Synthetic microbes - An overview of these multipurpose microbial tools

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Outline

1. Synthetic microbe - Concept and Science
2. Creating a synthetic microbe - What are the resources that we have and can use?
3. Application of synthetic microorganisms - Successful developments and future implications
Synthetic microbe

Concept and Science
**Synthetic microbes**

- Microbes are ubiquitous
- Relatively simple genomes - very well studied
- Relatively easy to manipulate
- Can be engineered to perform specific tasks
- Manipulate simplest life forms to solve problems on a global scale (Microbial machines)

**Synthetic Microbes:** ‘Organisms synthesized or engineered by human beings to perform specific tasks, that can grow, reproduce and develop without further human intervention’

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Science behind synthetic microbes

• **Synthetic biology** – “Design and construction of novel biologically based parts, devices and systems or redesigning existing natural biological systems”

• **Aim:** Design an efficient biological system to achieve a specific desired output

• **Two approaches to creating synthetic microbes:**
  • **Bottom-up approach:** Creating life *de novo*
  • **Top-down approach:** Designing and inserting elements inside cells to perform specific tasks

Bringing ‘engineering’ back in genetic engineering

• Decades of genetic ‘manipulation’ through conventional methods

• Very little ‘engineering’ (Not much ‘designing’ and ‘building’ involved)

• Problems with conventional molecular biology techniques
  • Dated
  • Slow and time consuming
  • Lack of standardisation

• Design and create standardised components that can be assembled easily to create new reliable things
‘Creation’ as opposed to ‘manipulation’

Synthetic biology

Major drivers towards the development of synthetic biology- ability to synthesize DNA
Creating a synthetic microbe

What are the resources that we have and can use?
Synthetic microbes - the vision

- Microbes are ubiquitous
- Relatively simple genomes - very well studied
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- **DNA** - software or instructions for making a specific product (genes for a function/genome)

- Living cell - ‘Micro factory’
- Synthetic Microbes: ‘Organisms synthesized or engineered by human beings, that can grow, reproduce and develop without further human intervention’

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Biobricks

• “Standard DNA sequences with defined structure and function and share a common interface”¹

• Overcome lack of standardisation of traditional molecular biology methods

• Open source- used to assemble complex biological circuits from simple building blocks

• Introduced in 2003 (MIT)

• Biobricks foundation: Non profit organisation. Focused on further standardising and promoting these biological parts
  • Easily accessed and used by students!

## Biobricks

<table>
<thead>
<tr>
<th>Parts</th>
<th>Devices</th>
<th>System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Building blocks. Encode basic biological functions</td>
<td>Collection of Parts for a defined function.</td>
<td>Combination of devices to perform a higher level task</td>
</tr>
<tr>
<td>E.g.: Coding sequences, promoters, terminators etc.</td>
<td>E.g: Riboregulator producing a fluorescent protein in response to an environmental trigger</td>
<td>E.g: Multiple fluorescent signals in response to multiple environmental triggers working in consortium</td>
</tr>
</tbody>
</table>

Synthetic microbes - the vision

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- DNA - software or instructions
- Living cell - ‘Micro factory’ - platform to run the ‘software’

Synthetic Microbes: ‘Organisms synthesized or engineered by human beings, that can grow, reproduce and develop without further human intervention’

The ‘Minimal cell’

RESEARCH ARTICLE SUMMARY

SYNTETIC BIOLOGY

Design and synthesis of a minimal bacterial genome

JCVI-syn3.0

- J. Craig Venter Institute (JCVI) and Synthetic Genomics, Inc. (SGI)
- Modified *Mycoplasma mycoides* genome
- Deletion of genes not essential for growth under laboratory conditions
- Genome 581 kbp, 473 genes - smaller than any autonomously replicating cell in nature
- Whole genome design, Chemical synthesis and genome transplantation into *M. capricolum* recipient

The ‘Minimal cell’ approach for a more ideal chassis


Application of synthetic microorganisms

Successful developments and future implications
‘E.chromi’
(University of Cambridge)

- *E.coli* with a sensitivity tuner (biosensors) and colour generator (Biobricks)
- Turn into a certain colour when environmental toxin of a certain concentration is detected
- Potential application in diagnostics- Digestive tract disorders

http://2009.igem.org/Team:Cambridge/Project/Amplification
Synthetic yeast – micro factories for an antimalarial production

• **Artemisinin:** Antimalarial drug produced by the plant *Artemisia annua.*
  - Global supply exclusively by farmers that cultivate the plant- success highly variable
  - Production occurs naturally in this plant using sugars generated by photosynthesis

• **Professor Jay Keasling** (UC Berkeley)- cheap and reliable alternative to agricultural production

• Using engineered yeast for production of the antimalarial precursor at an industrial scale- > 25 g per Litre of artemisinic acid

Production of biofuels

- Algae - natural production of high biomass
- Accumulate energy dense oils which can be used as fuels
- Synthetic algae - optimization of fuel production pathways
- Replace fossil fuels in the future?


Other applications

- Potential to revolutionise the manufacturing of ‘everyday products’
  - Detergents, cosmetics, food etc.
  - Terpenes- Work towards producing synthetic yeast for industrial levels
  - Bioacrylic – **OPXBIO**. Application in detergents, paints etc.

- Living therapies/vaccines
  - **EnBiotix**- EP001 phage- target bacteria to produce biofilm destroying enzymes
  - **Prokarium**- ‘tamed’ Salmonella, enters immune cells, but does not cause disease

- Environmental
  - Biosensors for pollution detection?


Why have we not moved forward with synthetic microbes?

• Currently time consuming and high costs
  • Decades of research required
  • Although continuously falling, costs of synthesizing DNA still high

• Technology is not ready
  • Artimisinin (Been around for over a decade, but never made it to market)

• Bioethical factors (!!)
  • Difference of opinions amongst the general public
  • Creation of “Frankenstein’s monsters” (unnatural beings)

• Potential risks
  • Accidental release into the environment –
    • cannot predict how it would adapt and affect the biosphere
    • ‘Unnatural organisms’
  • Increased threat of bioterrorism- Deliberate misuse

Summary

- Synthetic Microbes are any non-biological organisms capable of self replication
- Microbial factories can be designed for optimal function using synthetic biology
- Availability of resources like “BioBricks” will largely facilitate development of synthetic microorganisms
- Development of “minimal cells” for further optimisation of production
- Despite the risks, these multipurpose microbial tools hold great promise in the future, potential to replace products derived from scarce resources
Thank you!