

# Synthetic Biology

Dreams of a new Industrial Revolution

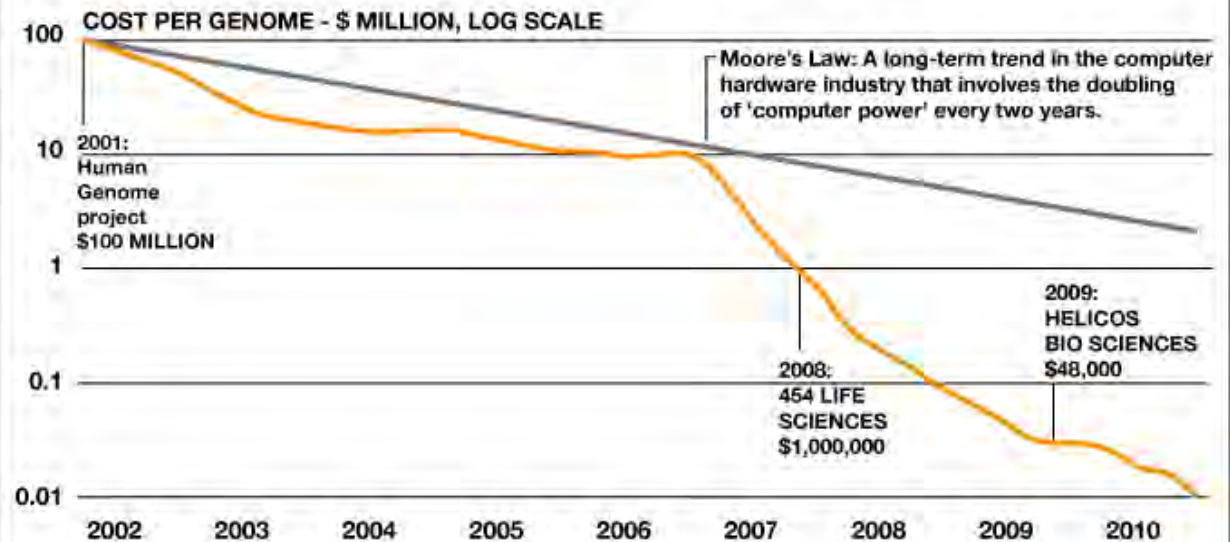
Rainer Breitling



The University of Manchester

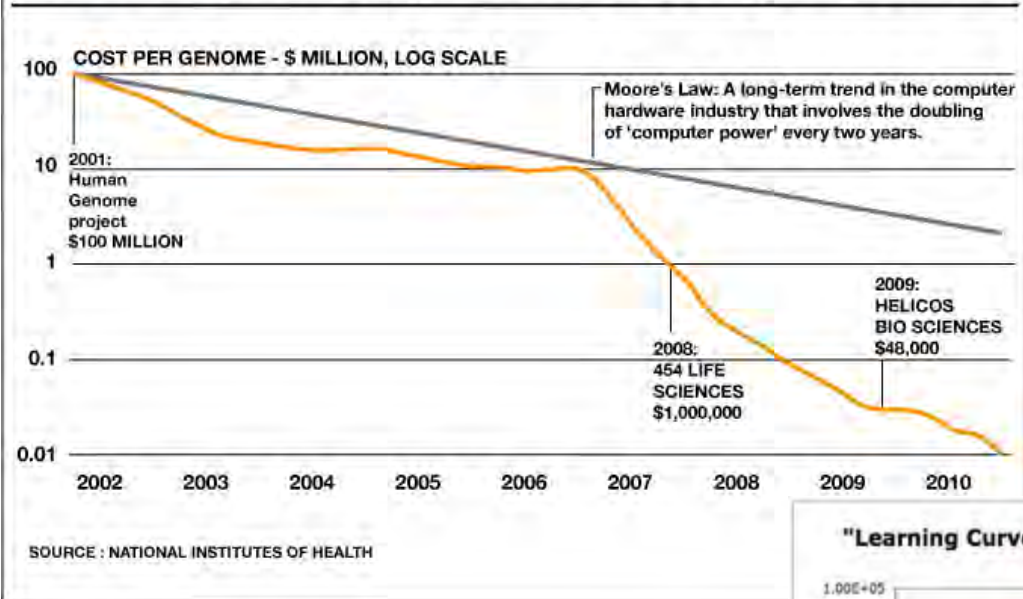


## DNA sequencing costs have gone down



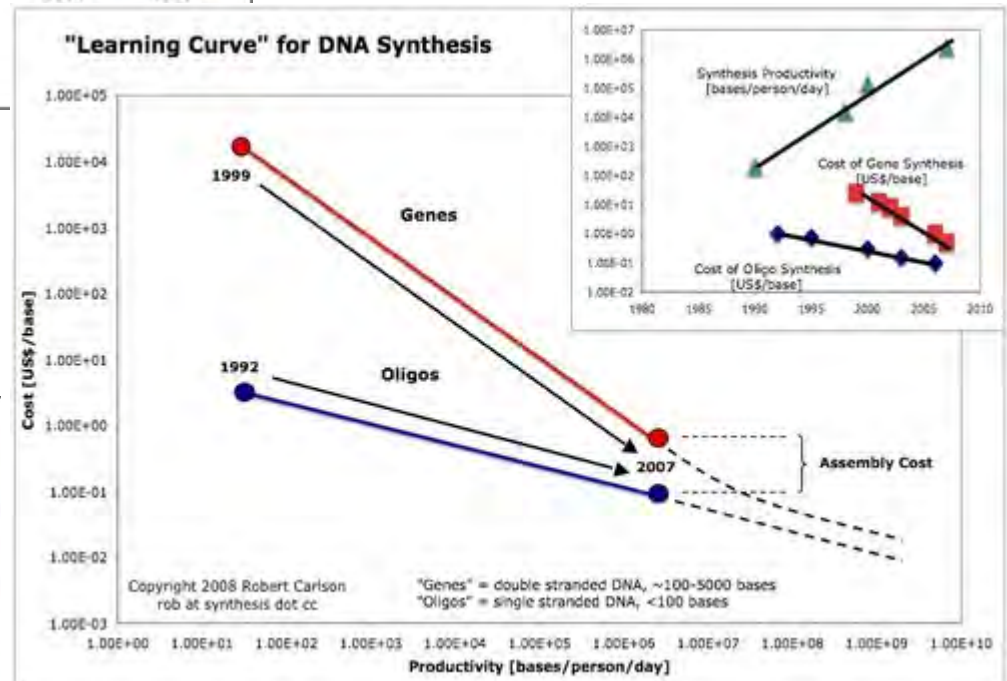
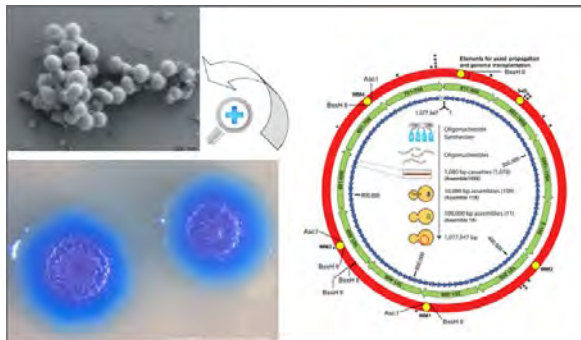
SOURCE : NATIONAL INSTITUTES OF HEALTH

# DNA sequencing costs have gone down



Reading

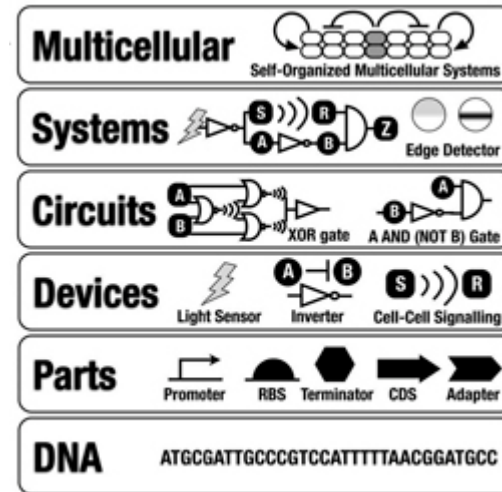
Writing





# Synthetic Biology =

Revitalizing the engineering metaphor in biology

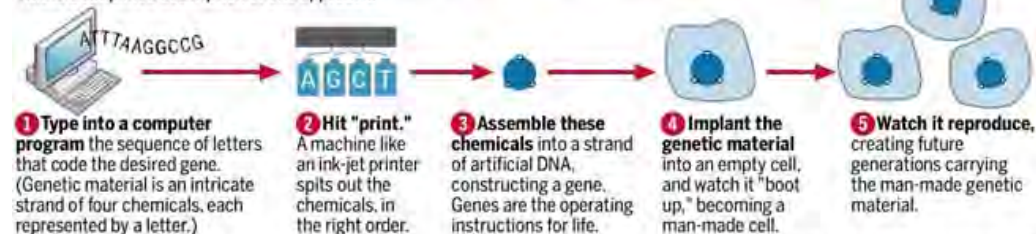


- Modular design & Composability
- Standardization (e.g., biobricks)
- Orthogonality (e.g., XNA)
- Refactoring
- ...



## One way synthetic biologists make cells

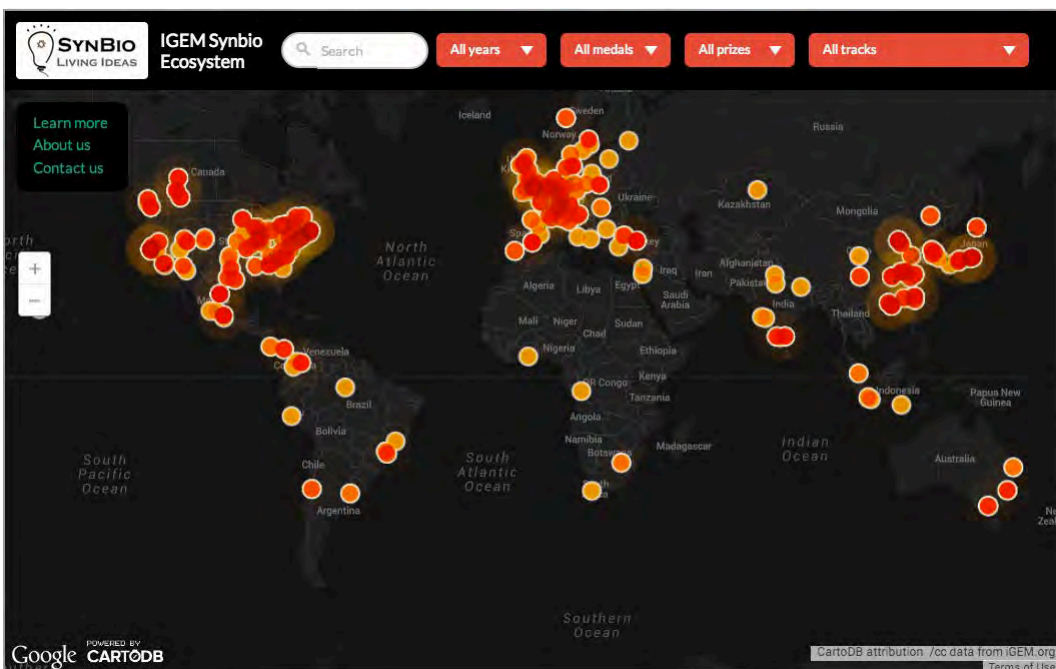
Synthetic biologists are trying several strategies to design and build communities of one-celled organisms. This is a simplified description of one approach.



Source: J. Craig Venter Institute

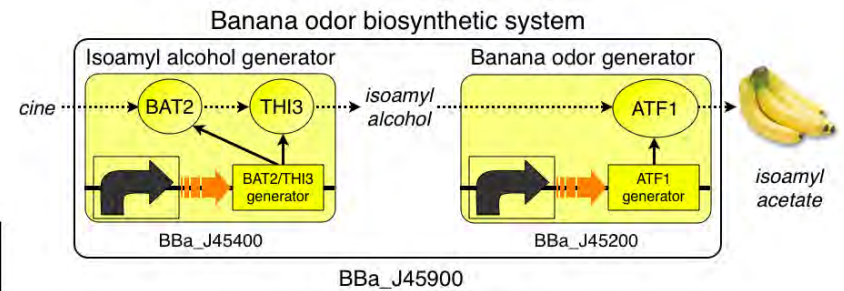
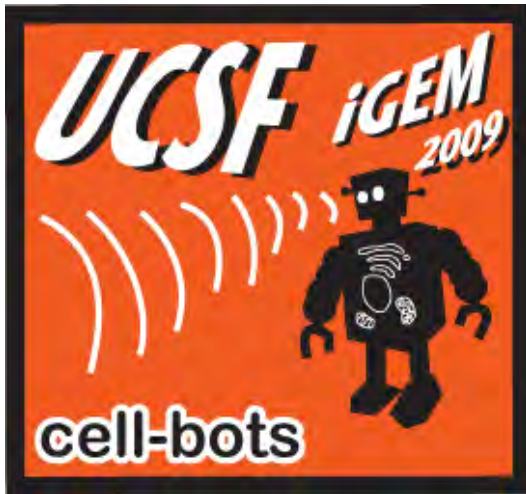
KARL KÄHLER/BAY AREA NEWS GROUP





245 registered teams in this year's competition







### 3A Assembly Kit

Learn to assemble more parts faster!

Our 3A assembly kit is only available to high schools during the 2013 iGEM season.

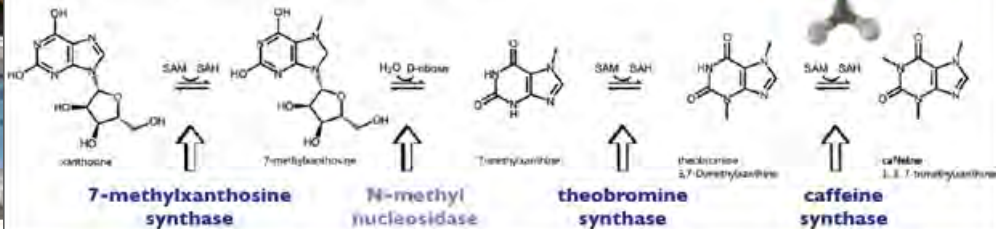
This kit and subsequent protocols provide you with most of the materials you need to learn 3A assembly. This assembly strategy is faster and more efficient than standard BioBrick assembly. You will need a few other things to get started:

- An NEB BioBrick kit or equivalent enzymes
- A copy of the Distribution (for your own assemblies)



### Caffeine Biosynthesis Pathway

Caffeine is a stimulant in humans, well known by coffee and tea drinkers worldwide. It is also a natural pesticide and a reward memory enhancer in some pollinating species. The Registry has genes and operons to allow you to synthesize individual enzymes or the whole pathway.



### Gas Vesicle Expression Cassette

Make your project float!

These composite parts contain modules that allow your organism to increase its buoyancy. You can make your organism rise to the surface of a static culture flask.

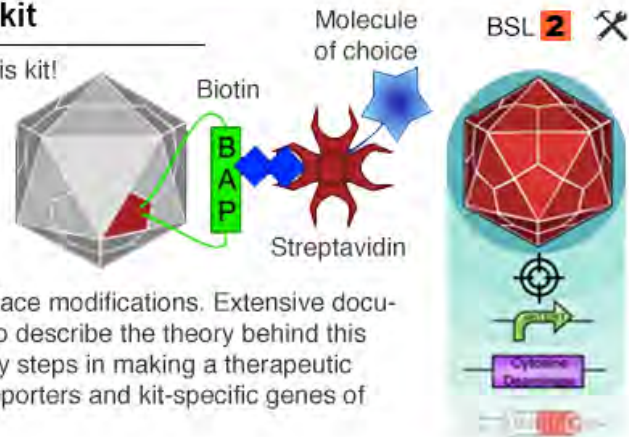
The polycistronic gene cassette contains 11 open reading frames coding for gas vesicle genes. At close to 6 kb, this is a large cassette but will add novel functionality to your system!



### Therapeutic Virus Toolkit

Want to build a virus? Use this kit!

Design and build your own virus for mammalian cell line transfection. This kit uses a recombinant Adeno-associated virus (rAAV) based system and incorporates many known surface modifications. Extensive documentation has been written to describe the theory behind this work, protocols and assembly steps in making a therapeutic virus. Contains promoters, reporters and kit-specific genes of interest.



### Team Uppsala 2012 Chromoproteins

Do you have a project in need of a great reporter? Do you want to build colorful iGEM projects?

Chromoproteins are responsible for the color in corals or sea anemones. When expressed, they can be seen by the naked eye.



### Ribosome Binding Sites

To make a protein in a cell you need a promoter, an RBS, a CDS and a terminator. Ribosomes bind to the RBS and begin translation at the start codon, which is ATG on the registry. Your choice of RBS will affect protein expression levels. RBSs are small so can be synthesized or assembled. We have have about 150 RBS parts on the Registry. The most used is BBa\_E0034. There are many RBS collections on the Registry:

Anderson Collection	By expression level	E. coli	Eukaryotic
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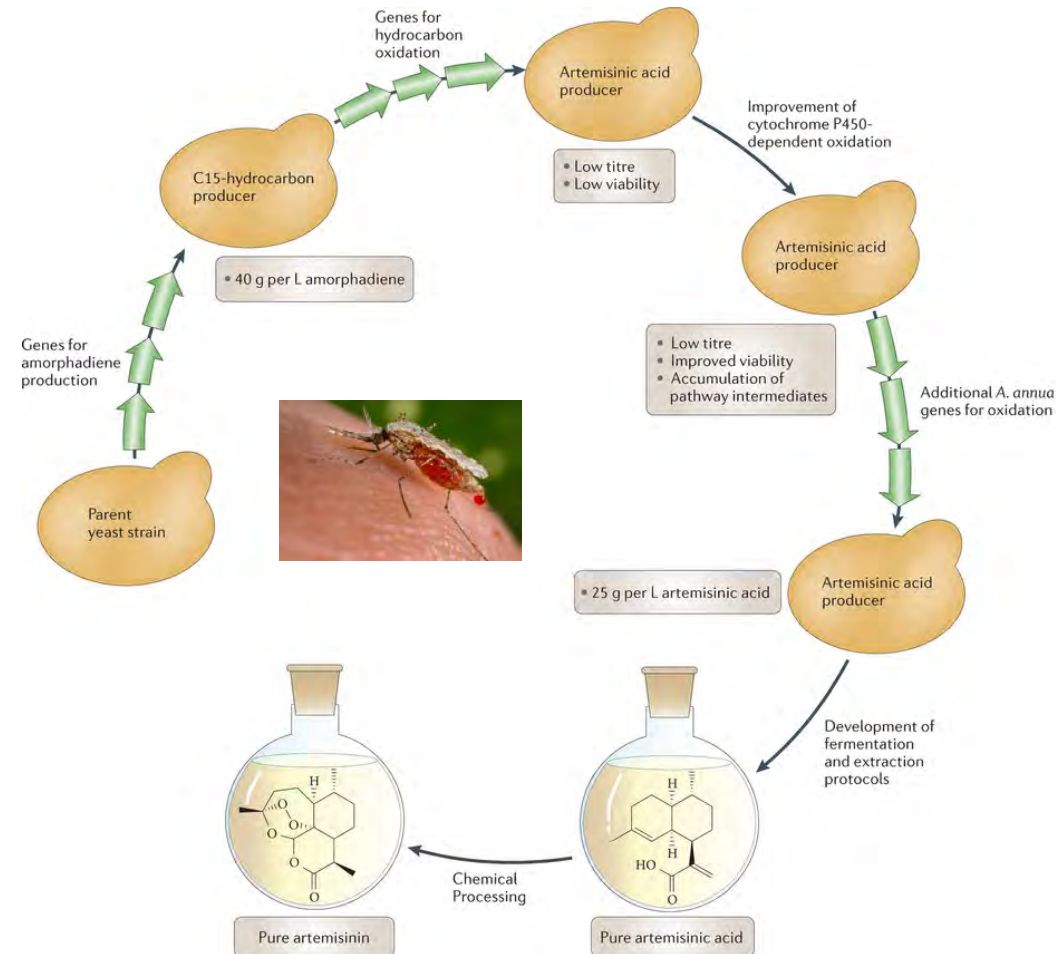
Promoter Ribosome binding site Start Codon  
...TCTAGAGAAAGANNNGANNNACTAGATG...



# Artemisinin anti-malarial

## Amyris + Sanofi

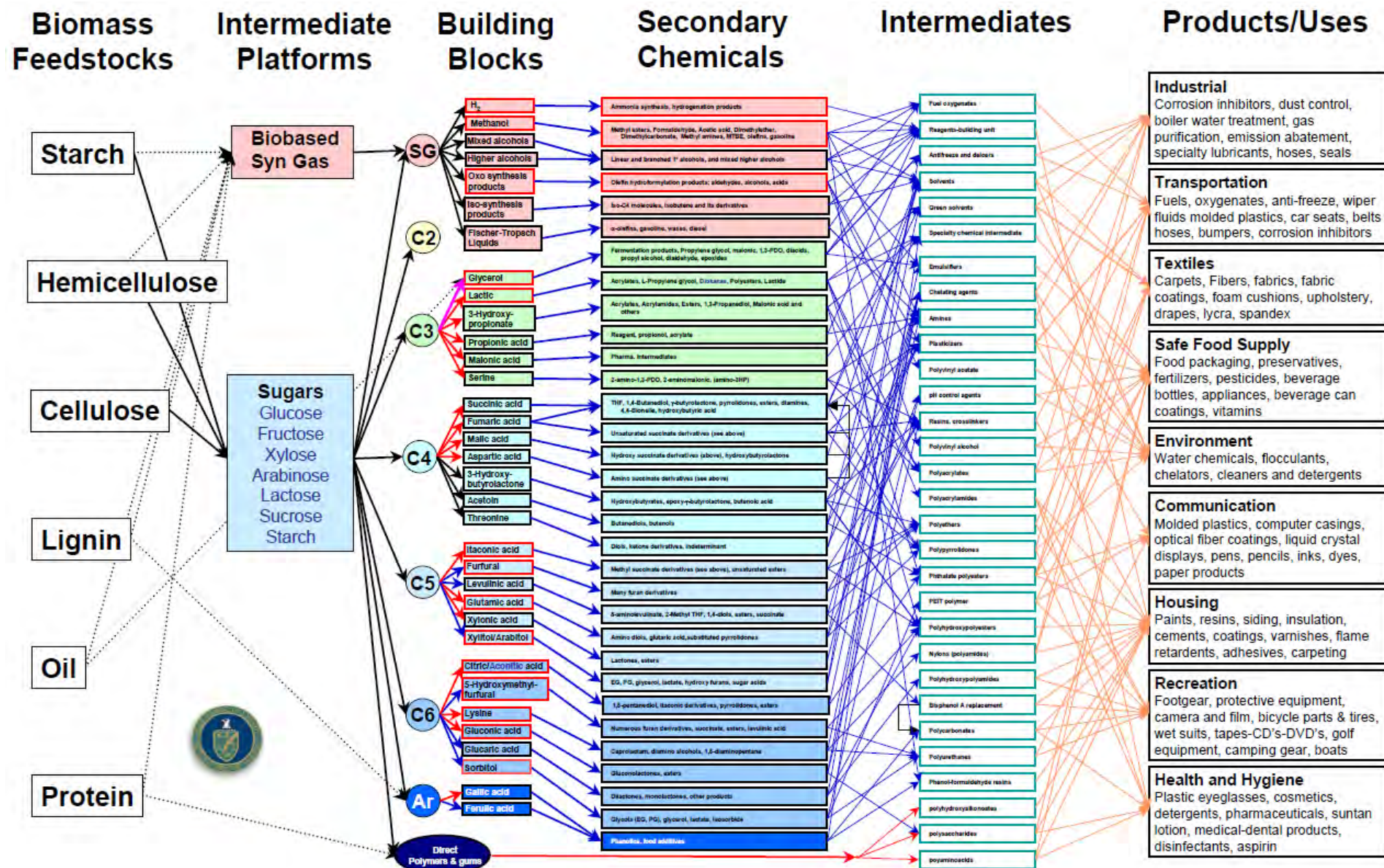
- First commercial SynBio product
- \$42M grant from Gates Foundation
- UC Berkeley patents (Keasling)
- Replaces fluctuating plant supply
- Global market: about \$90M p.a.



Nature Reviews | Microbiology







Predicted market value of SynBio by 2016: **\$10.8 billion** (from \$1.6 billion in 2011)



Category	Product	Organization	Timeframe	Market Status <sup>1</sup>			
				Near-Term	Medium-Term	Long-term	On the Horizon
Biofuel	Algal Biofuels (Bio-oil)	Synthetic Genomics/ExxonMobil	Long-term				
Biofuel	Diesel alternatives (a fatty acid methyl ester (biodiesel ASTM 6751) and an alkane (ASTM D975) from sugar)	LS9 (San Francisco, CA)	Long-term				
Biofuel	Diesel and other "Electrofuels" (Biofuels from Electricity and CO <sub>2</sub> )	Ginko Bioworks (Boston, MA)	Long-term				
Biofuel	Ethanol from Hybrid Algae	Algenol (Bonita Springs, FL)	Long-term				
Biofuel	Algal Biofuels (Bio-oil) (Green Crude) (Fermentation)	Sapphire Energy (San Diego, CA)	Medium-term				
Biofuel	Butanol	Butamax/DuPont (Wilmington, DE)	Medium-term				
Biofuel	<u>Diesel - Helioculture</u>	Joule Unlimited (Cambridge, MA)	Medium-term				
Biofuel	Ethanol - Cellulosic (Mascoma Grain Technology)	Mascoma	Medium-term				
Biofuel	Algal Biofuels Solazet, SolaDiesel (bio-oil jet fuel, diesel) (Fermentation)	Solazyme (San Francisco, CA)	Near-term				
Biofuel	Biofuel Feedstock	Chromatin (Chicago, IL)	Near-term				
Biofuel	Biofuel Feedstock - Accellerase TRIO (enzymes for rapid breakdown of cellulose feedstocks)	Genencor (Rochester, NY)	Near-term				
Biofuel	Ethanol - Cellulosic (Process Licenses)	Qteros (Marlborough, MA)	Near-term				
Biofuel	Renewable Diesel and Jet Fuels	Amyris (Emeryville, CA)	Near-term				
Chemicals	<u>DL-Lactic Acid</u>	Myriant (Quincy, MA)	Near-term				
Chemicals	<u>Isobutanol</u>	Gevo (Englewood, CO)	Near-term				
Chemicals	<u>Squalane</u>	Amyris (Emeryville, CA)	Near-term				
Chemicals	<u>Succinic Acid</u>	BioAmber (Minneapolis, MN)	Near-term				
Chemicals	1,4-butanediol	BioAmber (Minneapolis, MN)	Long-term				
Chemicals	Adipic Acid (nylon precursor)	BioAmber (Minneapolis, MN)	Long-term				
Chemicals	Bio-dispersants (useful for oil spill cleanup)	Modular Genetics, Inc. (Woburn, MA)	Long-term				
Chemicals	butadiene	Genomatica (San Diego, CA)	Long-term				
Chemicals	Fatty Acid, acrylamide	OPX Biotechnologies (Boulder, CO)	Long-term				
Chemicals	Isobutene	Global Bioenergies (Evry, France)	Long-term				
Chemicals	l-Methionine	Metabolic Explorer (Clermont Ferrand, France)	Long-term				
Chemicals	Pomecin B (Anti-fungal)	Evolva (Reinach, Switzerland)	Long-term				
Chemicals	Succinic Acid	DSM (Heerlen, Netherlands)	Long-term				
Chemicals	Surfactants	LS9 (San Francisco, CA)/Proctor & Gamble (Cincinnati, OH)	Long-term				
Chemicals	1,4-butanediol (Bio-BDO)	Genomatica (San Diego, CA)/Tate & Lyle (London, UK)/Novamont (Novara, Italy)	Medium-term				
Chemicals	Adipic Acid (nylon precursor)	Verdezyne (Carlsbad, CA)	Medium-term				





Category	Product	Organization	Timeframe	Market Status <sup>1</sup>			
Chemicals	<a href="#">BioAcrylic</a>	OPX Biotechnologies (Boulder, CO)	Medium-term				
Chemicals	Plasticizers (phthalate free)	BioAmber (Minneapolis, MN)	Medium-term				
Chemicals	Succinic Acid	Myriant (Quincy, MA)	Medium-term				
Chemicals	Surfactants (myristoyl glutamate - used for cleaners, paints, coatings, their version is 10x more effective than conventional versions)	Modular Genetics, Inc. (Woburn, MA)	Medium-term				
Chemicals	1,3-propanediol (Bio-PDO™)	DuPont (Wilmington, DE)/Tate & Lyle (London, UK)/Genecor (Palo Alto, CA)	Near-term				
Chemicals	Biofene (Farnesene) Engineered Yeast	Amyris (Emeryville, CA)	Near-term				
Chemicals	Bacterial "tracking history"	Ginko Bioworks (Boston, MA)	On The Horizon				
Chemicals	H2S sourced fuels and organic compounds	Ginko Bioworks (Boston, MA)	On The Horizon				
Chemicals	Mandelic Acid	Chinese Academy of Sciences	On The Horizon				
Energy	Microbial Fuel Cells efficiency improvement	Nanyang Technological University (Singapore)	On The Horizon				
Food	<a href="#">Vanillin</a>	Evolva (Reinach, Switzerland)	Medium-term				
Food	<a href="#">AnimalFeedProcessing Yeast(MascomaGrain Technology)</a>	Mascoma	Near-term				
Food	<a href="#">Valencene(CitrusFlavoring)</a>	Isobionics (Geleen, Netherlands)/DSM and Allylix (San Diego, CA)	Near-term				
Food	Improvements and modifications to fermentation for food and beverages	Kluyver Centre for Genomics of Industrial Fermentation (Delft, Netherlands)	Long-term				
Food	Stevia (Artificial Sweetener)	Evolva (Reinach, Switzerland)	Long-term				
Food	Sun-driven microbial synthesis of chemicals in space	Harvard/NASA	Long-term				
Materials	Isoprene (Synthetic Rubber precursor)	Goodyear (Akron, OH)/Genencor (Rochester, NY), Amyris (Emeryville, CA)/Michelin (Boulogne-Billancourt, France)	Medium-term				
Materials	PHA (plastics)	MetaboliX (Cambridge, MA)	Medium-term				
Materials	Modified polybutylene succinate (mPBS) (Plastic)	BioAmber (Minneapolis, MN)	Near-term				
Medicine	<a href="#">EngineeredInsectStrainsfor population/disease control</a>	Oxitec (Oxford, UK)	Medium-term				
Medicine	<a href="#">AttenuatedVirusCultures for vaccine production</a>	Novartis (Basel, Switzerland)/Synthetic Genomic Vaccines (Rockville, MD)	Medium-term				
Medicine	<a href="#">Antibiotic - Improved processforCephalexin</a>	DSM (Heerlen Netherlands)	Near-term				
Medicine	A1AT deficiency treatment - Intrexon-Alpha 1-Antitrypsin	Intrexon (Blacksburg, VA)/Halozyme (San Diego, CA)	Long-term				
Medicine	Antibiotic - EV-035 (lab testing)	Evolva (Reinach, Switzerland)	Long-term				
Medicine	Arsenic water contamination sensor	Lumin Sensors/iGEM (Team Edinburgh 2006)	Long-Term				

**Update 2014:**  
Commercial  
production  
has begun



Category	Product	Organization	Timeframe	Market Status <sup>1</sup>			
Medicine	pulmonary arterial hypertension (PAH) therapy	Intrexon (Blacksburg, VA)/Synthetic Genomics (formerly Adeona Pharmaceuticals) (La Jolla, CA)	Long-term				
Medicine	Recombinant Antibodies	Fabrus (La Jolla, CA)	Long-term				
Medicine	<u>Cancer Therapeutics ZIN-ATI-001 (Ad-RTS-IL-12 + AL)(INXN2001/1001) and ZIN-CTI-001 (DC-RTS-IL-12+AL)(INXN3001/1001) araphase/crphaselb</u>	ZIOPHARM (New York, NY)/Intrexon (Blacksburg, VA)	Medium-term				
Medicine	Diabetes drug - EV-077 (phase Iia)	Evolva (Reinach, Switzerland)	Medium-term				
Medicine	Artemisinin – Anti-malarial Therapeutic	Amyris (Emeryville, CA)	Near-term				
Medicine	Diabetes drug - Improved manuf process for Sitagliptin	Codexis (Redwood City, CA)/Merck (Darmstadt, Germany)	Near-term				
Medicine	Synthetic lantibiotics	Intrexon (Blacksburg, VA)/Oragenics (Tampa, FL)	On The Horizon				
Medicine	Antibiotics - Nicin variants - New variety of antibiotics (that potentially avoid standard drug resistance)	Carroll, et. Al. (Cork, Ireland)	On The Horizon				
Medicine	Bacteriophage treatment as antibiotic alternative or supplement	Harvard/BU	On The Horizon				
Medicine	Electrical-Organic interfacing efficiency	Lawrence Berkeley National Laboratory/HHMI	On The Horizon				
Medicine	EnLact probiotics - VT301 for inflammatory bowel disease	ViThera Pharmaceuticals (Cambridge, MA)	Long-term				
Medicine	Using engineered gut bacteria to prevent cholera	Cornell (Ithaca, NY)	On The Horizon				
Other	Tissue-engineered biomimetic jellyfish	Caltech/Harvard	On The Horizon				
Other	Cyberplasm (small swimming robot)	Northeastern University, University of Alabama, MIT and Newcastle University U.K.					



# SYNDISTRY

The news of "Synthia," the world's first human-made species, is just the latest from a rapidly growing artificial life industry. Synthetic biology (or "Syn Bio") aims to profit from the design and construction of industrially useful life-forms.

## THE EMERGING SYNTHETIC BIOLOGY INDUSTRY



### Syn Bio's Big Shots

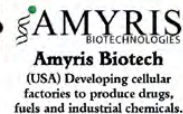
Global corporations are investing in synthetic biology labs and partnering with start-up companies.

*"Over the next 20 years synthetic genomics is going to become the standard for making anything."* - Craig Venter



### Synthetic Startups

A bevy of 'pure play' syn bio companies is attempting to design synthetic microbes for fuel, chemicals and drugs. Many are university spin-offs.



### DNA Synthesis Foundries

DNA foundries produce the raw material for creating artificial life: synthetic DNA (sDNA).

Over 70 DNA foundries worldwide manufacture sDNA for genetic engineers and synthetic biologists. The market for sDNA already exceeds a billion dollars annually. Even long DNA sequences - entire genes, for example - can be ordered over the Internet and delivered within two weeks. The speed of producing accurate DNA sequences is doubling every two years and costs are halving even faster.



## synthetic biology roadmap



### for the integrated production of chemicals



### NEW DIRECTIONS

The Ethics of Synthetic Biology and Emerging Technologies

## POSITIONING SYNTHETIC BIOLOGY

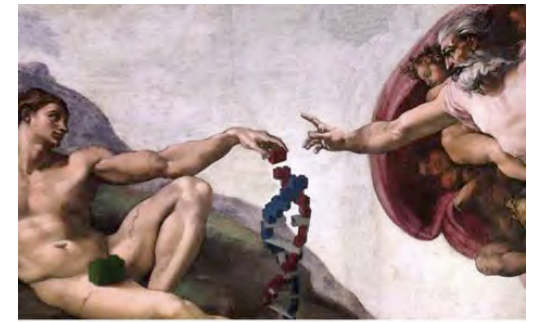
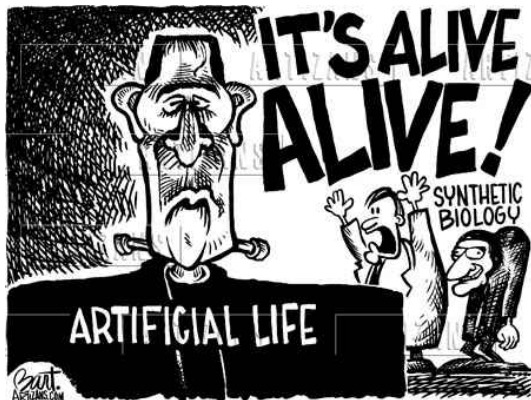
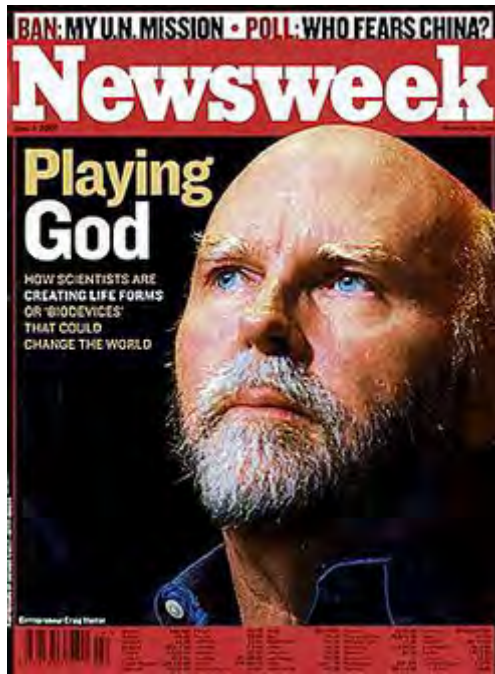
TO MEET THE CHALLENGE OF THE 21st CENTURY

SUMMARY REPORT OF A SIX ACADEMIES SYMPOSIUM

NATIONAL RESEARCH COUNCIL AND NATIONAL ACADEMY OF ENGINEERING OF THE NATIONAL ACADEMIES

### The Principles for the Oversight of Synthetic Biology





# EXTREME GENETIC ENGINEERING

*An Introduction to Synthetic Biology*

**Extreme Genetic Engineering in Your Ice Cream?**



**TAKE ACTION:** Tell Dryer's, Baskin Robbins, and Haagen Dazs to reject synbio vanilla.

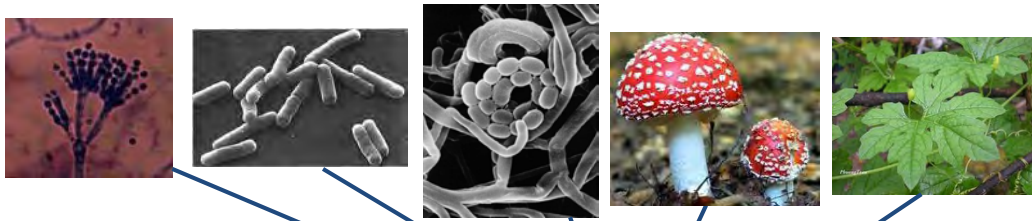


**MANCHESTER**  
1824

The University of Manchester

rainer.breitling@  
manchester.ac.uk

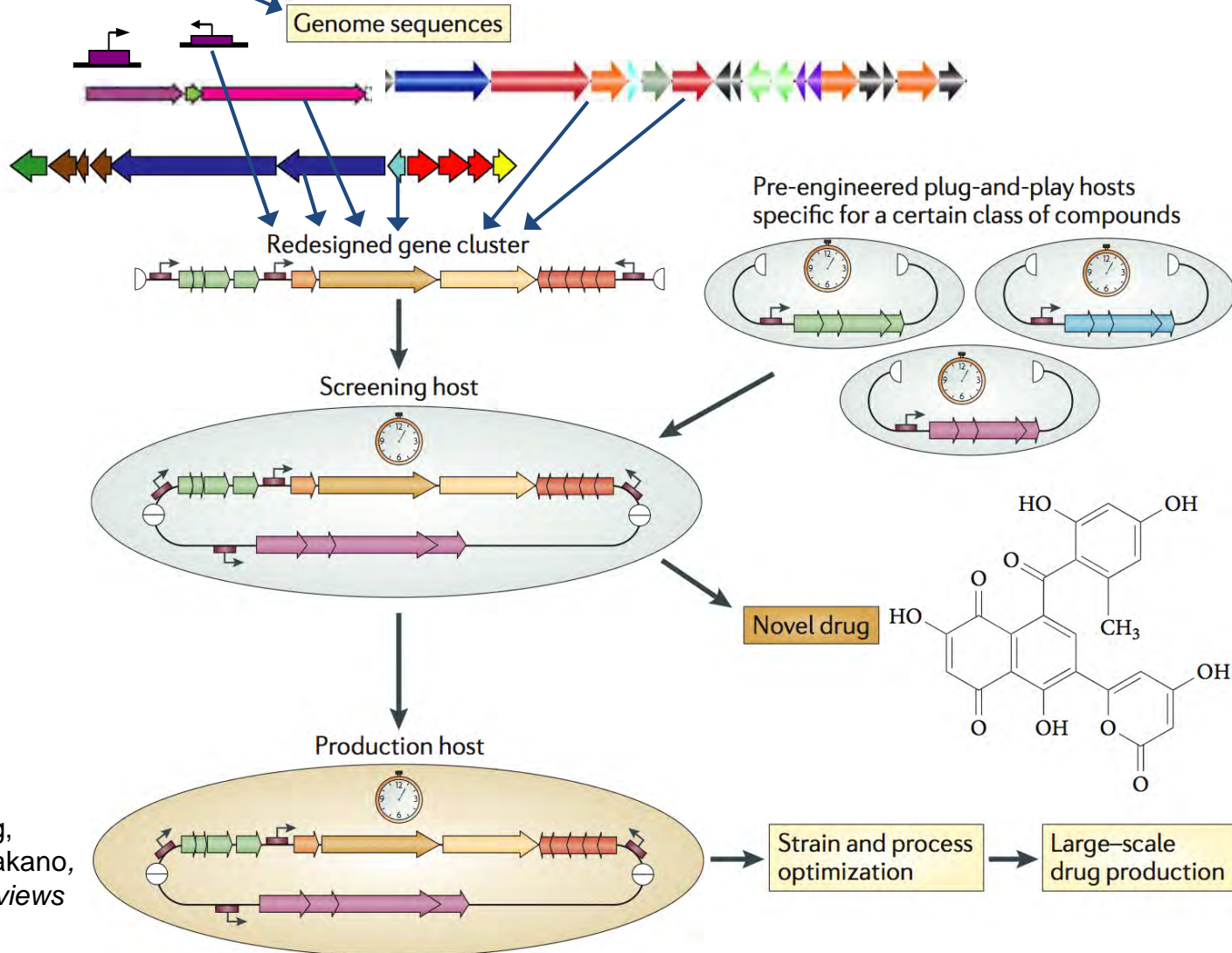




# Synthetic Biology in

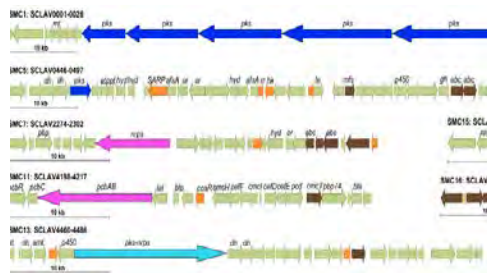
MANCHESTER  
1824

The University of Manchester



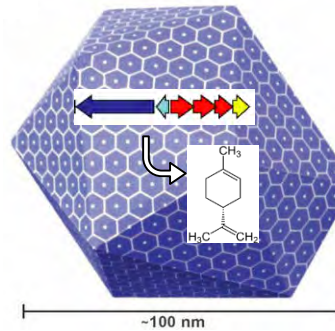
# Tools for SynBio of high-value chemicals

## Biosynthetic genes from different sources = library of parts

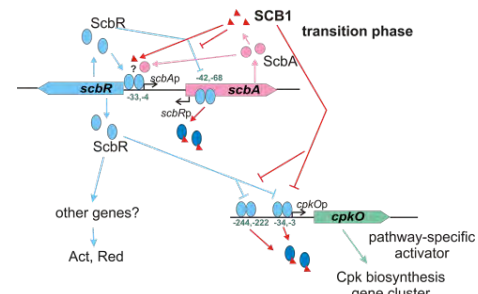


Medema et al., (2011) *Microb. Biotechnol.*

## Engineering a chassis

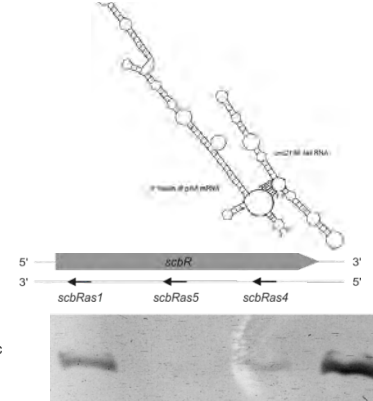


## Regulatory circuits



Hsiao et al., (2009) *Chemistry and Biology*

## Control of gene expression

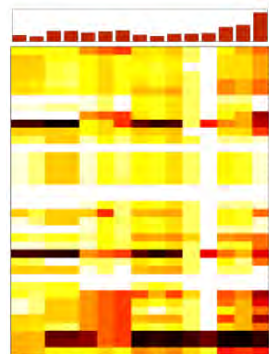
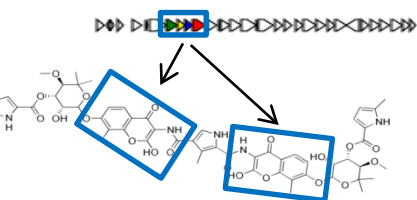


D'Alia et al., (2010) *J Bacteriol.*

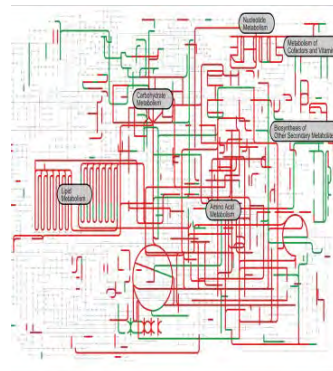
## Computational software/modelling/analysis



Medema et al. (2011) *Nucl. Acids Res.*,

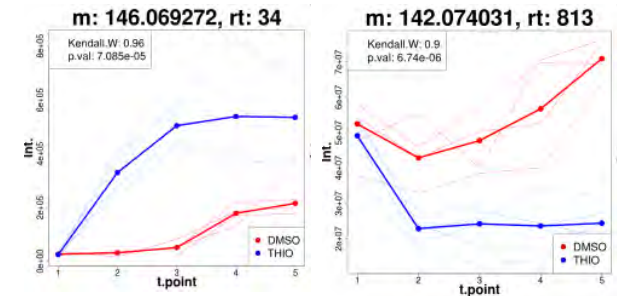


Zakrzewski et al., (2012) *PLoS ONE*



Medema et al., (2011) *Bioengineered Bugs*,

## Debugging routines



Jankevics et al. (2011) *Proteomics*,