Opinion II
Risk assessment methodologies

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Biofaction

- is a research and science communication company based in Vienna, Austria.
- provides expertise and service in the following areas:
  - technology assessment of new and emerging (bio)technologies
  - science communication incl. film production, gamification
  - navigating the science-society interface
  - art-science collaboration

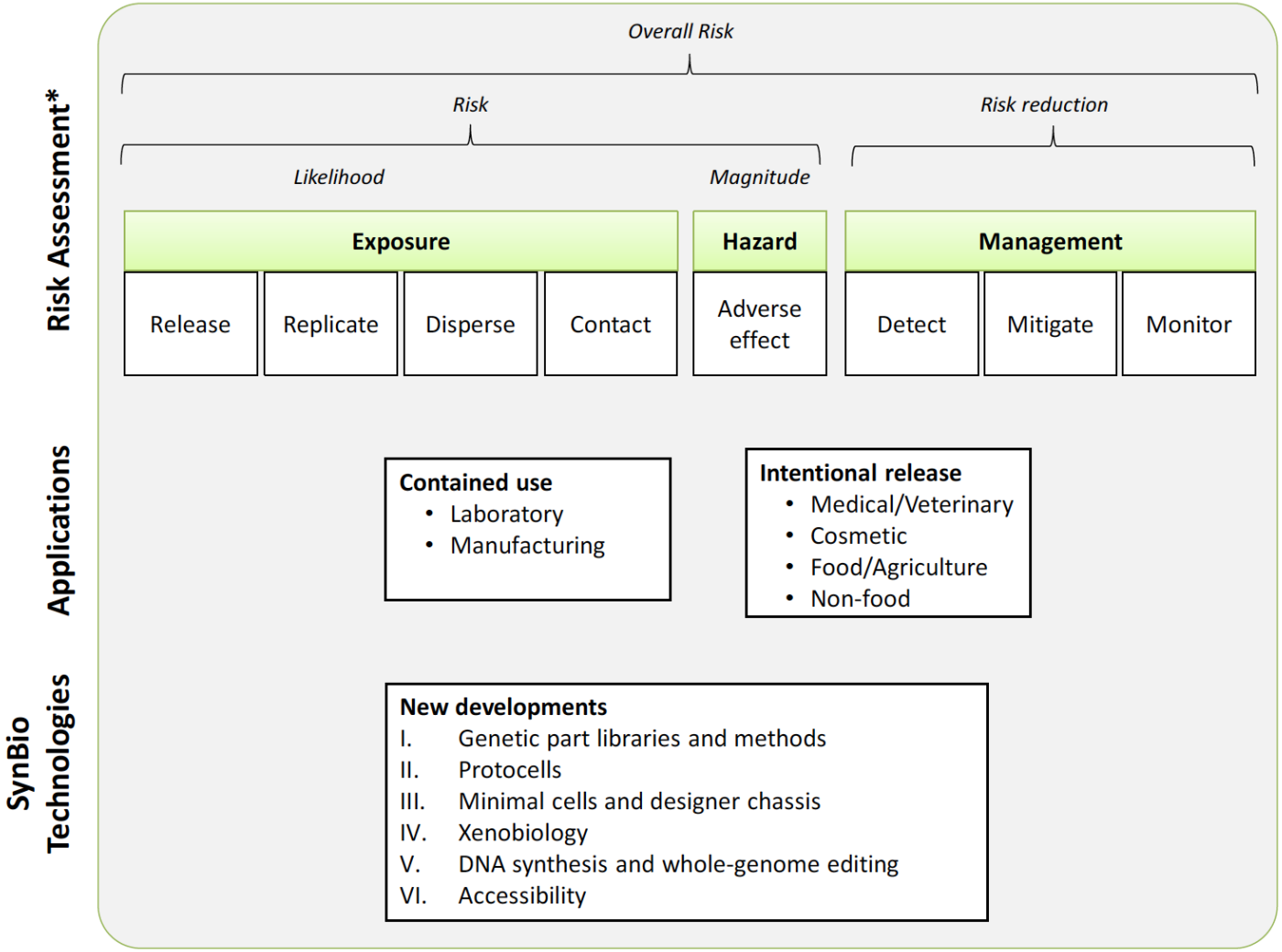
SCENIHR Opinions

European Commission
Health and Consumers

SCIENTIFIC COMMITTEE ON EMERGING AND NEWLY IDENTIFIED HEALTH RISKS (SCENIHR)

- Opinion on Synthetic Biology I – Definition. 25 September 2014
- Opinion on Synthetic Biology II - Risk assessment methodologies and safety aspects. 4 May 2015
- Opinion on Synthetic Biology III: Research priorities. Autumn 2015
- .

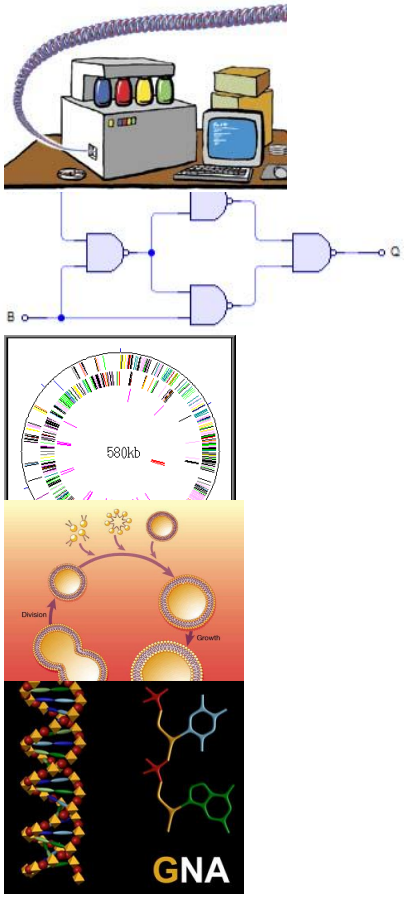
An outline of the assessment process



*Quantification of risk is typically carried out through comparative and/or step-by-step approaches

New Developments in SynBio

1. DNA Synthesis
2. Genetic Parts
3. Minimal genome
4. Protocells
5. Xenobiology
    A. Accessibility



DNA Synthesis

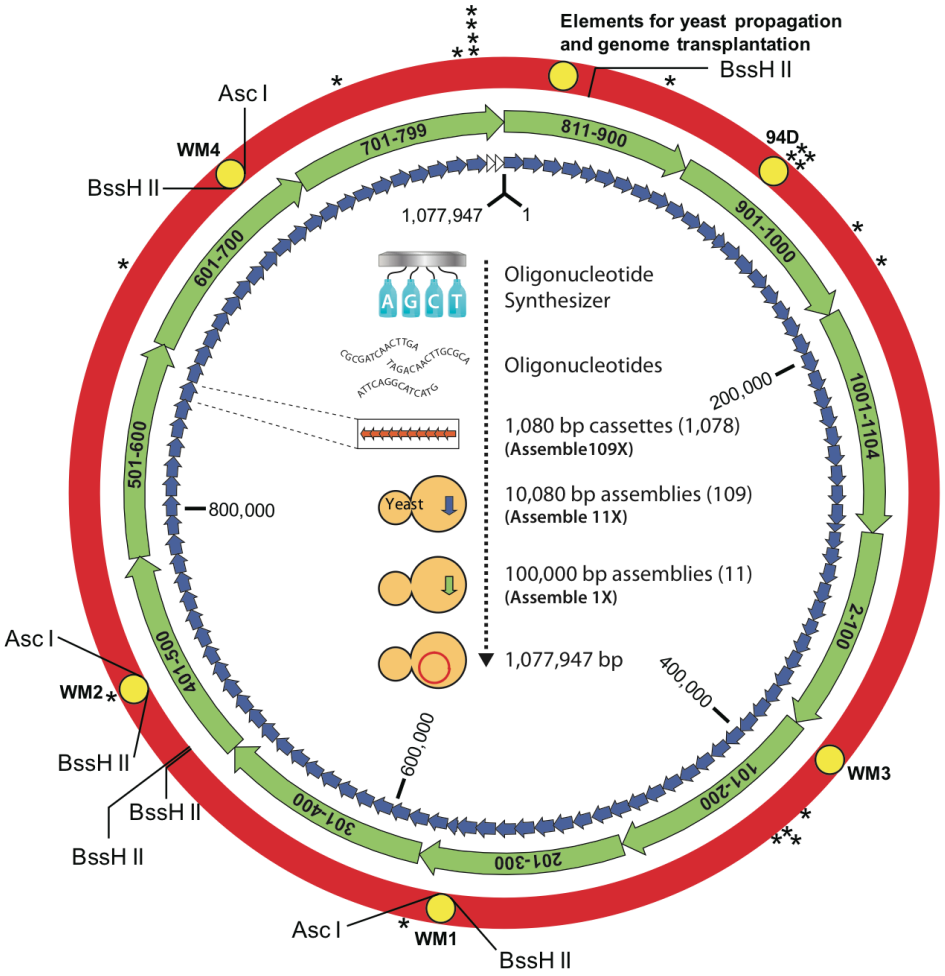
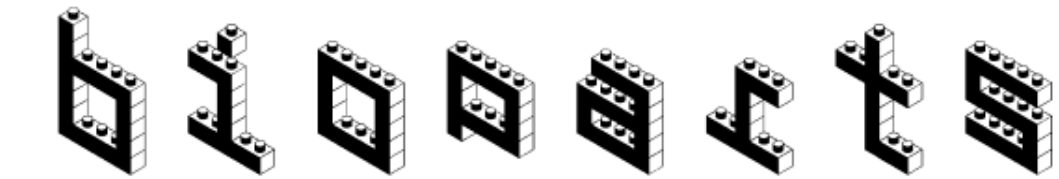


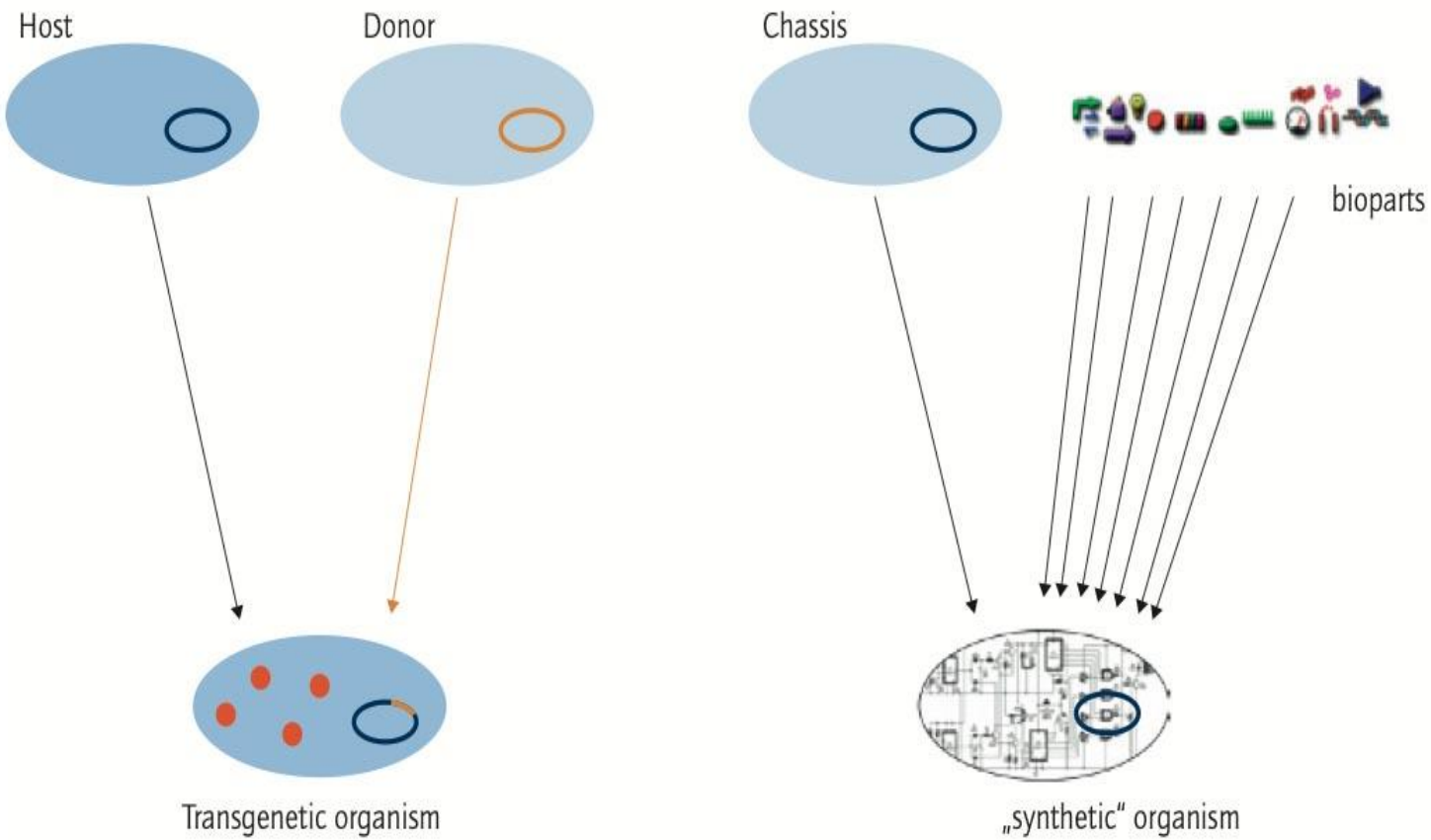
Figure by JCVI

Creating „standardized“

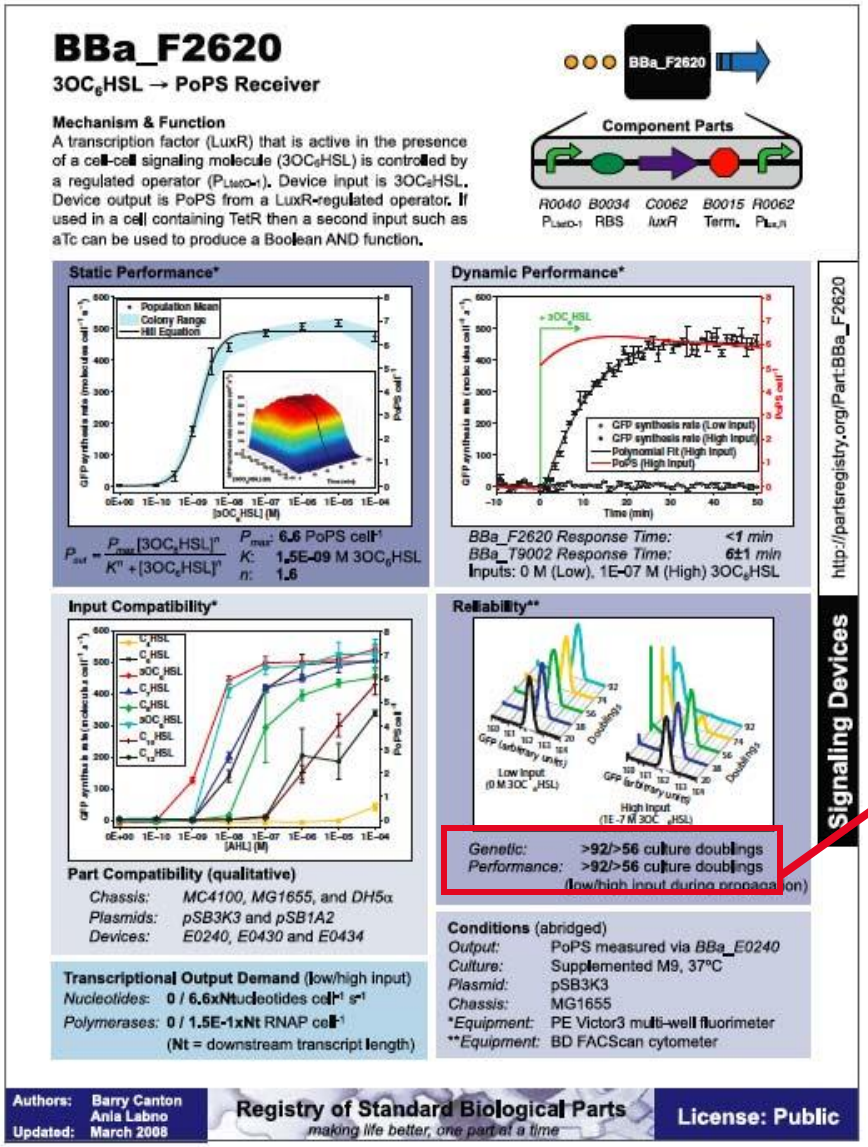


Registry of standard biological parts: biobricks

Engineering *systems*



Safety standards required



Genetic: **>92/>56** culture doublings
Performance: **>92/>56** culture doublings
(low/high input during propagation)

Minimal Genome

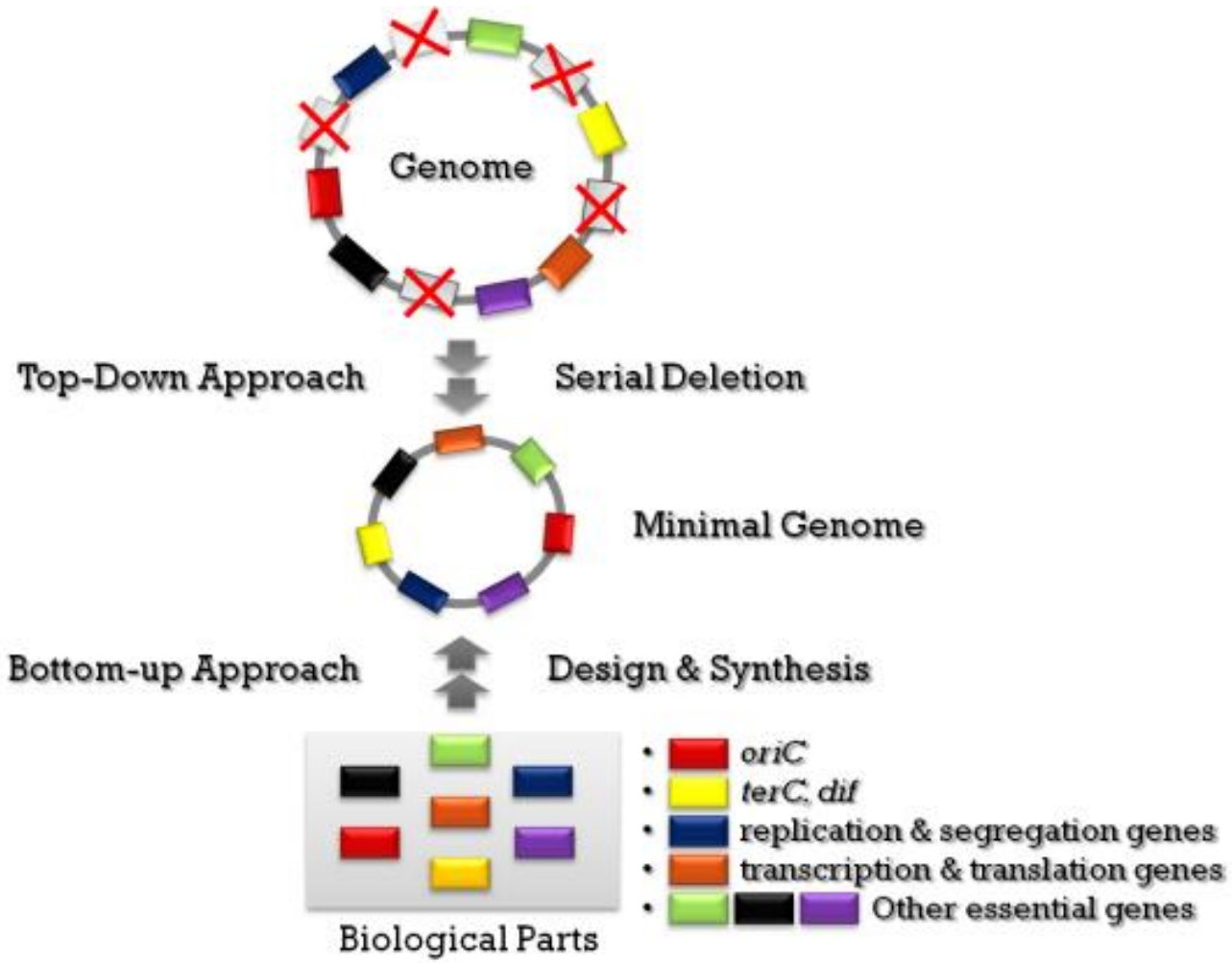
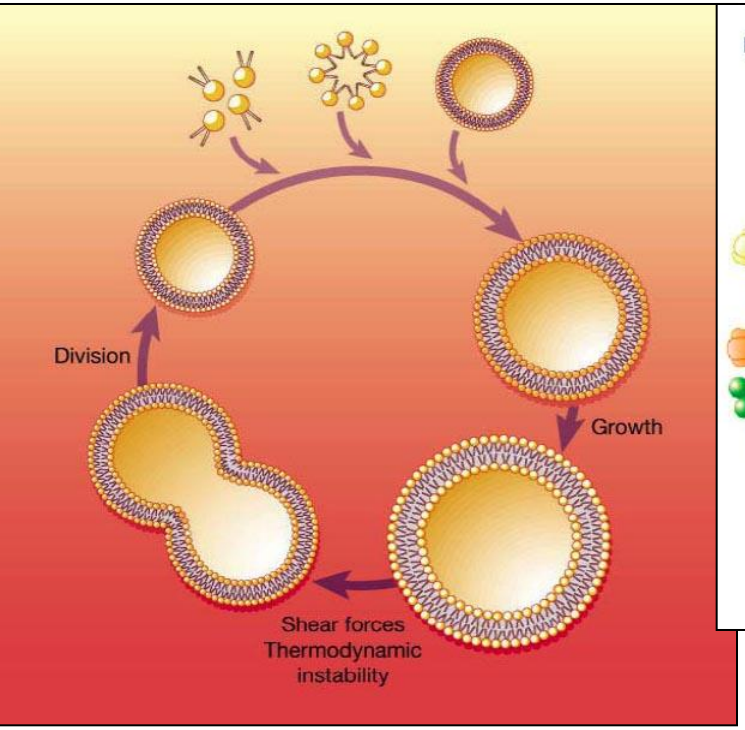
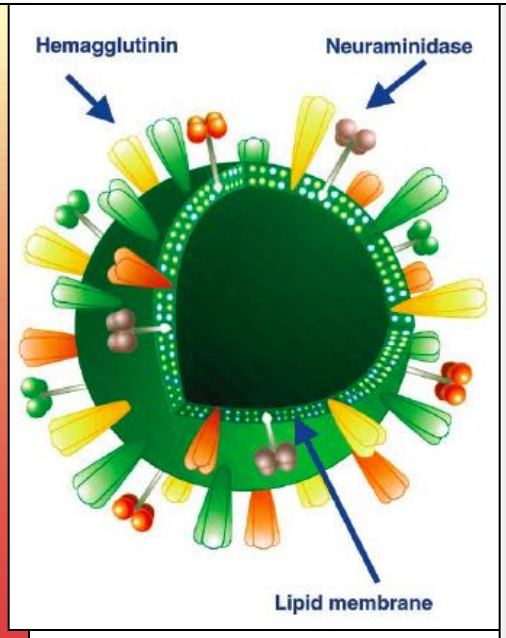
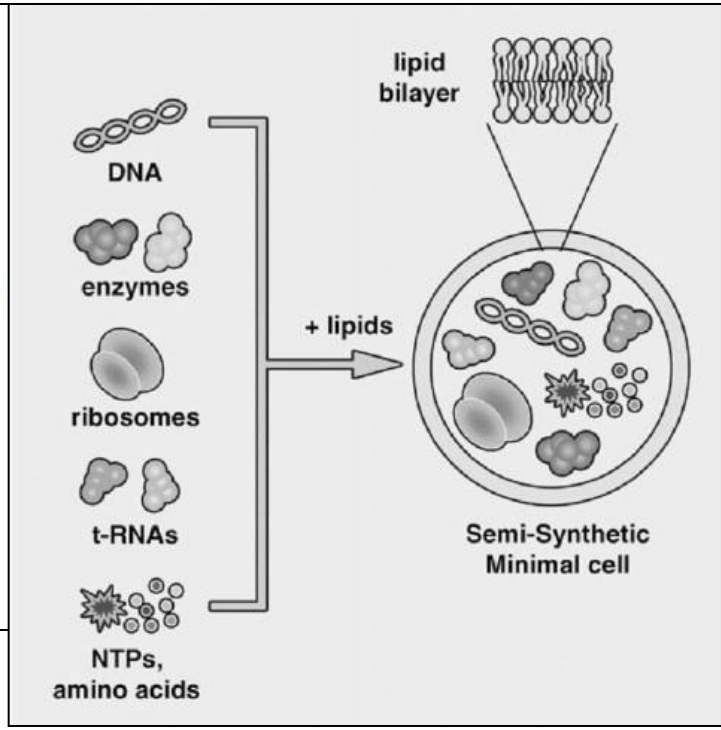


Figure by IGEM 2010

Protocells







Liposome, made from phospholipids, grows and divides.

Virosome

Semi-synthetic cell

Biofaction

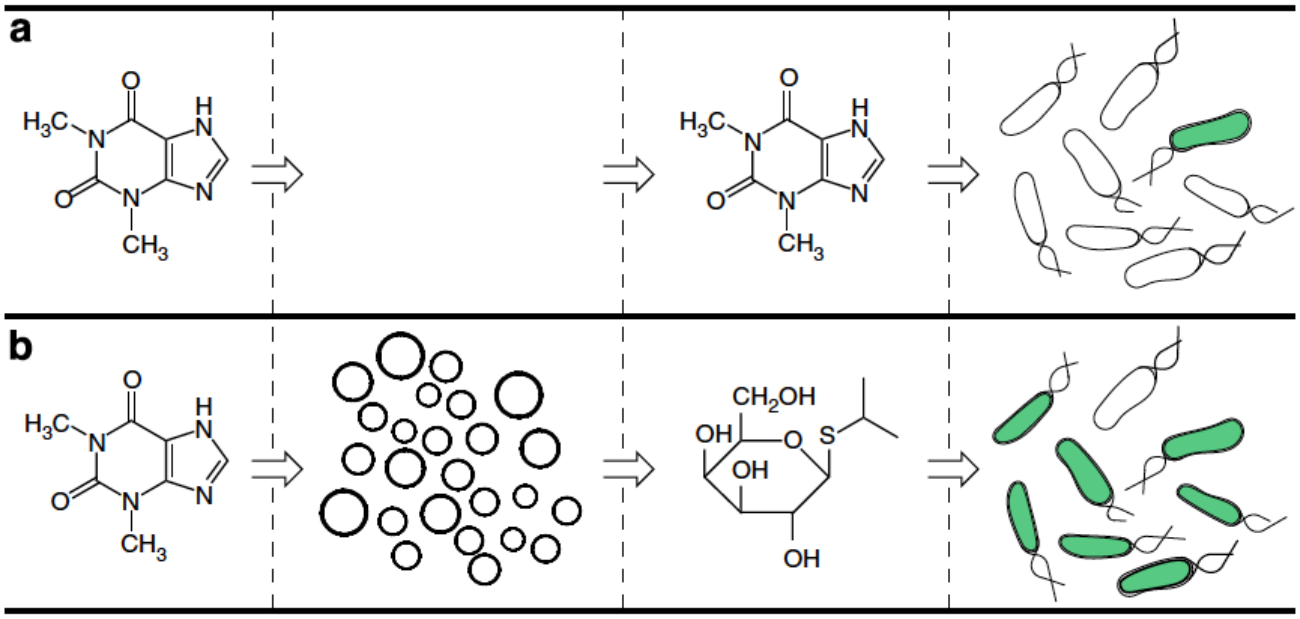
www.biofaction.com
Research and Science Communication Vienna

Szostak et al. 2001, Nature

Zurbriggen 2003. Vaccine

Chiarabelli et al. 2009 Curr Opinion Biotech

„Symbiotic“ protocells

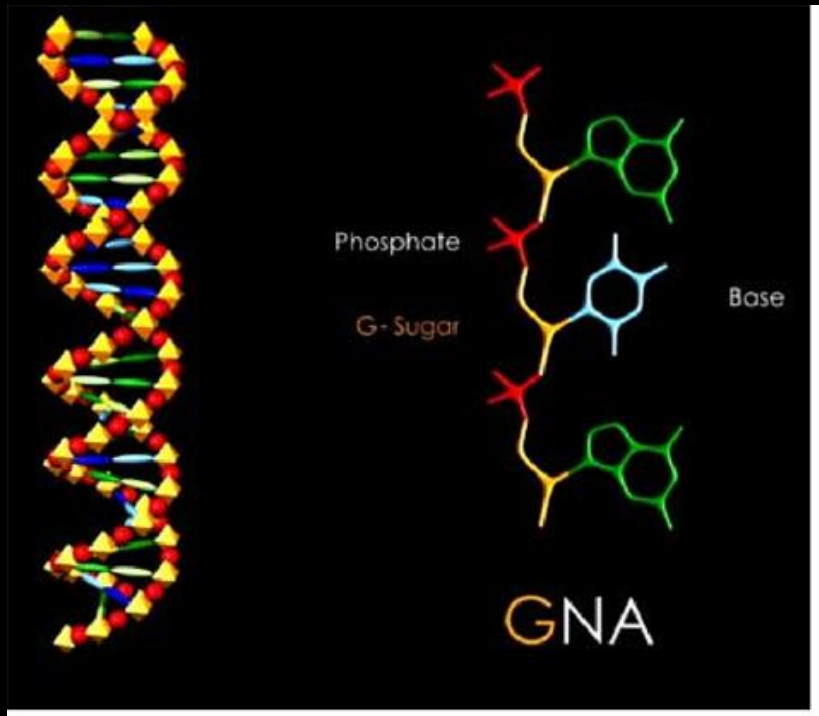


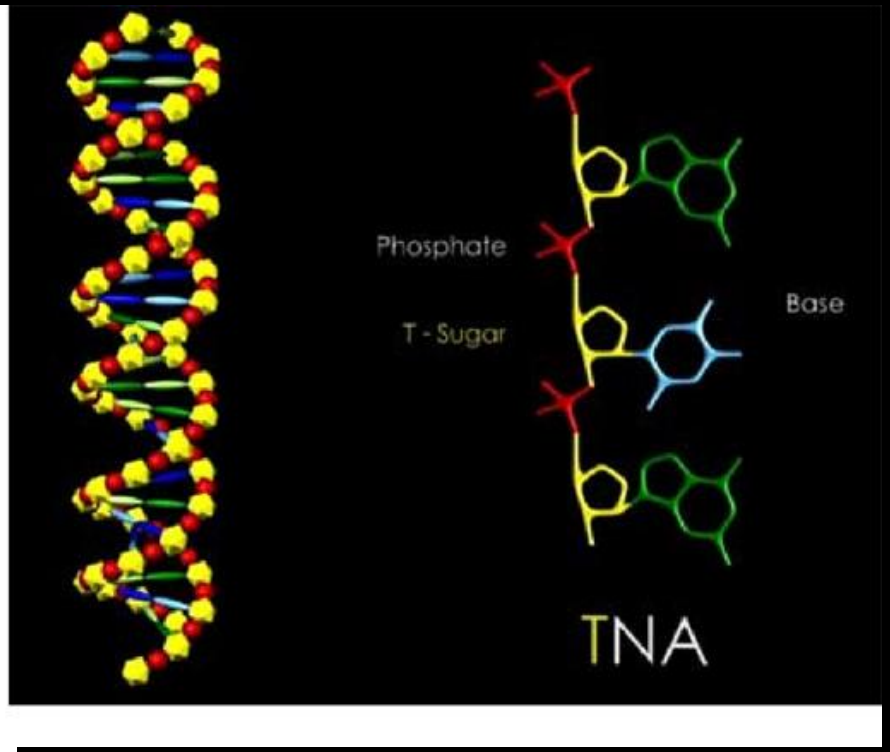
Artificial cells translate chemical signals for E. coli. (Lentini et al 2014)

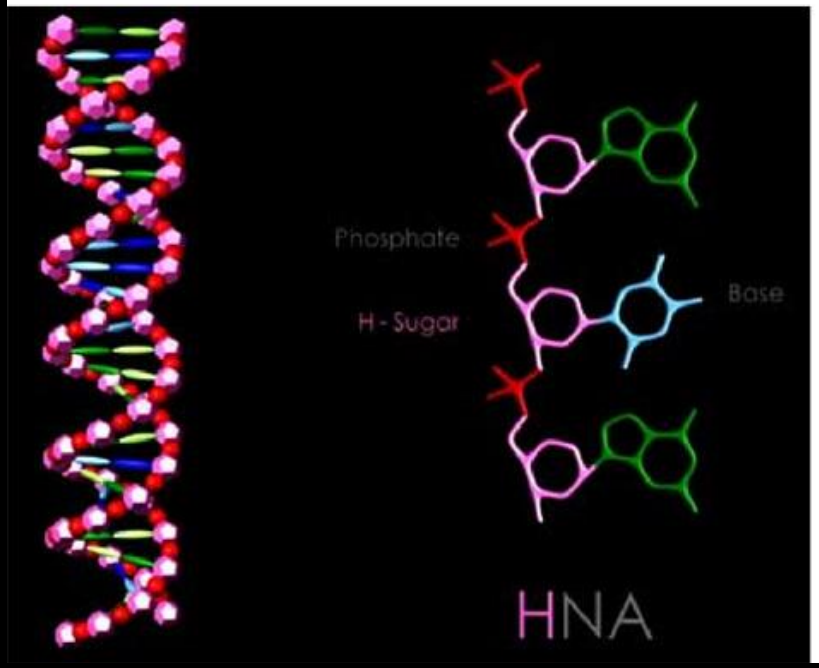
(a) In the absence of artificial cells (circles), E. coli (oblong) cannot sense theophylline.

(b) Artificial cells can be engineered to detect theophylline and in response release IPTG, a chemical signal that induces a response in E. coli.

Xenobiology



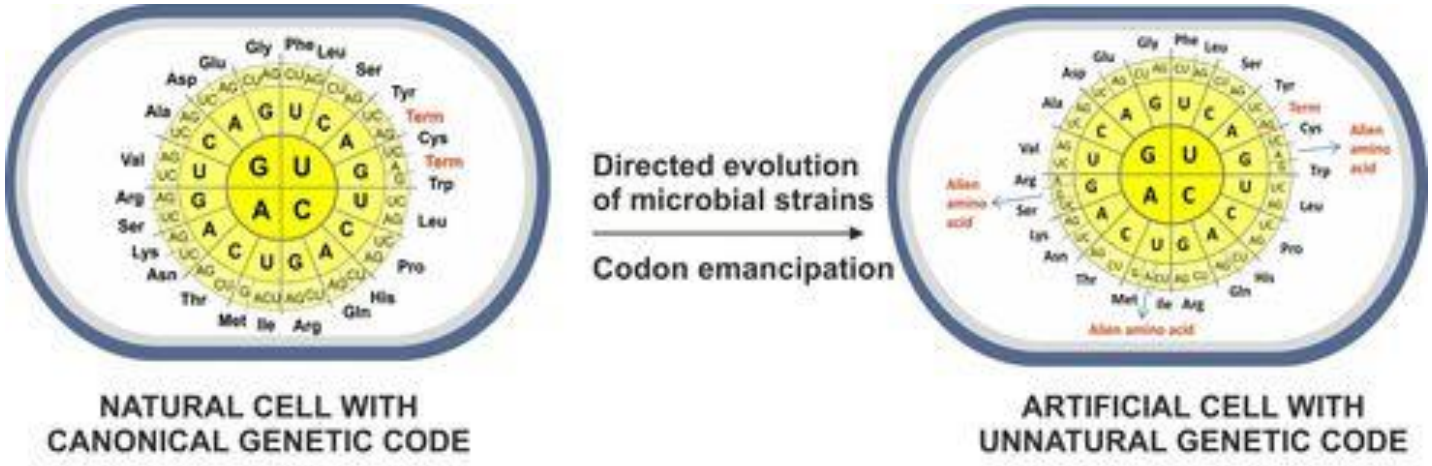




Xeno nucleic acids

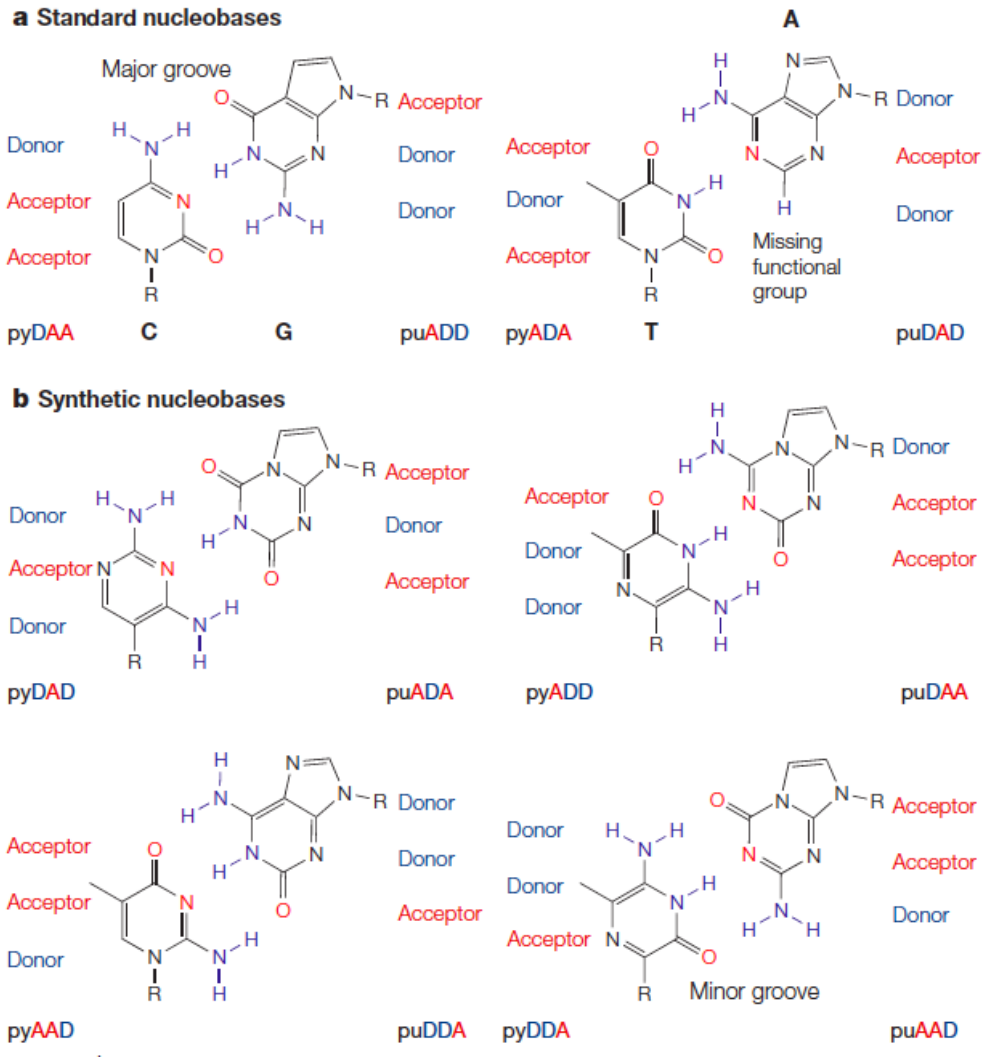
XNA

Code engineering



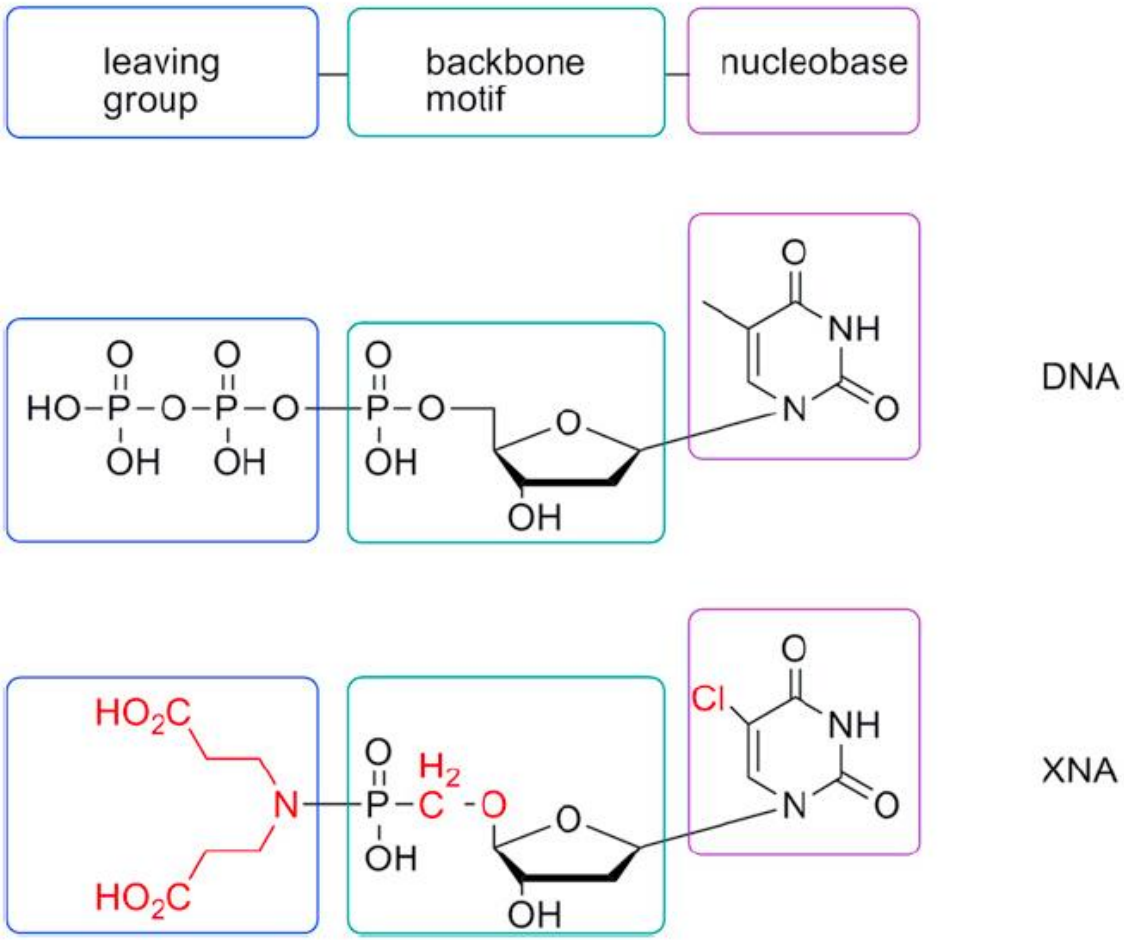
Ned Budisa: http://www.biocat.tu-berlin.de/menue/forschung/synthetische_biologie/

More letters to the genetic alphabet



Benner and Sismour. 2005 Synthetic Biology. Nature

XNA: À la carte



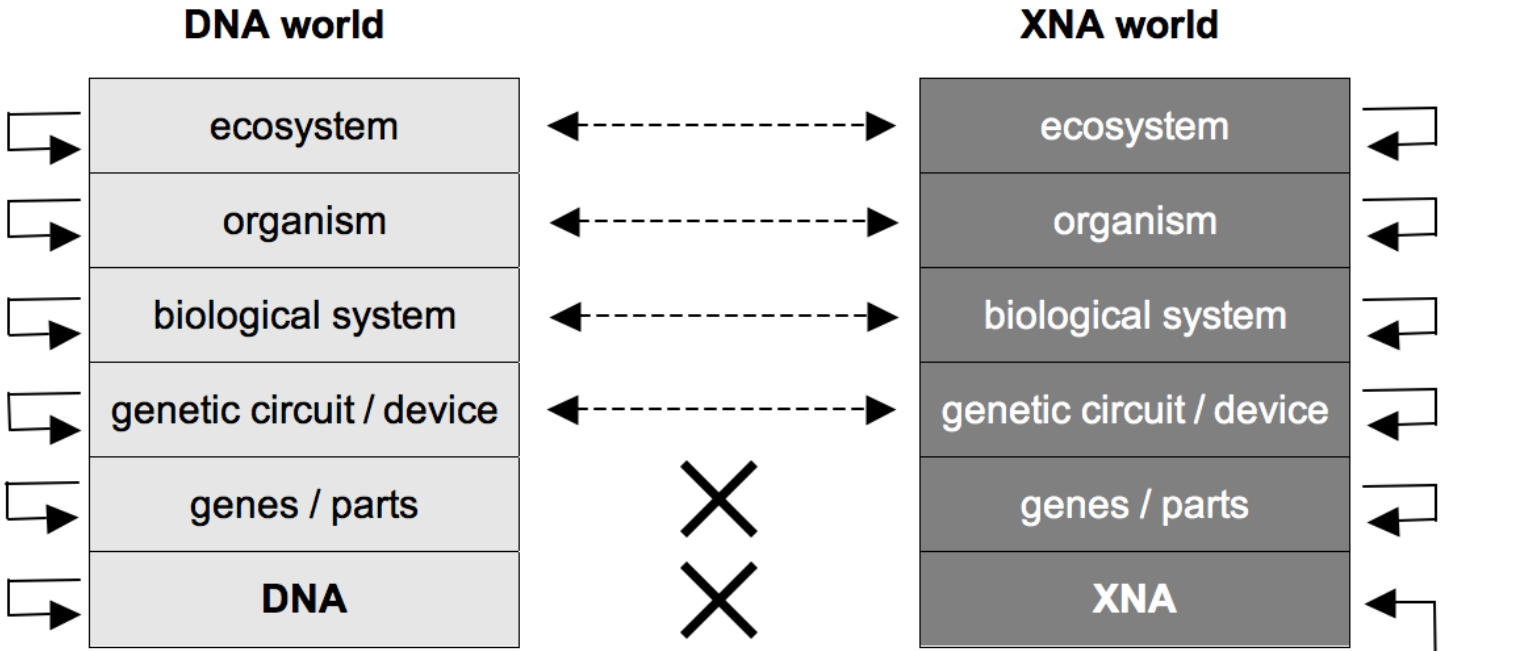
Mi-Yeon Jang et al. 2013. A Synthetic Substrate of DNA Polymerase Deviating from the Bases, Sugar, and Leaving Group of Canonical Deoxynucleoside Triphosphates

Navigating the virtual Biospace

Vitor B. Pinheiro and Philipp Holliger. 2012. The XNA world: progress towards replication and evolution of synthetic genetic polymers

Current Opinion in Chemical Biology

Constructing a genetic firewall



Citizen Science / DIYBio

Question 4

What are the implications for human and animal health and the environment of likely developments in SynBio resulting or not in a genetically modified organism as defined in the Directive 2001/18/EC?

Q4:Genetic part libraries and methods

- More complete, precise and accurate information on the biological function of parts in genetic libraries will improve the effectiveness of risk assessment.
- SynBio library construction and parts characterisation may increase the frequency of use of uncharacterised components, and/or the diversity of biological functions used which requires diligent application of established safety procedures.
- Emergent properties of more extensive genetically engineered systems may present some new challenges in predicting or testing for risks.

Q4: Protocells and artificial cells

- Likely to fall within a regulatory framework covering chemicals rather than within the current GMO regulatory framework.
- Integration of protocells into living organisms and future developments of autonomous protocells warrants the examination of possible routes of exposure and adverse effects.
- The framework for the risk assessment of such cells should draw on, but not necessarily be confined to, the methodology used for GMO risk assessment.

Q4: Xenobiology

- The new variants have to be tested for their risk to human health and the environment
- The xenobiological systems might be engineered to allow for improved biocontainment, i.e. the so-called genetic firewall which aims at avoiding exchange of genetic material through horizontal gene transfer or sexual reproduction between the xenobiological organisms and natural organisms.

DNA synthesis and genome editing

- Genetic modifications in higher animals are now possible within a single generation, by direct genome editing of zygotes.
- Many of the new methods allow multiplexed genetic modifications, which affect a large number of loci at the same time. ...Their risk is not necessarily assessed individually.
- The number of genetic modifications introduced in parallel by large-scale DNA synthesis and/or highly-parallel genome editing increases the distance between the resulting organism and any natural or previously modified organism to which it could be compared to for risk assessment purposes.

Citizen science

- In principle, citizen science (DIYbio) does not pose any new hazard to humans and the environment
- increasing the number of participants that could cause harm, it is important that established safety practices among DIY biologists are maintained
- Verifications by an independent biosafety entity should be encouraged, newcomers trained, etc.

Question 5:
Are existing methodologies appropriate...?

- **Genetic part libraries and methods**: The existing methodologies for risk assessment are applicable and appropriate. However, difficult to accurately assess properties that emerge from interactions of many parts in more complicated systems. Tools to assist in such assessments may be needed.
- **Minimal cells and designer chassis:** It is possible to use existing methodologies because minimal cells do not raise additional concerns compared to the wild type organisms they are derived from.
- **Protocells and artificial cells**: Protocells fall in between chemistry and biology. Therefore, it is crucial to choose the most appropriate combination of methodology for assessing risk.

Question 5:
Are existing methodologies appropriate...?

- **Xenobiology**: Existing methodologies are possible to use. However, it is necessary to create and collect data sets and knowledge about the interaction between xenobiological and natural organisms for risk assessors to apply the established methodologies to xenobiological organisms.
- **DNA synthesis and genome editing**: It is possible to use existing methodologies. The acceleration of the genetic modification process by advances in synthetic genomics and DNA synthesis calls for accelerated procedures for risk assessment, especially where genetic modifications are introduced in a highly parallel manner.
- **Citizen science**: The existing methodologies are appropriate. It is essential that the existing methodologies are applied even outside the traditional institutional settings.

Question 6: If existing methodologies not appropriate ..., how should existing methodologies be adapted and/or completed?

- **Minimal cells and designer chassis**: No change in the existing methodologies is necessary.
- **Protocells and artificial cells**: There is a need to establish new combined methodologies addressing both chemical and biological hazards/risks.
- **Xenobiology**: It is necessary to create and collect data sets and knowledge about the interaction between xenobiological and natural organisms for risk assessment.

Question 6: continued

Genetic Parts:

- Characterise function of biological parts
- Develop computational tools to predict emergent properties and potential failure modes
- Research ways to streamline and standardise methods for submitting genetic modification data and genetic parts information to risk assessors
- Develop guidelines for risk assessors on how to evaluate potential emergent properties
- Research use of GMOs with a proven safety record as acceptable comparators for risk assessment

Question 6: continued

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Question 7: How, when, and to what extent can safety (safety locks) be inherently built into products of SynBio?

- Currently available safety locks (auxotrophy and kill switches) not sufficiently developed for SynBio.
- SynBio might lead to improved types of containment
- Xenobiology promises new bacteria strains with built-in safety locks,
  - genetically recoded organisms with reassigned codon triplets, i.e. altered genetic code,
  - targeted replacement of DNA, base pairs and amino acids throughout the whole organism, with equivalent biochemistry (e.g. XNAs) resulting in constructs with the potential to be significantly different from natural organisms, which would severely impede horizontal gene flow or sexual reproduction with natural organisms.

Question 7: How, when, and to what extent can safety (safety locks) be inherently built into products of SynBio?

- In protocells, the priority will be to address the integration of protocells with natural organisms.
- Ephemeral nature of currently available protocells allows for a time-limited application of new metabolic features, which might be relevant wherever safety and long-term concerns e.g. evolutionary uncertainties, are identified.