Laboratory for Cellular and Metabolic Engineering

Engineering cells to produce industrially-relevant biomolecules, biofuels, and biopharmaceuticals through novel genetic tools and methodologies

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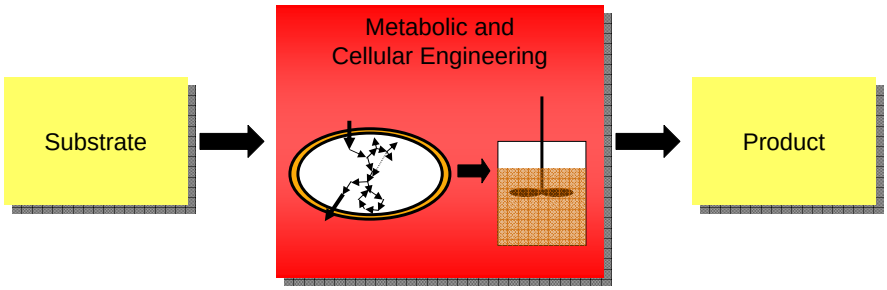
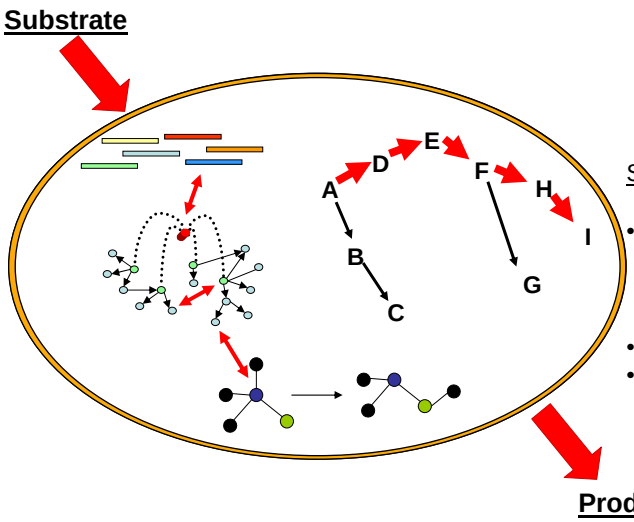
Contextual Background



Metabolic and cellular engineering as an enabling technology:

Enhancing natural function and/or augmenting cellular capacity through recombinant DNA and genomic technologies

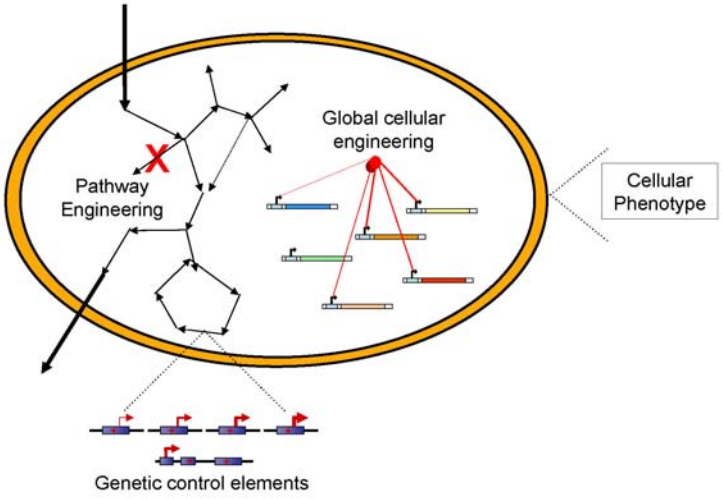
Metabolic and cellular engineering: exploiting cellular complexity



Sources of complexity

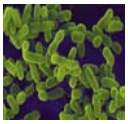
- Components
  - Genomic level
  - Proteomic level
  - Metabolic level
- Interactions
- Pathways

Utilizing novel tools and approaches to engineer cellular systems

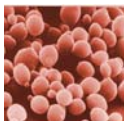


Model systems and phenotypes

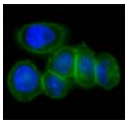
Cell Models



Microbial Engineering
(e.g.: *Escherichia coli)*



Fungal Engineering
(e.g.: *Saccharomyces cerevisiae* and other yeasts)



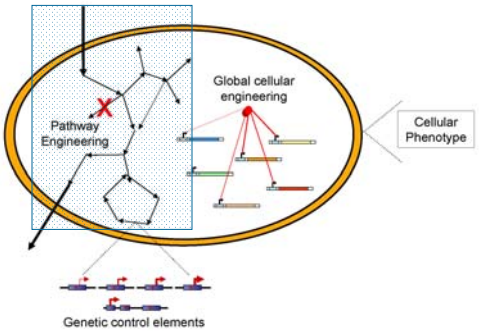
Mammalian Cell Engineering
(e.g.: Chinese Hamster Ovary Cells)

Cell Phenotypes

Production phenotypes
- Ethanol/alternative biofuels
- Hydrocarbons
- Lipids and fatty acids
- Protein drugs
- Commodity chemicals

Other Phenotypes of Interest
- Chemical tolerances
- Disease states
- Biodegradation capacity
- Alternative sugar utilization

Metabolic pathway engineering



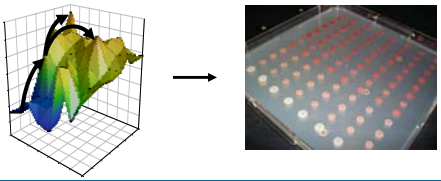
Pathway Engineering Approaches

- Combinations of systematic and combinatorial approaches can optimize phenotypes since phenotypes are complex, nonlinear surfaces
- Not a 1-to-1 genotype-phenotype mapping
- Combinations of protein engineering and pathway engineering to increase metabolic flux

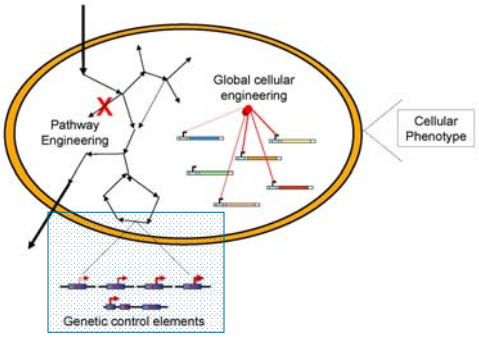
Lycopene Metabolic Pathway Example

Dissection and identification of gene targets for pathway engineering

Alper et al. ***Nature Biotechnology***, 2005.
Alper et al. ***Metabolic Engineering***, 2005.
Alper et al. ***Appl Micro Biotech***, 2008.



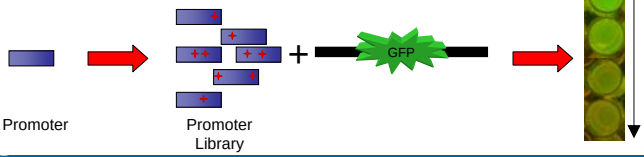
Designer genetic control elements



Genetic control elements for pathway engineering

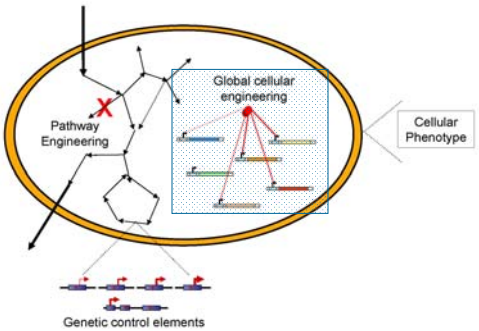
- Essential tools for quantifying the genotype-phenotype relationship
- Optimality is gene-specific: Need well characterized, continuum of expression
- Library of low promoters to reduce essential gene expression
- Controlling gene expression to modify pathways

Promoter engineering example



Alper et al. ***PNAS***, 2005.

Global approaches to cellular engineering

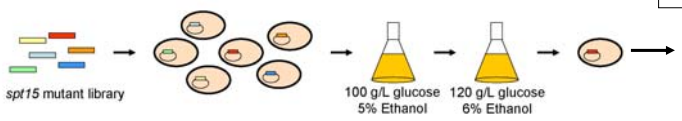


Global Cellular Engineering Efforts

- Complex, important phenotype are regulated by multiple genes
- Engineering transcription machinery and other molecular regulators can elicit multiple, simultaneous modifications
- Generic (Eukaryotic and Prokaryotic) and high level cellular engineering through protein engineering

global Transcription Machinery Engineering (gTME) Example

Alper et al. ***Science***, 2006.
Alper et al. ***Metab Eng***, 2007.



Laboratory themes/goals

- **Strategies and tools** for engineering eukaryotic and prokaryotic systems
- Host strains for high level production of **small molecules and biofuels**
- Engineer complex cellular phenotypes in an effort to identify **novel genetic targets**
- Designer elements for tunable and combinatorial **control of gene expression** and regulatory networks
- Metabolic and cellular engineering **through protein engineering**

Laboratory for Cellular and Metabolic Engineering

The Alper Laboratory will be offering **2-3** graduate research assistant positions in Fall 2008. These positions will be in the areas of engineering **biofuels** production, developing methods for **metabolic pathway engineering**, and in **mammalian cellular engineering**.

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