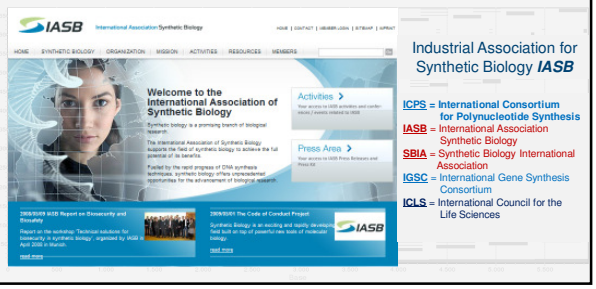
Applications in SynBio: Present and Future



Industrial Association for Synthetic Biology ***IASB***

ICPS = **International Consortium for Polynucleotide Synthesis**
IASB = International Association Synthetic Biology
SBIA = Synthetic Biology International Association
IGSC = International Gene Synthesis Consortium
ICLS = International Council for the Life Sciences

Applications in SynBio: Present and Future

"The field has had its hype phase. Now it needs to deliver!"
Martin Fussenegger in **Kwok R. (2010)** Five hard truth for Synthetic Biology, Nature 463:288ff.

ERA:biosynthetics

Impact of
Synthetic Biology
on Integrative Synthetic Biotechnology Projects

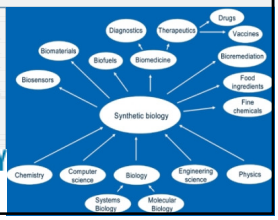
TESSY

www.SB.info

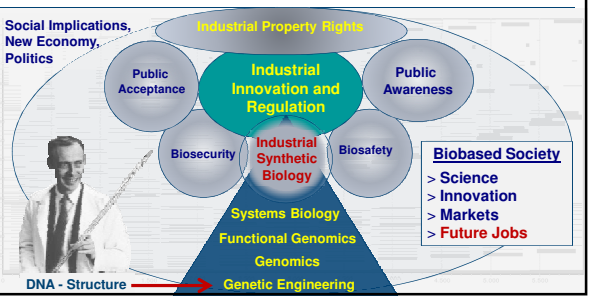
Synthetic Biology in Pharma Conference

Cambridge, UK
March 30-31, **2010**

SYNBIOLOGY



Innovation Cycles are Paralleled by Application Value Chains



Biobased Society
> **Science**
> **Innovation**
> **Markets**
> **Future Jobs**

Information-Driven Discovery Process – Enabling Technologies From Understanding to Engineering

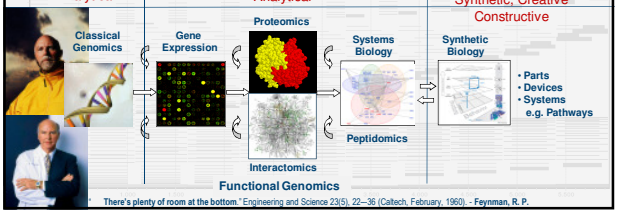
"What I *cannot* create, I do not understand." *Richard P. Feynman*

*Genom*X – Craig Venter

"An alternative to understanding complexity is to get rid of it" *Tom Knight (MIT)*

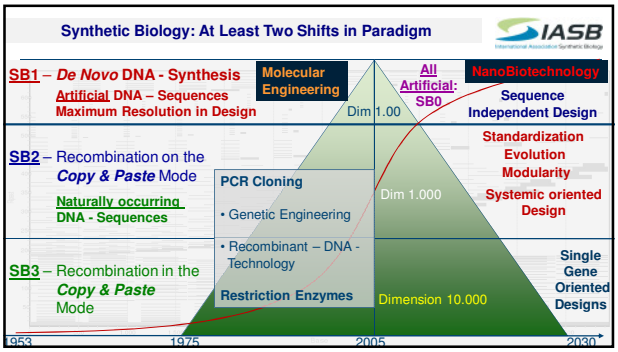
"We can't solve the problems of today by thinking the way we thought when we created them." *Albert Einstein (1879-1955)*

"Everything should be made as simple as possible but not simpler" *Albert Einstein (1879-1955)*



"There's plenty of room at the bottom." Engineering and Science 23(5), 22–36 (Caltech, February, 1960). - **Feynman, R. P.**

Synthetic Biology: At Least Two Shifts in Paradigm



The Dilemma Between „Science and Market“

Like all other technology developments - Synthetic Biology - is in the **tension field** of a **dilemma** where on the one hand scientists like to show what is possible and to explore the **borders of knowledge and technology** – but on the other side the markets who always asks:

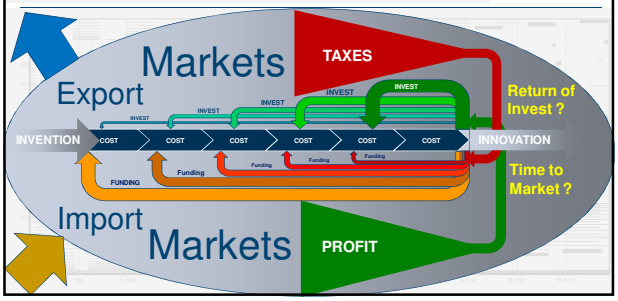
Who needs it? – **Is there any benefit for the customers? Is there actually a market?**
What are the cost ? What are the return of invest time-lines and which profit can be achieved.

Synthetic Biology 1: – has clearly not arrived on the ***B2B*** nor the ***B2C*** consumer market.

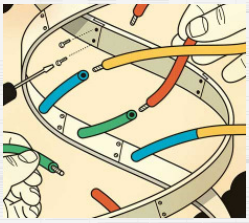
Synthetic Biology 2: – secondary gene products – small molecules has entered the market

Synthetic Biology 3: – primary gene products (proteins like enzymes, cytokines, biopharmaceuticals etc.) –heterologous expression

In a Knowledge Based Society all Societal Domain Components Need to Work Together in a Highly Integrative Interdisciplinary Process



Bottom UP: Idealistic Technology Driven Visionary Phase



But the real challenge will start when we enter the synthetic biology phase of research....This would be a field with...hardly any limitations to building..."synthetic" organisms, like a "new better mouse." — Waclaw Szybalski, "***In Vivo*** and ***In Vitro*** Initiation of Transcription," 1974

versus

“It can take months if not a year or years to get the network to behave. You have to do an awful lot of tweaking to get your network to work the way you want.”
James J. Collins

Top Down: Realistic Market Driven Phase – Who needs it?

***.....means* Hard Work of Realizing Products**

Sequence Independent Rational Design
Principles for Functional Elements

Principles of Hierarchy in Design :

- Parts (Module)
- Devices (Function)
- Systems (Application)

Silicon IT – Technologies
versus
Carbon – IT
→ Integrated Carbon Technologies
MAC – IT and **MAB – IT**
Integrating Molecular Function of ***magE*** **- IT**

- **Abstraction:** Circuitry design – models – simulation – improvement
- **Hierarchy:** Different levels of Design
- **Modularity:** Parts work together for functional fit in device function
- **Standardization:** Documentation of high quality to insure it works
- **Decoupling:** of Gene or Pathway Design and DNA-Synthesis→ Software vs. Hardware
- **Evolution:** Gene Diversification, Shuffling, Functional Optimizations, Selection of Variants
- **Orthogonality:** Systems independency no cross-talk
- **Reproducibility:** Robustness of function in a defined environment
- **Sequence Independency:** Molecular Function Provided
- ***magE*** **- Minimal artificial elements Catalysts MACs and Binders MABs as**
- From ***magE*** **-Elements to Minimal Artificial Genomes**
- **Programming of *Minimal Genetical Cell Systems* (MGCS)**

Sources :
Endy D. (2005) Foundations for engineering biology, Nature Review, **438:449-453**
Goler et al. (2008) Genetic design: rising above the Sequence, Trends Biotechnol., **26:538-44**

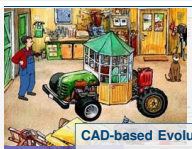
Are There Principaly New Future Synthetic Biology Markets ?

The Potential Biotech - Markets are The Same for Synthetic Biology :

- **Science Market** - heterogeneous - **Reagents, Devices, Enabling Technology**
- **RED – Biotech – Medical/ Pharma---------- Science and R&D Market**
- **WHITE – Biotech – Industrial Market----------Science and R&D Market**
- **GREEN – Biotech – Agro-Industrial Market-----Science and R&D Market**
- **BLUE – Biotech – Nutrition, Pharma, Materials, Enzymes …**

Club of Rome Postulated the Age of Qualitative Growth !

Rational - From Parts → To Devices → To Systems – *Versus* Evolutionary Design



CAD-based Evolutionary Design Optimization with CATIA V5
Oliver König, Marc Wintermantel
EVEN - Evolutionary Engineering AG, Zurich, Switzerland



Basic Antipodes of **SB – Design of Requirement Specifications**

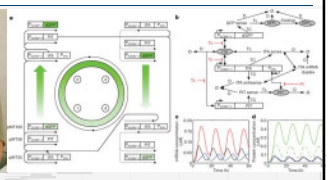
Flow of Matter in the Metabolism: Directions of Impact

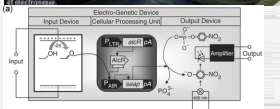
1. **Max. Flow** – **Production** – $R_{min.}$ requirement of optimal **stoichometry** and
   a. **low** or **no** complexity in regulation
   b. high production yields, high efficiency, high throughput
   c. comparable to electrical **strong current** for powering big machines

2. **Max. Regulation e.g. for Dosage of Drug Delivery**
   a. **highly regulated** with low throughput – oscillating schemes
   b. therapeutics with a high **efficiacy** on **low dose** (nM) $R_{max.}$ – high regulation
   c. comparable with electronics

3. **Combination of both 1. and 2. means Max. Regulation of Max. Production**

Regulation of Systems: Genetic Circuits II





A tunable synthetic mammalian oscillator, Tigges et. al. *Nature*, 457, 309-312.

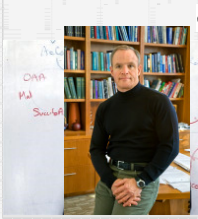
A synthetic mammalian electro-genetic transcription circuit, Weber et. al. *Nucleic Acids Research*, 37(4) e33.

Artificially regulated Genetic Circuits II

http://oscillatorblog.com/

Artificial Biosynthetic Pathways – Drugs, bioPharmaceuticals, bioPlastics, Building Blocks, Fine Chemicals…

Synthetic Biology is the **Logic Continuation** of **Synthetic Chemistry** by **Means of Biology**
- Jay Keasling -



- Self Replicating Systems
- Information Processing
- Compartimentation
- Systems Behavior
- Modularity
- Orthogonality
- Cellular Differentiation

High Throughput – Specific Molecules

Design of Requirement Specifications

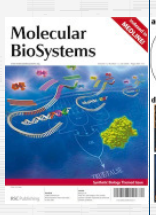
Structure and Functional Relationships – Functional Nanoarchitecture

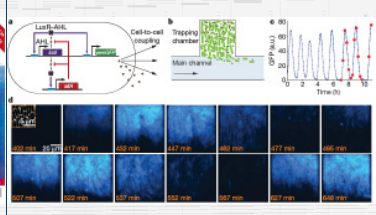
1. **Angström to low Nanostructures - Catalysis**– **Production** – $R_{min.}$ requirement of optimal **stoichometry** and
   a. Turnover (Kinetics)
   b. Specificity (Regio-selectivity,
   c. Stability (physical: heat, pressure etc.; chemical: solvents etc., biological)

2. **DNA-Nanostructuring or Microcompartments - Containments e.g. VLPs**
   e.g. for Dosage of Drug Delivery
   a. Self assembly properties
   b. Stability (physical: heat, pressure etc.; chemical: solvents etc., biological)
   c. Ability to functionalize

3. **Combination of both 1. and 2. means**

Regulation of Systems: Genetic Circuits I

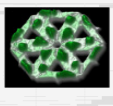




Artificially regulated Genetic Circuits I

Tal Danino, Octavio Mondragon-Palomino, Lev Tsimring & Jeff Hasty (2010) A synchronized quorum of genetic clocks nature 463: 326-330

"ssDNA Nanostructuring of Surfaces" – Paul W.K. Rothemund



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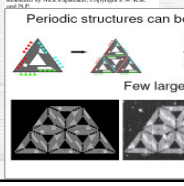
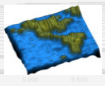
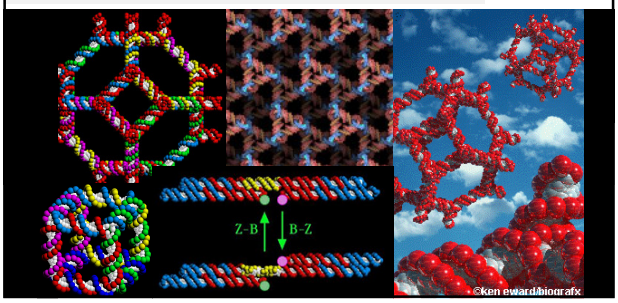




DNA Nanotechnology in Ned Seeman's Laboratory



Cleantech Quality Standards in – White Biotech
What makes Synthetic Biology better?

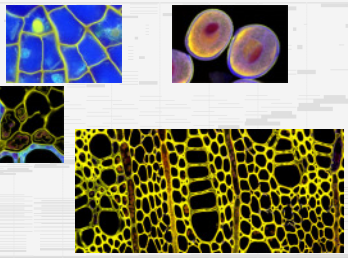
Classical bioProduction Technologies	Synthetic Biotechnology Production Technologies
• waste of energy	• high energy efficiency
• huge plants	• small and completely new types of plants
• high temperatures	• moderate to low temperatures
• high air pressures - reduced saftety	• normal air pressure
• toxic solvents	• solvent water
• reduced production flexibility	• high flexibility in production
• reduced working place safety	• high safety levels achievable
• only economically in huge volumes	• economical production even in smaller volumes

BMU - Förderkennzeichen (UFOPLAN) 202 66 326

Club of Rome Postulated the Age of Qualitative Growth !

Plant Synthetic Biology – Discredited by Ideologists

Dr. Jim Haseloff
Department of Plant Sciences
University of Cambridge
Downing Street
Cambridge CB2 3EA



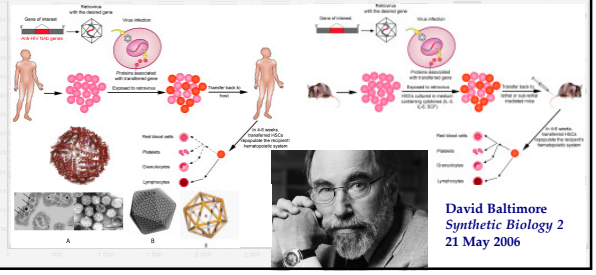
New Standards in Red Biotech – Will future *bio*Production
Provide Active Pharmaceutical Incredients and its **AutoDosage**?

Classical Pharma Industry based Medical Supply	Synthetic Biology Based Medical Supply
• Small molecules by **chemical synthesis**	• Sustainably **bio-produced small molecules**
• Application **extracorporal**	• Therapeutic proteins, mABs, BioLogics bioPharmaceuticals
• invasive therapies (Insuline)	• Application **intracorporal**
• oral application multiple	• e.g. sub-cutan
• rectal application multiple	• intravenuous single application
• intravenuous multiple	• **non-invasive therapies – artificial organs**
• Block busters – relative unspecificity	• Therapeutic genetic systems
• Many unwanted side effects	• Individualized therapies
• Multiple indications – no specificity	• Low to no adverse effects
• Permanent therapy – **no real curing**	• Highest efficiacy – **REAL curing**

Club of Rome Postulated the Age of Qualitative Growth !

New Strategies in Health Care e.g. Immunotherapies

"The future of humanity and microbes will likely unfold as episodes of a suspense thriller that could be titled 'Our Wits Versus Their Genes.'"
— Dr. Joshua Lederberg, 1958 Nobel laureate



David Baltimore
Synthetic Biology 2
21 May 2006

Integrative Synthetic Biotech Projects - High Impact on the Development New Markets on the basis of New Technologies for Future Economy

$$P(t)_{(Power)} = V_{(Potential)} \times I_{(Current)}$$

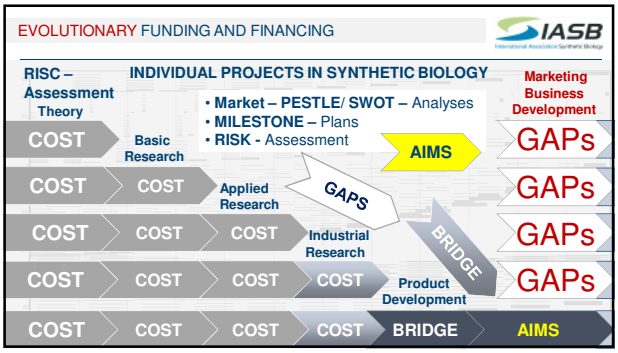
General Technology Transfer Value Chain

Theory	Basic Research	Applied Research	Industrial Research	Product Development	Marketing Business Development
COST	COST	COST	COST	COST	
Universities	Universities		AiF/ ProInno		
Max Planck Organization		Fraunhofer Organization			

GAPs

NO TRANSLATIONAL MONEY ???

BMBF – Federal Ministry of Education and Research


EVOLUTIONARY FUNDING AND FINANCING
IASB
RISC – Assessment
Theory
INDIVIDUAL PROJECTS IN SYNTHETIC BIOLOGY
• Market – PESTLE/ SWOT – Analyses
• MILESTONE – Plans
• RISK - Assessment
Marketing Business Development
COST
Basic Research
AIMS
GAPs
COST
COST
Applied Research
GAPS
GAPs
COST
COST
COST
Industrial Research
BRIDGE
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COST
Product Development
GAPs
COST
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COST
COST
BRIDGE
AIMS

"What can the EU do to promote mental health of older people"

Summary of the presentation by Anne-Sophie Parent, Director, AGE-the European Older People's Platform, 13 June 2008

Various factors make older people more vulnerable to mental health problems:

- The physiological ageing process which results in an increasing risk of dementia (increased risk both for the ageing individual and partner/carer)
- Adverse effect of overmedication and polypharmacy among the elderly
- Drug-alcohol interaction
- Increasing dependency which results in an increased risk of elder abuse
- The isolation and social exclusion faced by an increasing number of older people today due to modern lifestyles
- Abrupt change from employment to long term unemployment of (early)-retirement (losing sense of purpose in life)
- Lack of professional training in geriatric and gerontology
- Lack of training and support for informal carers
- The gender dimension: very older women are at higher risk

AGE welcomes the EU Pact on Mental Health and commits itself to support all actions implemented to promote better mental health for all.

As part of the Pact on Mental Health, Member States should agree to commit themselves to increase the number of Healthy Life Years by one year in 2013. This would encourage them to adopt a holistic approach to healthy ageing, including the promotion of good mental health in old age.

If the EU is to "foster good health in an ageing Europe" in the period 2008-2013, it should address each of these factors that affect older people's mental health. In addition to the recommendations listed in the policy brief, EU action is needed in the following fields and the Pact should include to use existing EU instruments to:

FP7:

- Research on old age dementia cause, treatment and prevention. Research should also cover the social and financial impact of old age dementia. (FP 7)
- Research on medication use for the elderly: EMEA should set up a "Geriatric Committee" similar to the "Pediatric Committee" to analyse effect of medication on the elderly, including polypharmacy and overmedication, and share information across the EU with healthcare professionals.

- Raise awareness of care professionals and older citizens/informal carers of potential interaction between medication and alcohol (a problem often overlooked in older people)

OMC Social Protection/Social Inclusion

- Social exclusion of the elderly both in urban and rural/remote areas and examples of good practice across the EU
- EU Strategy to fight against elder abuse: the EU should develop quality guidelines for long term care to help prevent elder abuse (OMC on Social Protection and Social Inclusion)

ESF and Lisbon Strategy:

- Promote active ageing and a more positive of ageing workers;
- Promote health and safety at work including stress reduction;
- Promote more flexible retirement and early preparation for retirement (ESF and Lisbon Strategy)

Health Strategy and Grundvig programme

- Develop geriatric/gerontology training at EU level as exist for paediatrics