries is already in the planning and will be hosted by University of Copenhagen in September 2014.

Links:

Related event
1st Danish-Brazilian Workshop on Biorefineries : Integrated Biorefineries for Energy and Chemical Production
02/12/2013 → 03/12/2013
Campinas, Brazil
Activity: Attending an event › Participating in or organising workshops, courses, seminars etc.

8th Danish Conference on Biotechnology and Molecular Biology
Period: 30 May 2013 → 31 May 2013
Jochen Förster (Organizer)
Novo Nordisk Foundation Center for Biosustainability

Research Groups

Description
Food biotechnology and nutrigenomics are rapidly growing research fields contributing to a better understanding of the interaction between nutrition, metabolism and gene expression. Recent investigations of the human gut have provided insight into the complicated interactions between nutrition and the gut microbiota. Advanced methods in biotechnology enables investigations of nutritional effects and interactions at the metabolomic and transcriptomic level in relation to health and the development of life style diseases. This way nutrigenomics provides the potential for development of individual diets. Furthermore food biotechnology provides the possibilities and sustainable methods to produce healthy food and food ingredients with specific properties. Together food biotechnology and nutrigenomics are research areas providing a deeper understanding of health and nutrition, and significantly contributing to the development of healthy food and way of living.

The present conference focuses on the latest achievements in the research fields of Nutrigenomics
Nutritional metabolomics
Nutritional systems biology and biomarkers
Prebiotics and functional food ingredients
Cell factories for production of food ingredients
Food allergens
Probiotics and human gut microbiota
Human gut microbiota and life style diseases

The conference will include a poster session covering a broad range of topics on biotechnology as well as a commercial exhibition of equipment, consumables and services to Danish biotechnology. The conference is organised in collaboration with Danish Society of Biochemistry and Molecular Biology as well as BioPeople.
Danish Biotechnological Society (DBS) is a scientific society established in 2006 in collaboration between Danish Biotechnology Forum and The Danish Society for Biochemistry and Molecular Biology. DBS is organised as part of The Danish Society of Engineers, IDA. The purpose of DBS is to facilitate networking within the field of biotechnology in Denmark, creating links between universities, research institutions, hospitals and companies. DBS represents professionals working with biotechnology and seeks to promote and communicate important issues on biotechnology, biochemistry and molecular biology to the public. DBS organises scientific conferences and meetings on biotechnology.

Links:
http://danishbiotechsociety.org/previous-conferences-events/abstract-book-dcb8/

Related event

8th Danish Conference on Biotechnology and Molecular Biology: Food Biotechnology and Nutigenomics
30/05/2013 → 31/05/2013
Vejle, Denmark
Activity: Attending an event › Participating in or organising a conference

2nd Conference on Constraint-based Reconstruction and Analysis
Jochen Förster (Organizer)
Novo Nordisk Foundation Center for Biosustainability
Research Groups

Description
The first conference was held July 2011 in Reykjavik and attracted such a high a number of participants that we cannot resist to repeat this successful event in 2012.

World-leading as well as young scientists will be brought together to discuss latest progress in Constraint-based Reconstruction and Analysis (COBRA).

Scientific Topics include

Chemical Production – Towards Second Generation Biorefineries for Chemical Production
Mammalian Metabolism
Novel Algorithms and Software Development
Adaption and Evolution

Links:
http://indico.conferences.dtu.dk/conferenceDisplay.py?ovw=True&confid=104

Related event

2nd Conference on Constraint-based Reconstruction and Analysis
07/10/2012 → 09/10/2012
Helsingore, Denmark
Activity: Attending an event › Participating in or organising a conference

Annual International Workshop on Energy, Environment, Water, and Sustainability
Period: 3 Nov 2011
Jochen Förster (Speaker)
Novo Nordisk Foundation Center for Biosustainability
Research Groups

Description
We invite you to the BioSustainability: KAIST EEWS Workshop 2011! KAIST has been hosting the annual International Workshop on EEWS (Energy, Environment, Water, and Sustainability) since 2008 with the objective of establishing a multi-disciplinary research and educational system to investigate the innovative technologies for green energies and solutions for climate change. One of the key issues for this purpose is the generation of biofuels, chemicals and materials from sustainable biological systems. Thus KAIST EEWS is organizing a special workshop on BioSustainability to be held on November 3, 2011 at the KAIST KI Building (1st floor Fusion Hall) on the Daejeon campus. This vision of a
biosustainable society was also recognized and shared by leaders in Denmark, a ‘first mover’ in clean energy technology. In fact, they realize that the issues of climate change, pollution, and depletion of energy sources do not belong to a single country, but rather are global issues. This shared vision was realized in May of 2011 in Copenhagen, Denmark. The Government of the Republic of Korea and the Government of the Kingdom of Denmark signed a Joint statement on the Establishment of a Green Growth Alliance between the two countries, hoping to create synergistic outputs from mutual collaborations. The collaborative research activities between the two nations toward biosustainability will take place at two leading universities, KAIST and Technical University of Denmark (DTU). BioSustainability is one of the first two research topics addressed by the Joint Statement, and will be pursued by the Center for Systems and Synthetic Biotechnology at KAIST and The Novo Nordisk Foundation Center for BioSustainability at DTU. In this respect, this joint workshop will be an excellent opportunity to exchange ideas and findings of research groups at KAIST and DTU.

We cordially invite academic researchers, industrial practitioners and students worldwide to participate and exchange ideas for the advancement of sustainable biotechnologies.

Sun Chang Kim
Professor and Director
Sang Yup Lee
Professor and Co-director
Institute for the BioCentury
KAIST;
Chairs of Workshop

Related event

Annual International Workshop on Energy, Environment, Water, and Sustainability
03/11/2011 → 03/11/2011
Daejon, Korea, Republic of
Activity: Talks and presentations › Conference presentations

Annual International Workshop on Energy, Environment, Water, and Sustainability
Period: 3 Nov 2011
Jochen Förster (Speaker)
Novo Nordisk Foundation Center for Biosustainability
Research Groups

Description
Production of nutraceutical ingredients using the yeast Saccharomyces cerevisiae

We invite you to the BioSustainability: KAIST EEWS Workshop 2011! KAIST has been hosting the annual International Workshop on EEWS (Energy, Environment, Water, and Sustainability) since 2008 with the objective of establishing a multi-disciplinary research and educational system to investigate the innovative technologies for green energies and solutions for climate change. One of the key issues for this purpose is the generation of biofuels, chemicals and materials from sustainable biological systems. Thus KAIST EEWS is organizing a special workshop on BioSustainability to be held on November 3, 2011 at the KAIST KI Building (1st floor Fusion Hall) on the Daejeon campus. This vision of a biosustainable society was also recognized and shared by leaders in Denmark, a ‘first mover’ in clean energy technology. In fact, they realize that the issues of climate change, pollution, and depletion of energy sources do not belong to a single country, but rather are global issues. This shared vision was realized in May of 2011 in Copenhagen, Denmark. The Government of the Republic of Korea and the Government of the Kingdom of Denmark signed a Joint statement on the Establishment of a Green Growth Alliance between the two countries, hoping to create synergistic outputs from mutual collaborations. The collaborative research activities between the two nations toward biosustainability will take place at two leading universities, KAIST and Technical University of Denmark (DTU). BioSustainability is one of the first two research topics addressed by the Joint Statement, and will be pursued by the Center for Systems and Synthetic Biotechnology at KAIST and The Novo Nordisk Foundation Center for BioSustainability at DTU. In this respect, this joint workshop will be an excellent opportunity to exchange ideas and findings of research groups at KAIST and DTU.

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Related event

**Annual International Workshop on Energy, Environment, Water, and Sustainability**
03/11/2011 → 03/11/2011
Daejon, Korea, Republic of
Activity: Talks and presentations › Conference presentations

Press clippings:

**Millioner til cellefabrikker: Massiv kapitalindsprøjtning skal hjælpe bioteknologisk selskab ind i verdenseliten.**
Jochen Förster
05/11/2005
Novo Nordisk Foundation Center for Biosustainability, Research Groups

**Media contribution (1)**

**Millioner til cellefabrikker: Massiv kapitalindsprøjtning skal hjælpe bioteknologisk selskab ind i verdenseliten.**
05/11/2005
Web
http://www.dtu.dk/Nyheder/2005/11/biotek
Jochen Förster
Novo Nordisk Foundation Center for Biosustainability, Research Groups
Press / Media