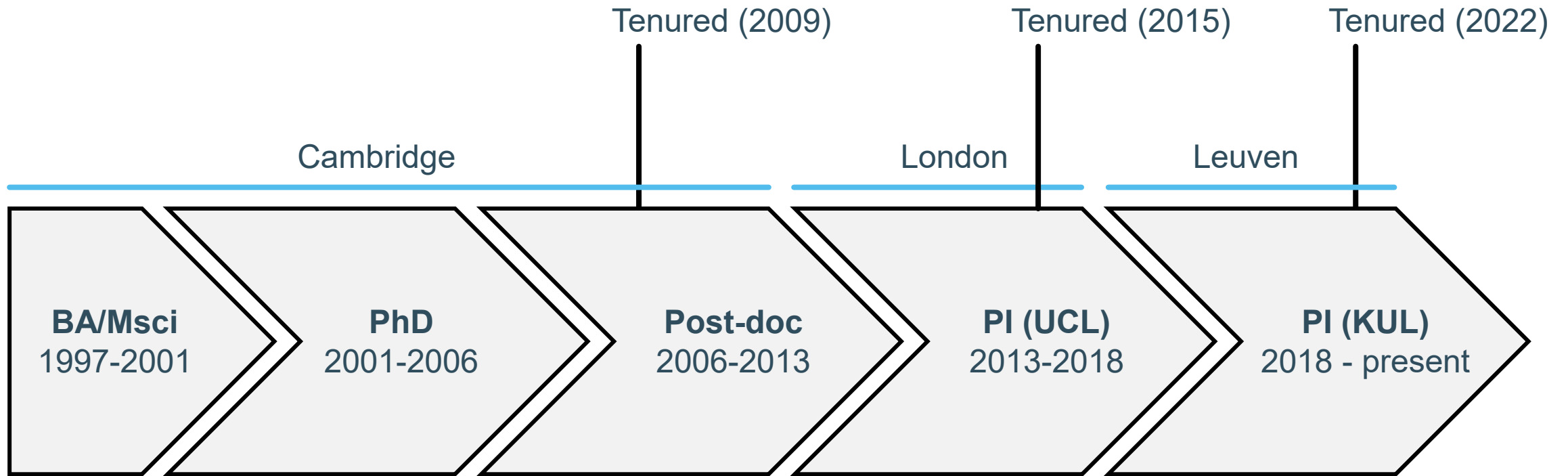


Reinventing biology one protein at a time

10 years a PI



On the surface, typical academic career



Coffees per day:

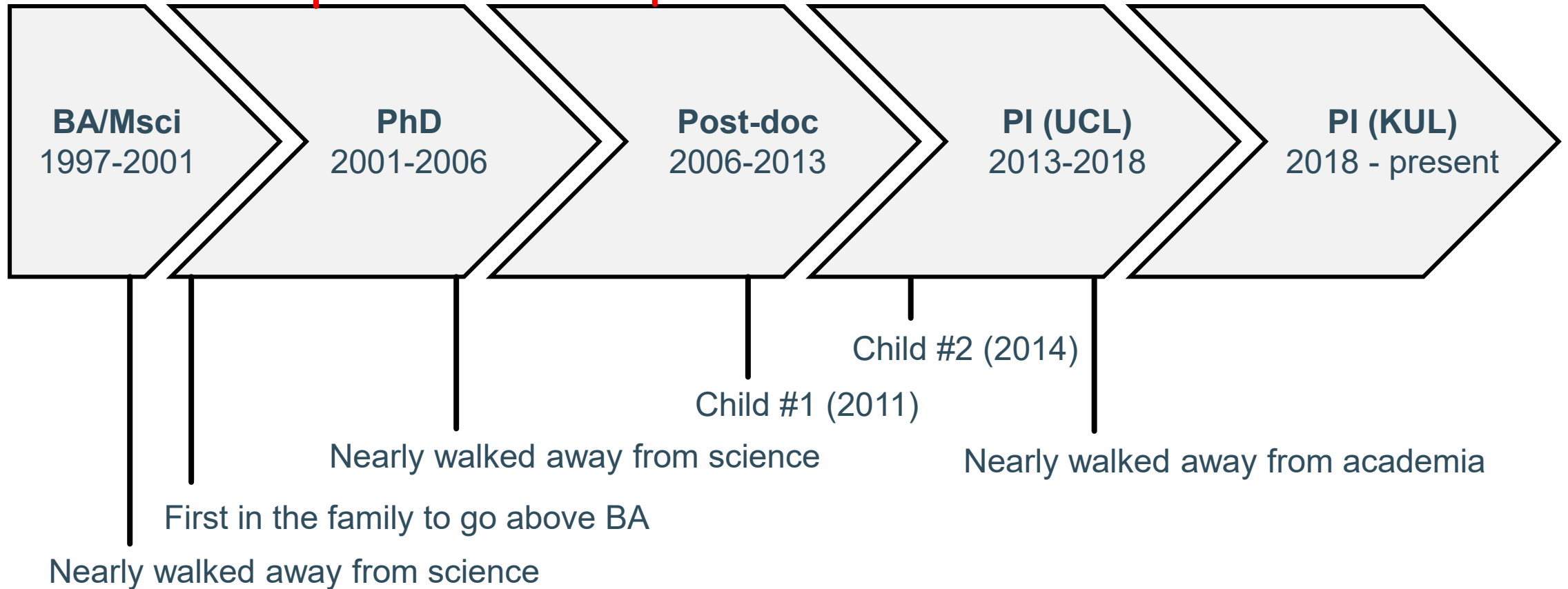
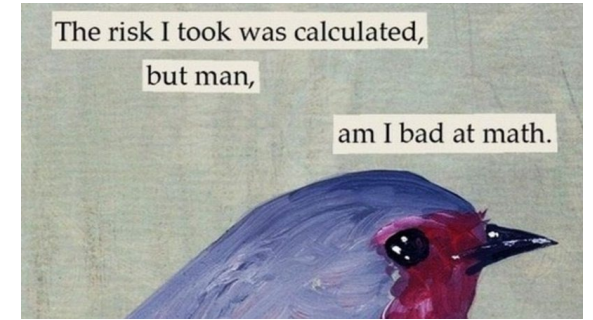


On the surface, typical academic career

Outdated methodology
Unfashionable field
2/3 publications
Back-stabbed by "collaborators"

Change of field
High-risk high-gain project
Too far from the field community

Learn by doing



Starting point – Developing Synthetic Genetic Materials

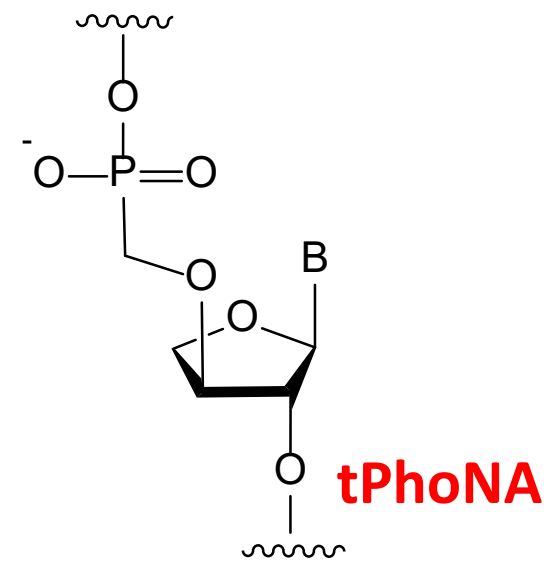
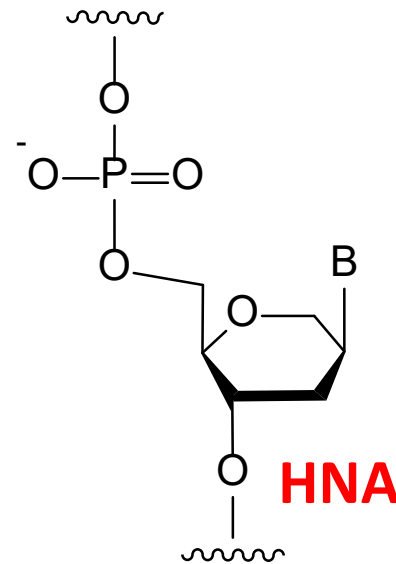
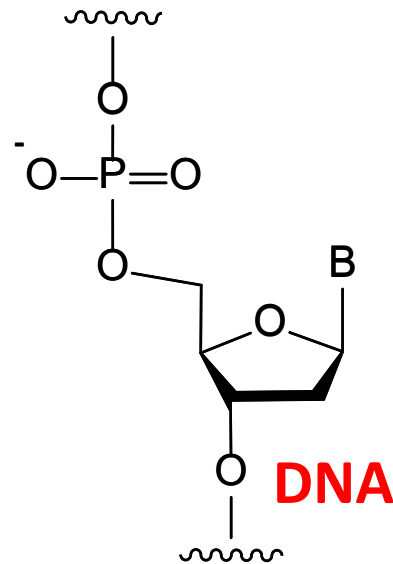


Proteins



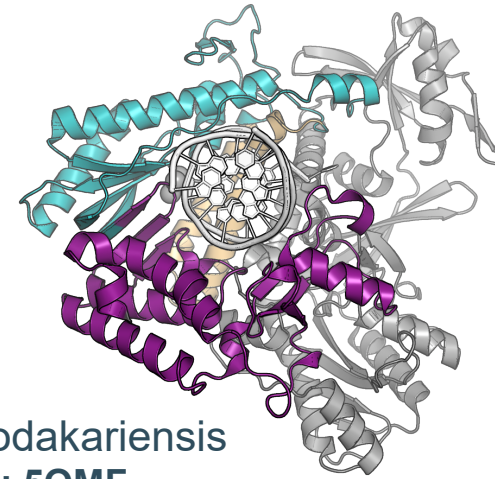
Metabolism

- DNA and RNA are the only genetic polymers in biology
- **Can there be other genetic polymers?**

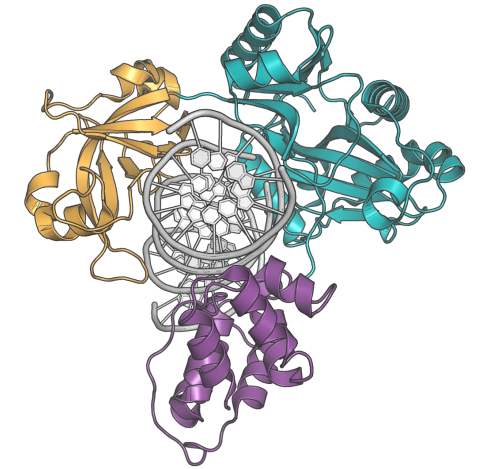


Challenges for XNA engineering

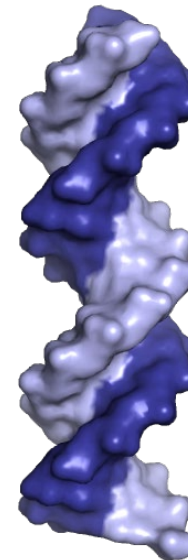
- Difference in XNA duplex structure
 - Difference in major and minor grooves
 - Helix width
- Few platforms for XNA nucleic acid processing enzyme engineering
- Mutational data in nucleic acid processing enzymes only available for DNA polymerases



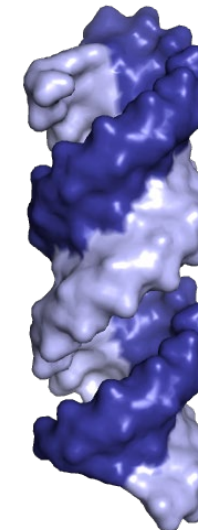
T. kodakariensis
PDB: 5OMF



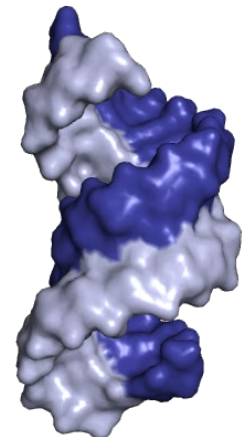
T4 bacteriophage
PDB: 6TD1



DNA



RNA



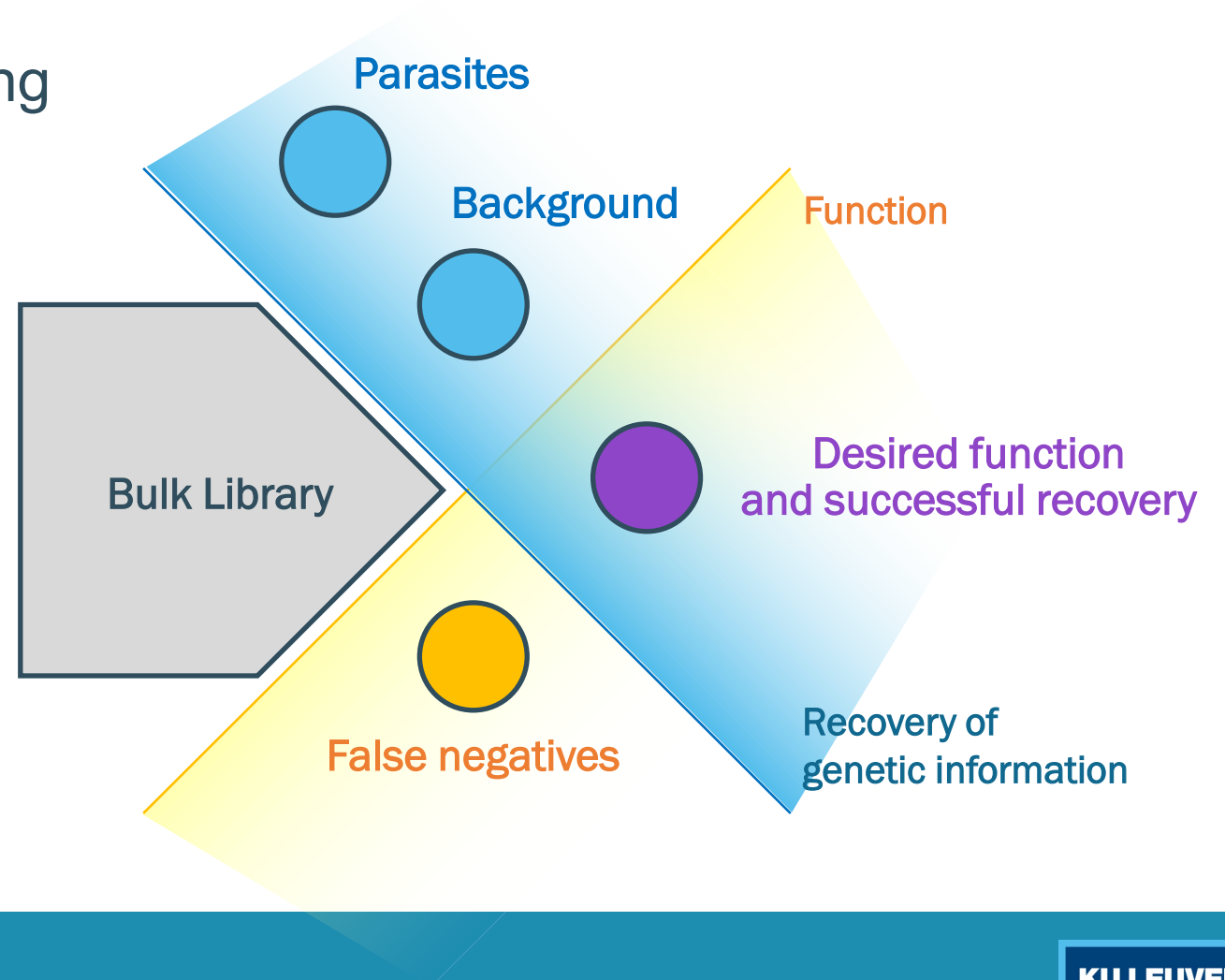
HNA

High-throughput directed evolution

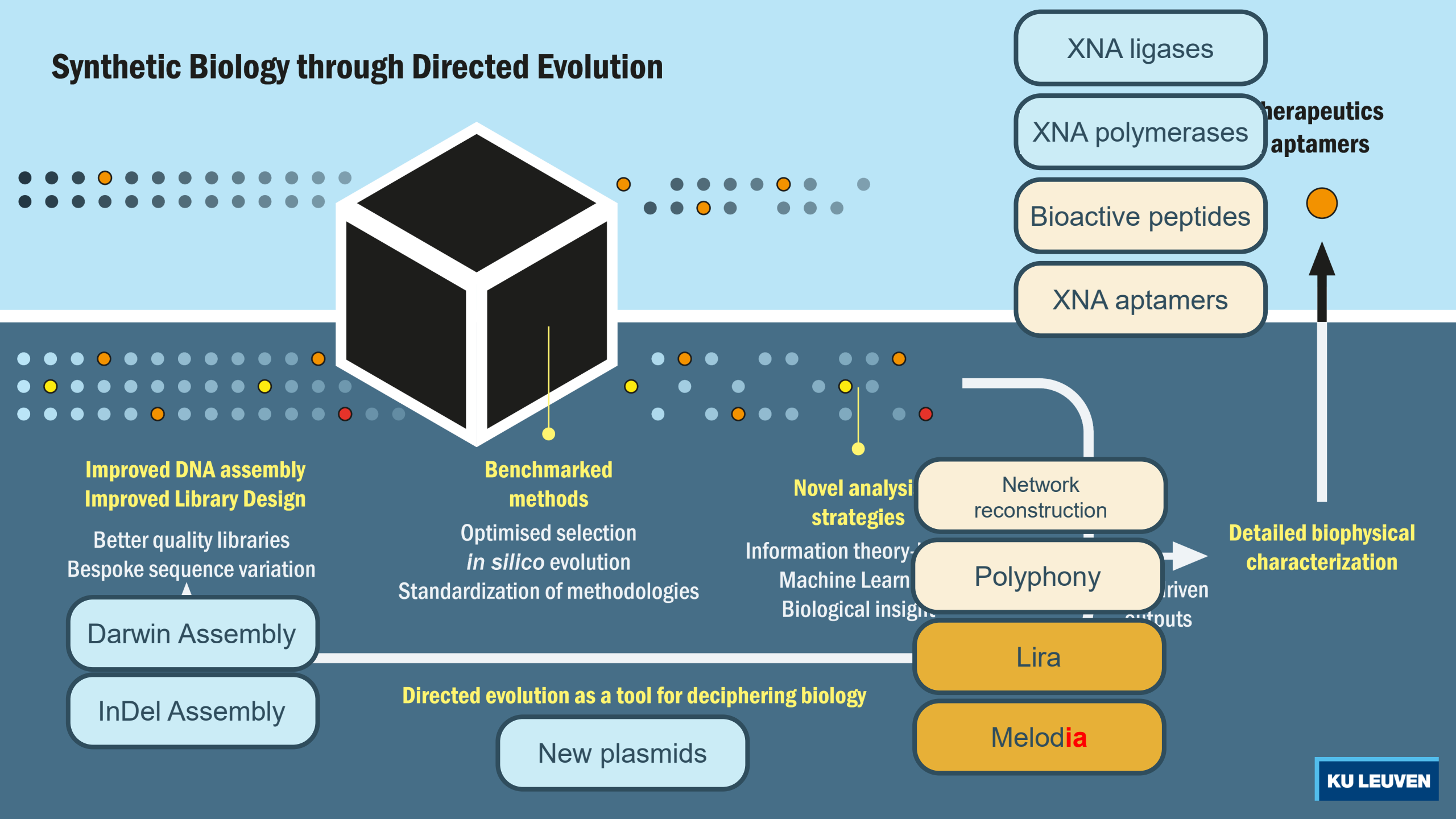
- Reminiscent of Darwinian evolution
- Cycles of diversification and purifying selection

“Evolution is cleverer than you are.”

Leslie Orgel



Synthetic Biology through Directed Evolution



**Improved DNA assembly
Improved Library Design**

Better quality libraries
Bespoke sequence variation

Darwin Assembly

InDel Assembly

**Benchmarked
methods**

Optimised selection
in silico evolution
Standardization of methodologies

**Novel analysis
strategies**

Information theory
Machine Learning
Biological insights

Network
reconstruction

Polyphony

driven
outputs

Lira

Melodia

Directed evolution as a tool for deciphering biology

New plasmids

XNA ligases

XNA polymerases

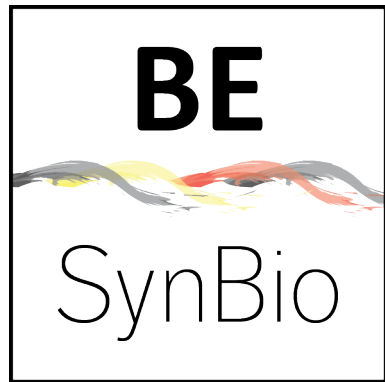
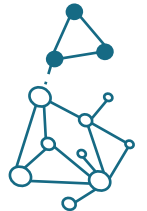
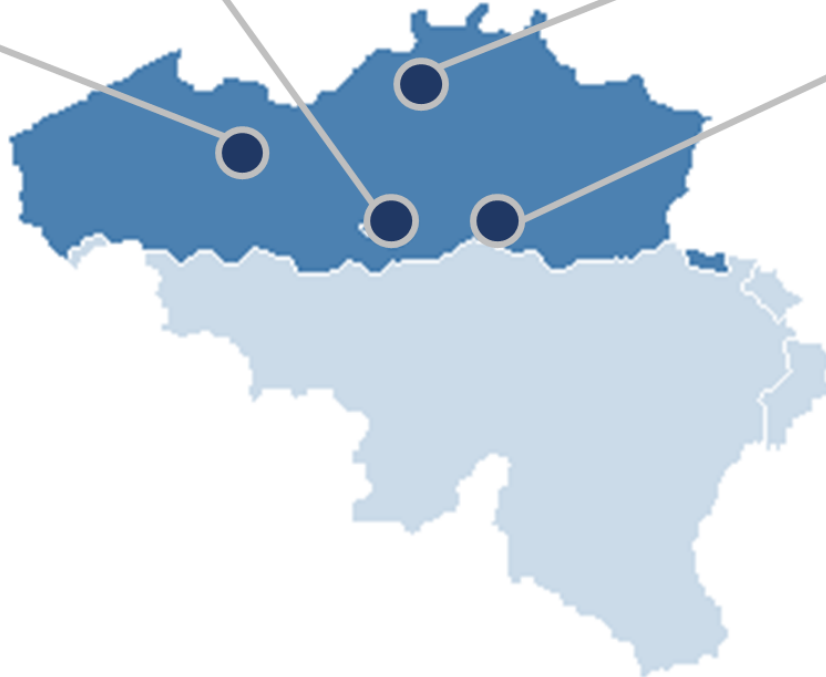
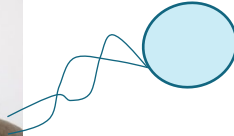
Therapeutics
aptamers

Bioactive peptides

XNA aptamers

**Detailed biophysical
characterization**

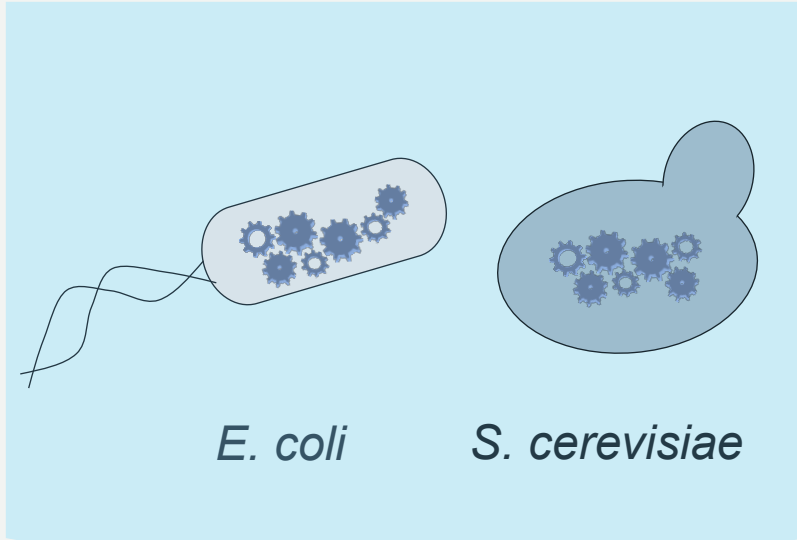
The POSSIBL consortium



POSSIBL tackles the “Grand Challenges” of Synthetic Microbiology

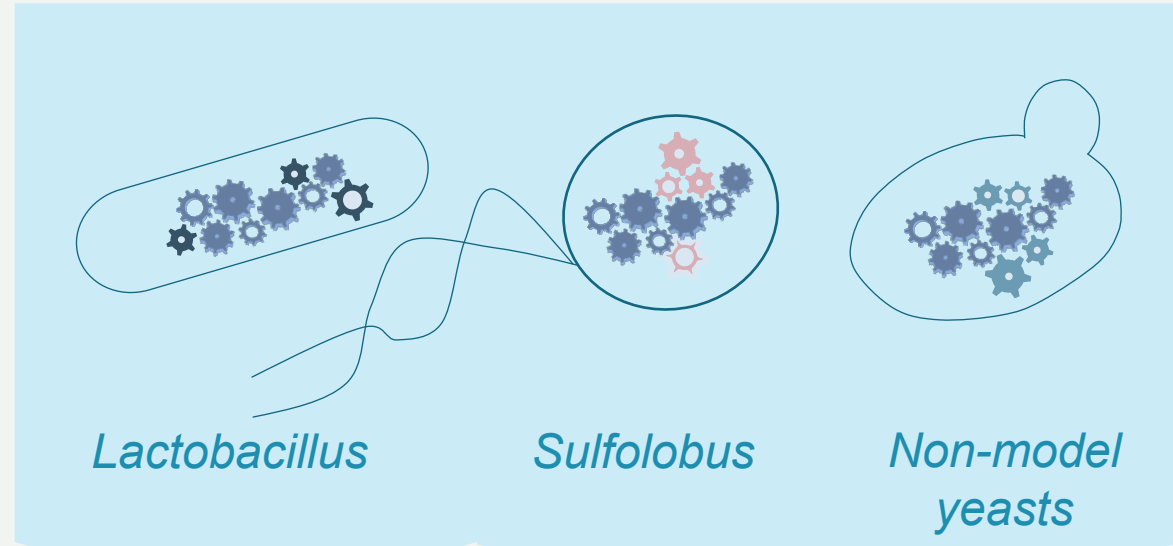
“Ethics by design” for SynBio

Model microorganisms



Sandbox
Exploratory production


Non-model microorganisms



Biomedical applications

Industrial Biotechnology applications

 Universal genetic circuits

 Highly specific & tailored genetic circuits

Acknowledgements



- Mentors and advisors
- Past and present PhD students
- Past and present Post-docs

