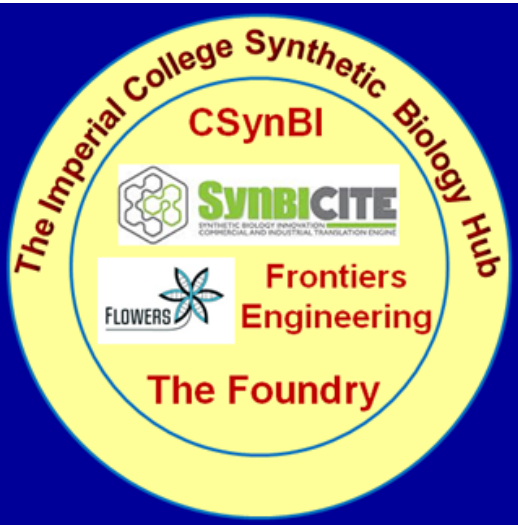
Imperial College London



Synthetic Biology Applied in the Bio Health Field

Barcelona 15th March 2016

Professor Richard I Kitney

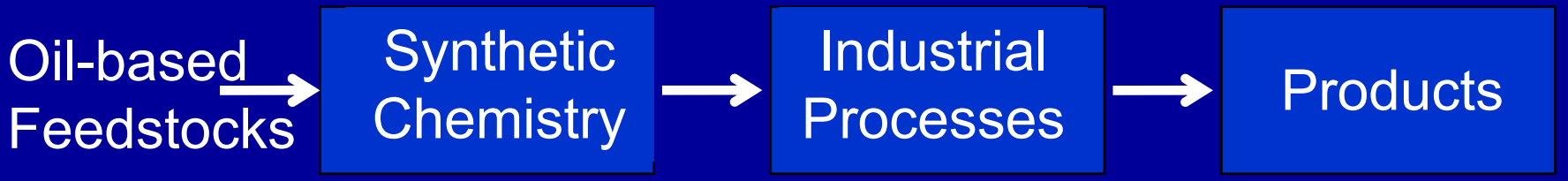
Co-Director and Co-Founder of The EPSRC National Centre for Synthetic Biology and Innovation (CSynBI) and the UK National Industrial Translation Centre for Synthetic Biology (SynBiCITE)

http://www.imperial.ac.uk/people/r.kitney

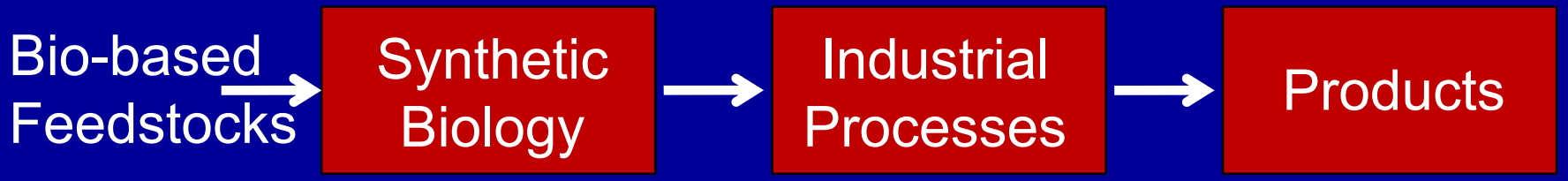
Background

Moving from Oil-based Feedstocks to Bio-based Feedstocks

20th Century

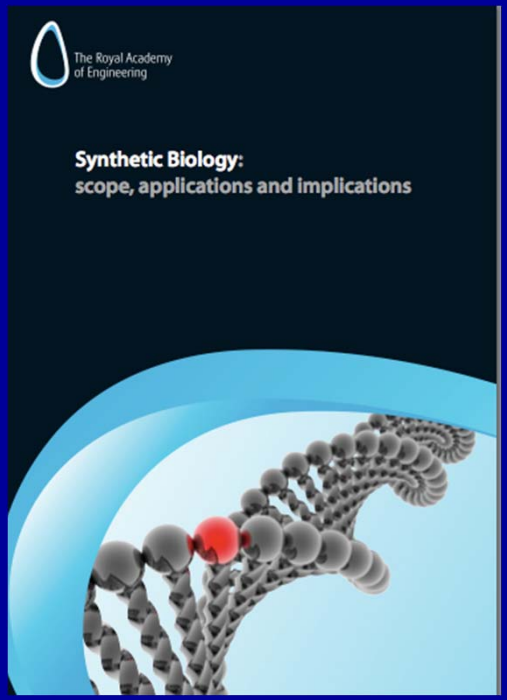


21st Century



The Engineering of Biology

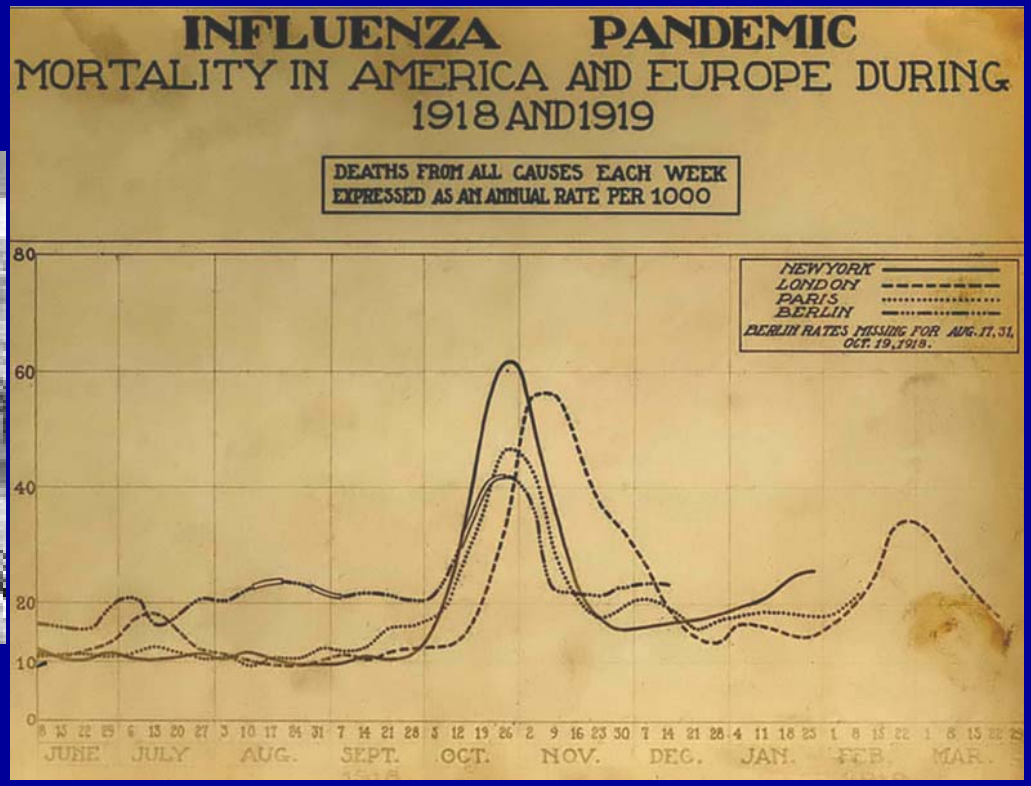
"Synthetic biology aims to design and engineer biologically based parts, novel devices and systems as well as redesigning existing, natural biological systems." May 2009



Greenpeace UK - At its core, synthetic biology is engineering applied to biology to deliberately (re)design and construct biological systems.

The Influenza Pandemic of 1918

The influenza pandemic of 1918-1919 killed more people than the Great War, know (WWI), at somewhere between 20 and 40 million people.



Flu

- 400,000 general practitioner consultations, 11,000 elderly respiratory hospital admissions - costing the UK health service over €30 million every winter.
- In England, during flu epidemics it is estimated that in excess of 6 million working days are lost

The Telegraph

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Flu vaccine: Ministers may have known of dangerous new strain last March

The World Health Organisation, who 'work closely' with the Government, knew last March that a dangerous new strain of flu had emerged

The Telegraph

Like 2,127,450

The new flu strain was not included in the vaccine even though public health officials were aware in March that it was causing problems in Australia

Currently it takes about 9 months to produce 10 million doses of a flu vaccine

What if it could be done in a month?

It can, using synthetic biology techniques

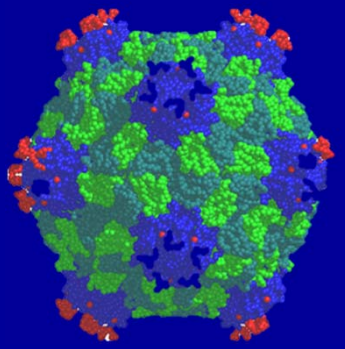
John Innes Centre

Professor George Lomonossoff

medicago

Rapidly multiplying a little known plant virus (cowpea mosaic virus, CPMV) in greenhouse grown plants is the solution to flu vaccine production

The technology uses the machinery of a modified CPMV to produce a non-infective viral shell called a virus like particle (VLP) and genetic information from the humanvirus, in this case influenza, to decorated the shell with influenza surface proteins



The VLPs can be used as a vaccine that can stimulate the human immune system to make antibodies.

Synthetic Biology

Why is it important?

WORLD ECONOMIC FORUM

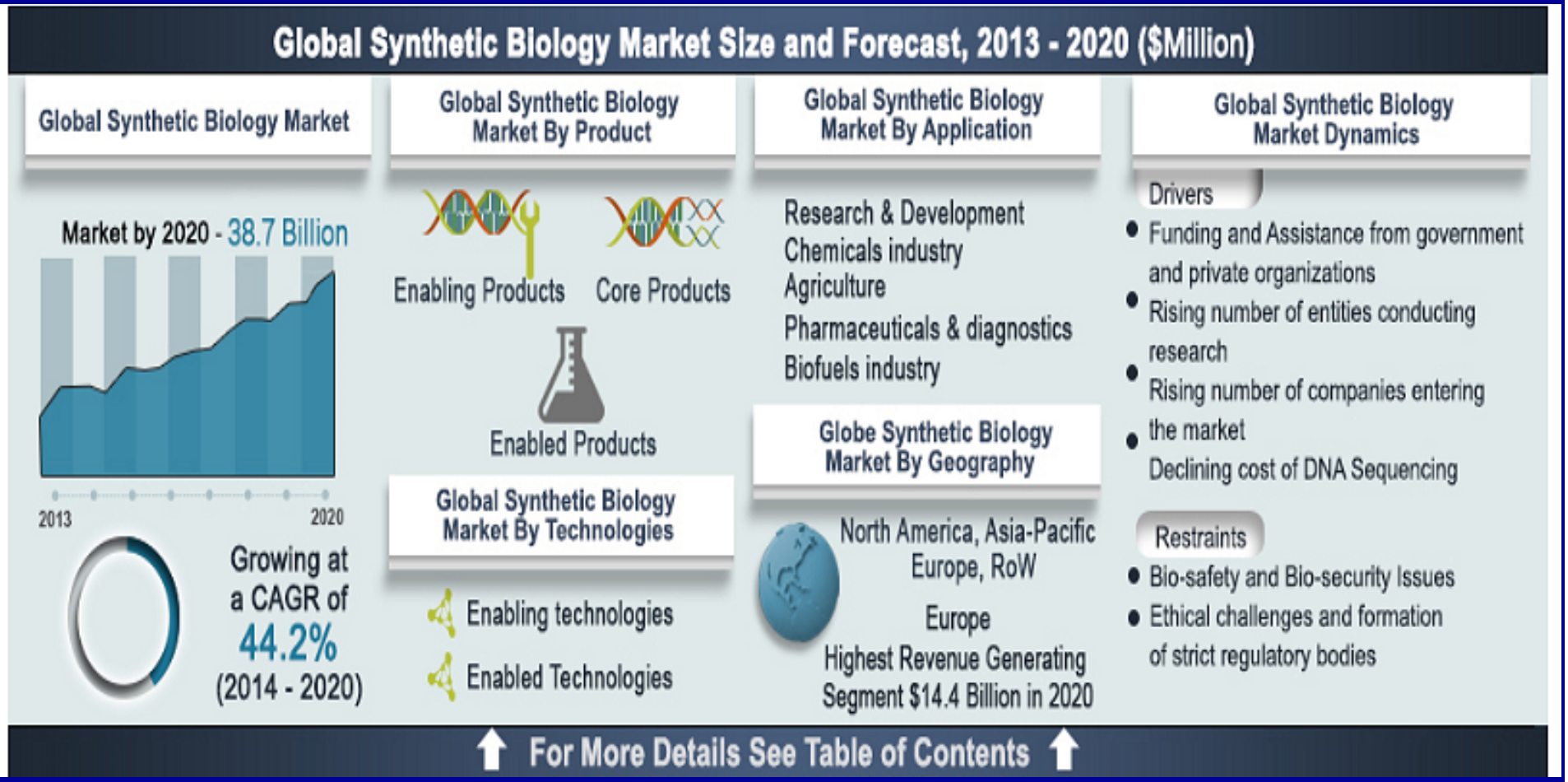
COMMITTED TO IMPROVING THE STATE OF THE WORLD

The top 10 emerging technologies for 2012

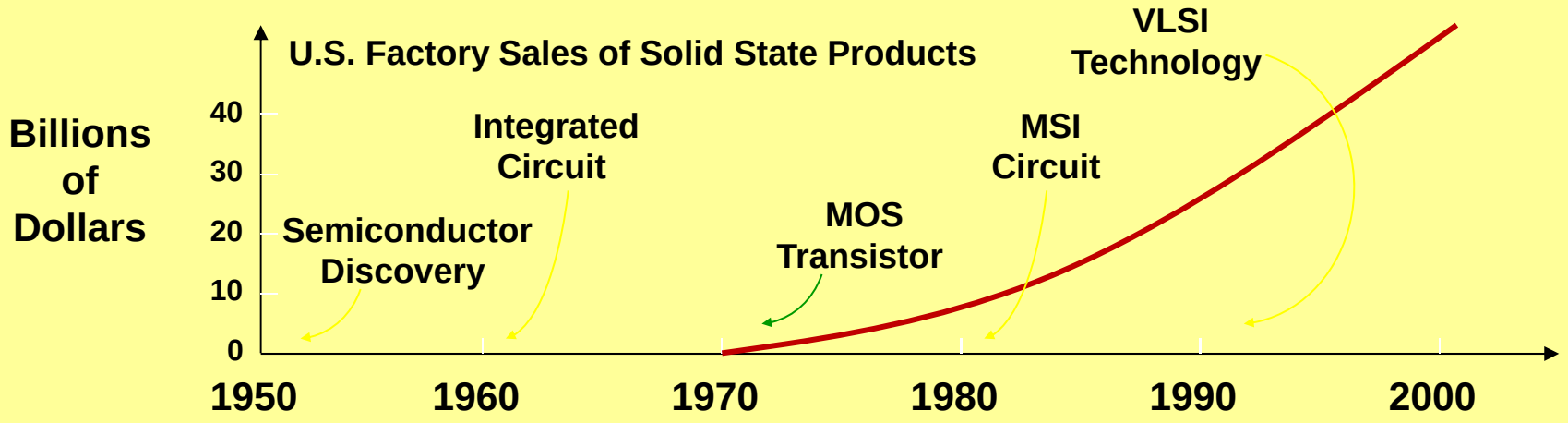
2. Synthetic Biology and Metabolic Engineering

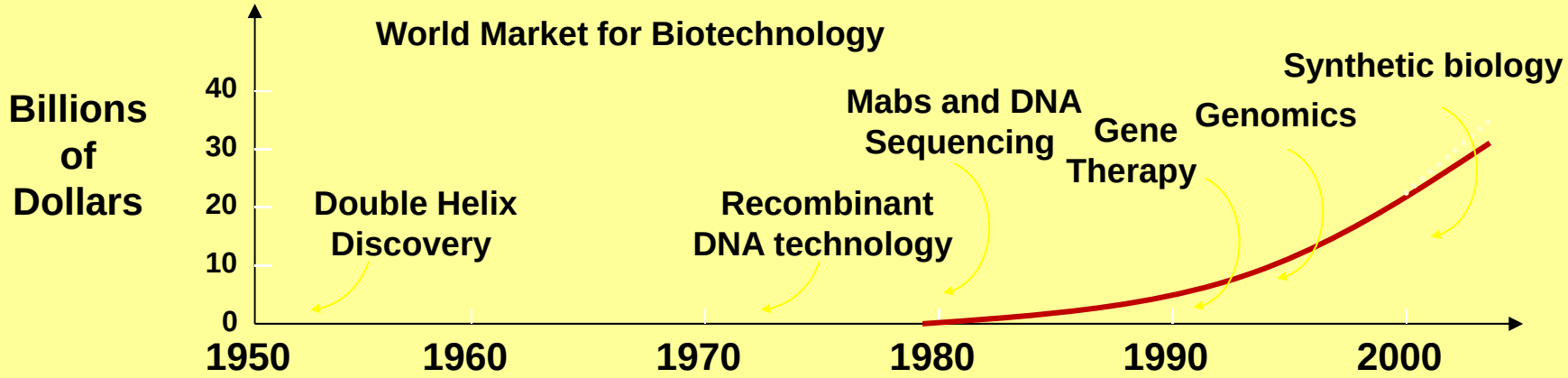
In 2009 the global market size for synthetic biology was estimated to be around $5.7b. In 2015 it had grown to $20b and by 2020 to $37.8, i.e. 44.2% CAGR (2014-2020).

https://www.alliedmarketresearch.com/synthetic-biology-market

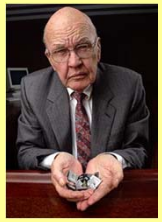


Allied Market Research.com. Arlington, TX
https://www.alliedmarketresearch.com/synthetic-biology-market-2015



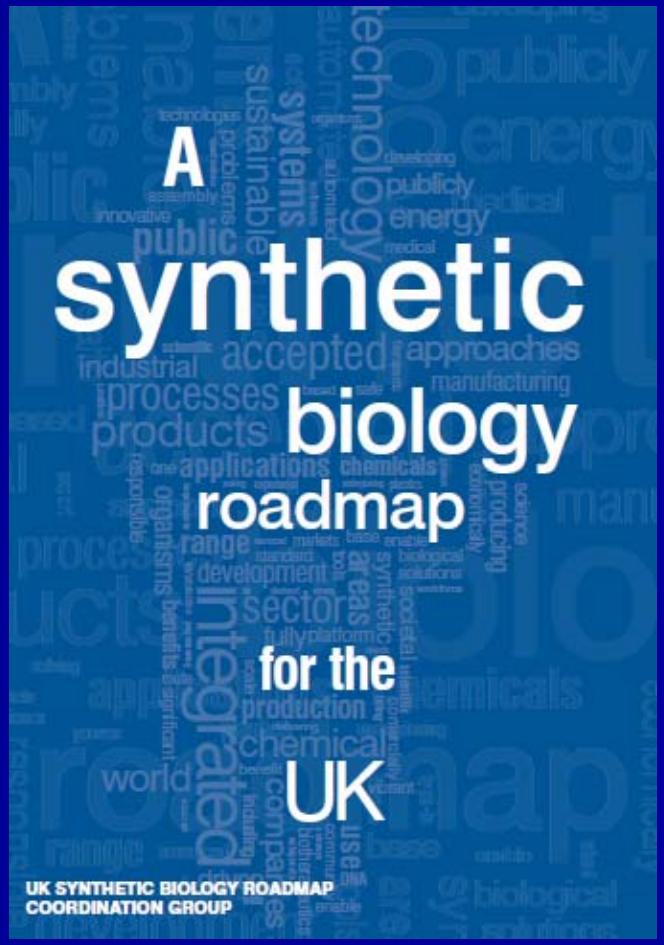


Prof. John Bardeen (UIUC)
Inventor of transistor
Nobel prize, 1956, 1972



Jack Kilby (BS, UIUC, 1947)
Inventor of integrated circuit
Nobel prize, 2000

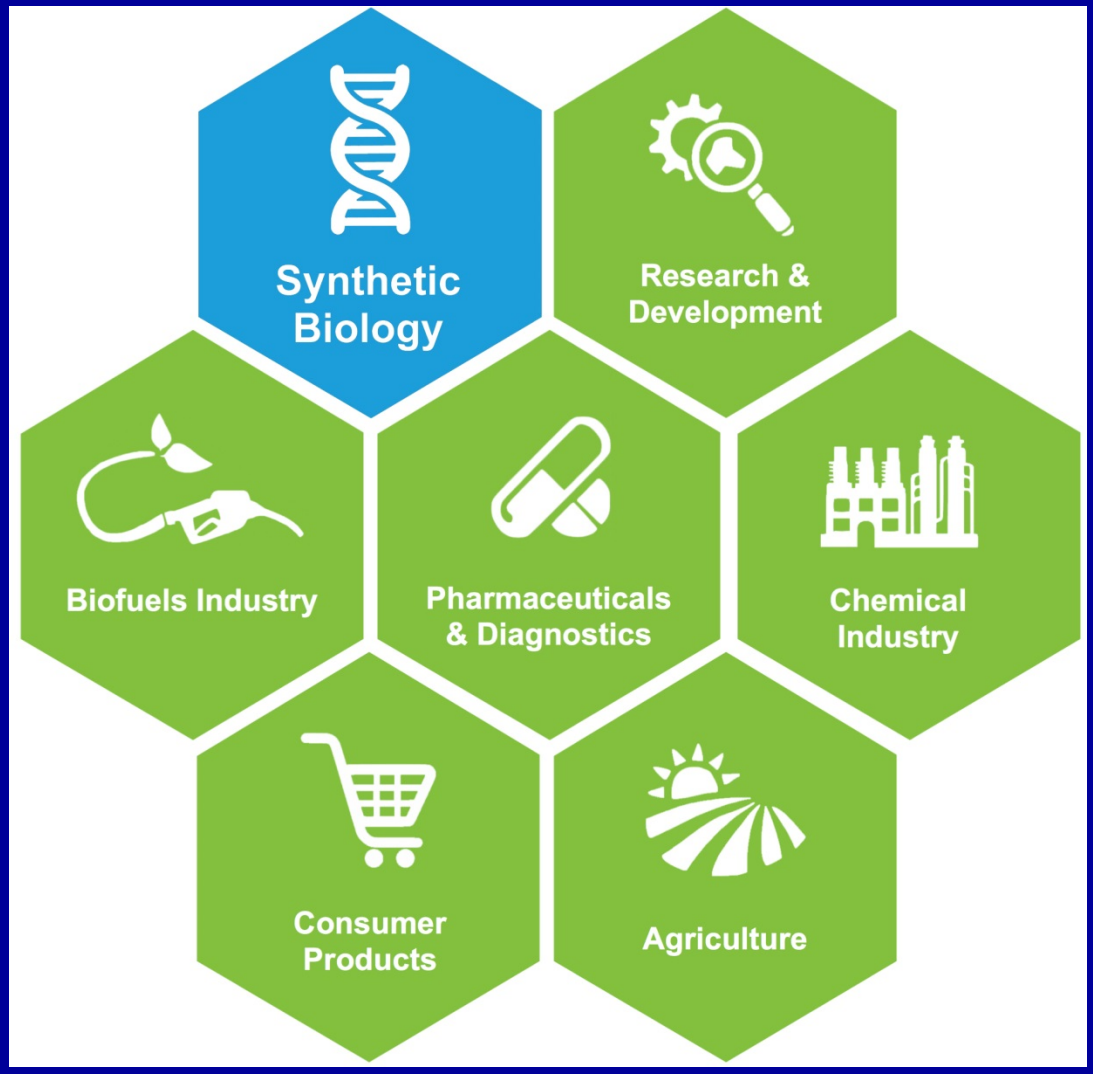
Sources bcc, OECD, US Gov



July 2012

February 2016

Engineering biology to make useful stuff



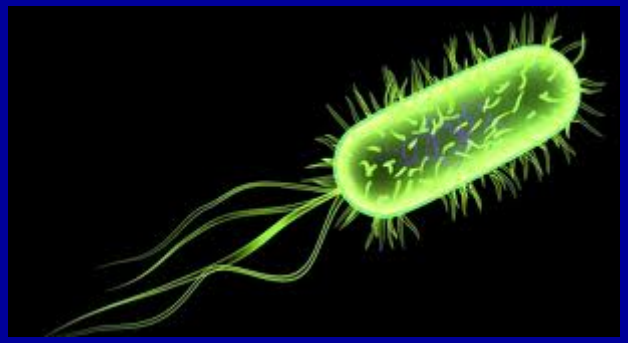
Synthetic Biology

Why is it different?

So what's new about synthetic biology?

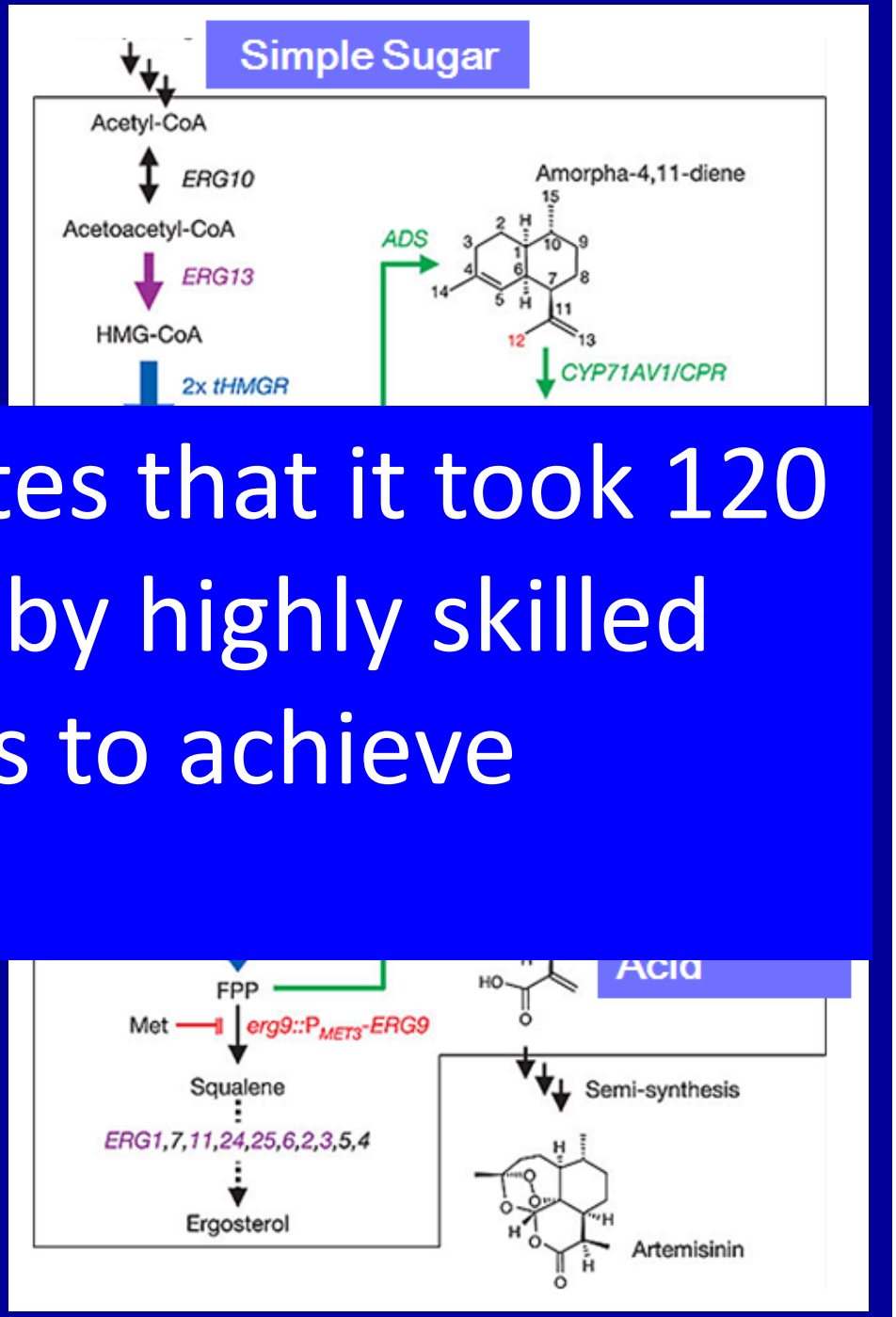
- It provides a framework for the systematic design of biological devices, systems and cells
- The application of engineering principles to biology (e.g. modularity, standardisation and characterisation)
- The integration of molecular biology, engineering and computational science - driven by fast DNA sequencing and synthesis

The Engineering of Biology



Malaria

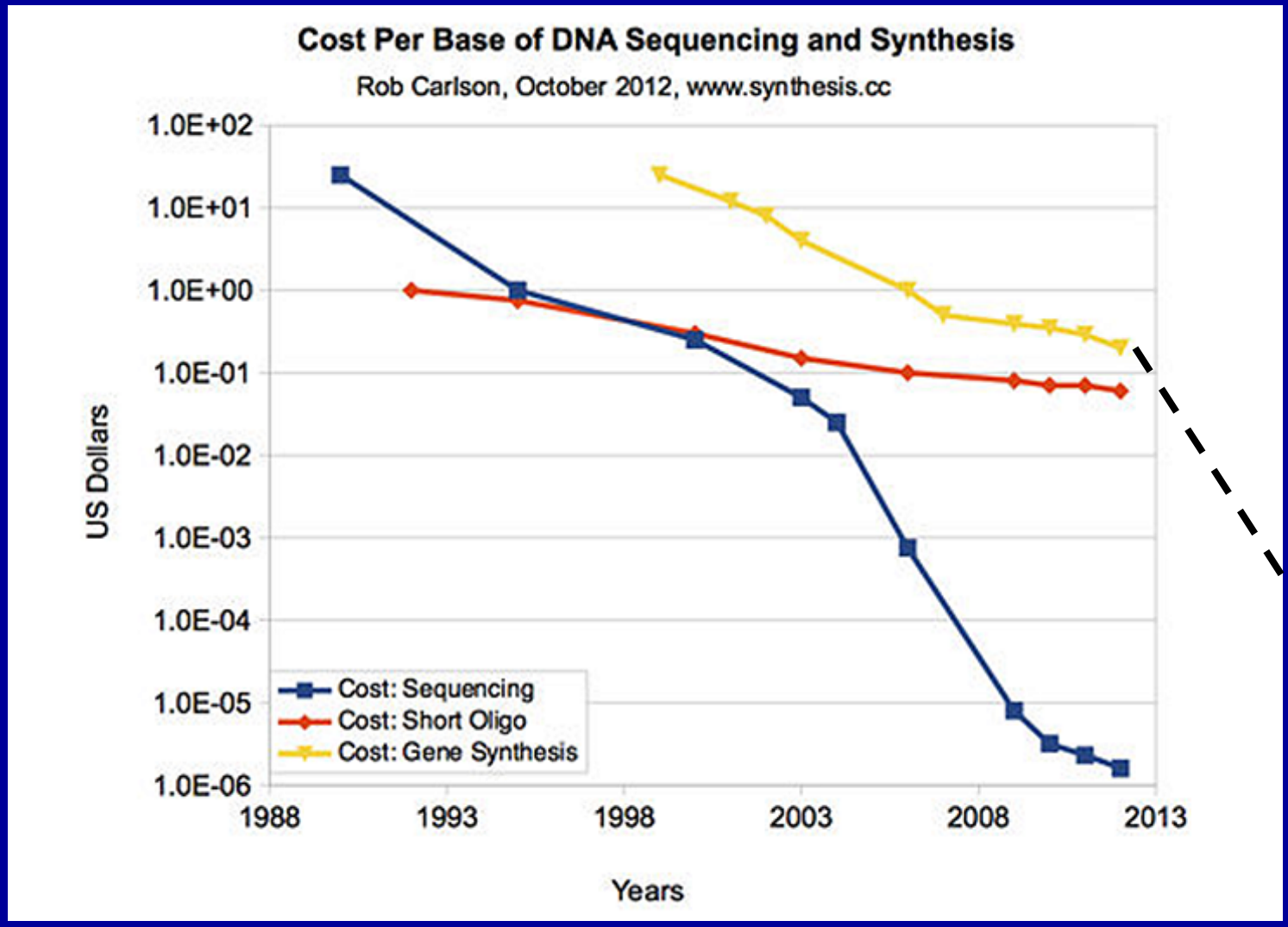
The Anti-malarial Drug Artemesinin



Jay Keasling estimates that it took 120 man years of effort by highly skilled metabolic engineers to achieve Artemesinin

Wormwood)

Keasling et al. Nature **440**, 940-943 (13 April 2006)



GENEART
THE GENE OF YOUR CHOICE

BIOMATIK
Life Science Products and Services

IDT

eurofins
mwg|operon

ORIGENE
Your Gene Company

DNA 2.0

GenScript
The Biology CRO

Systematic Design

Modularisation

Standardisation

Characterisation

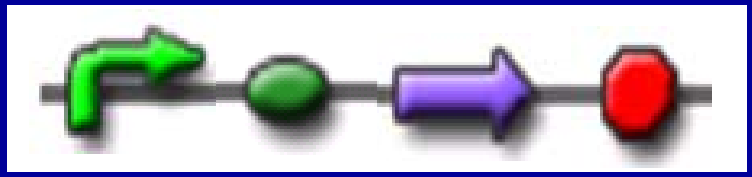
Controlling complexity

Responsible Innovation (RRI)

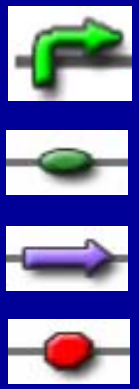
Basic Components

BioPart

GCATGTAAGCA GTTATAATGCGT TTATAATGCGAT



Typical gene transcription module



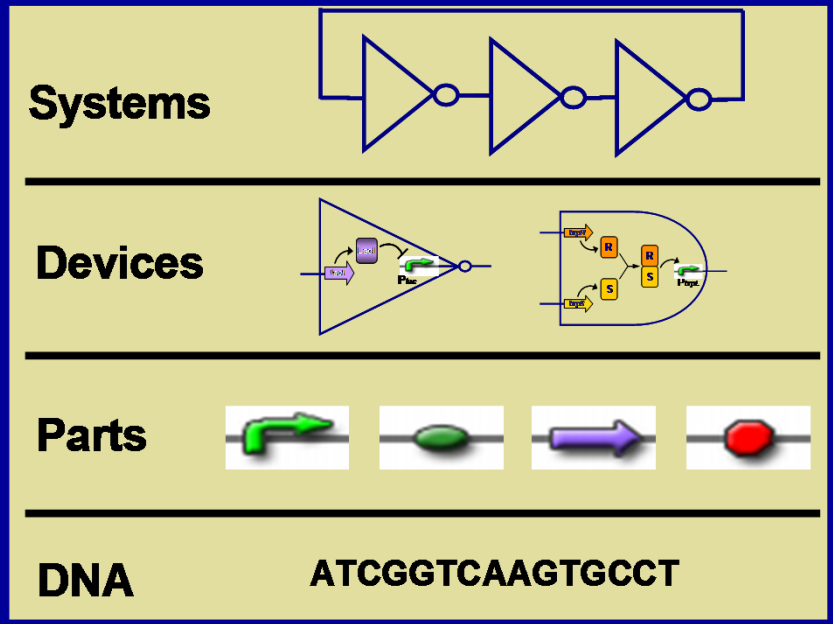
Promoter

Ribosome binding site

Protein coding sequence

Terminator

A hierarchy for synthetic biology

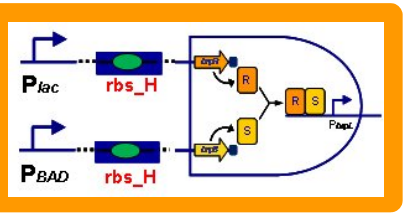


The Synthetic Biology Design Cycle

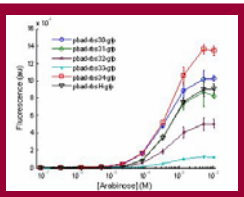
Human Factors (RRI)

Specifications

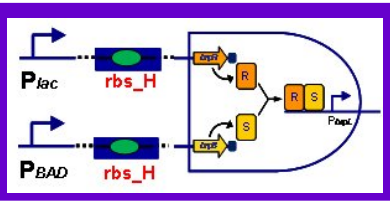
Design



Model

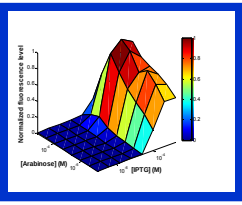


Build



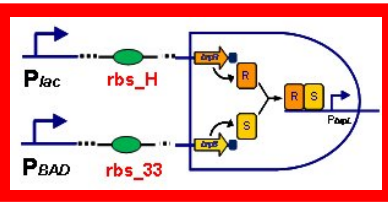
Parts + Assembly

Test/Validate



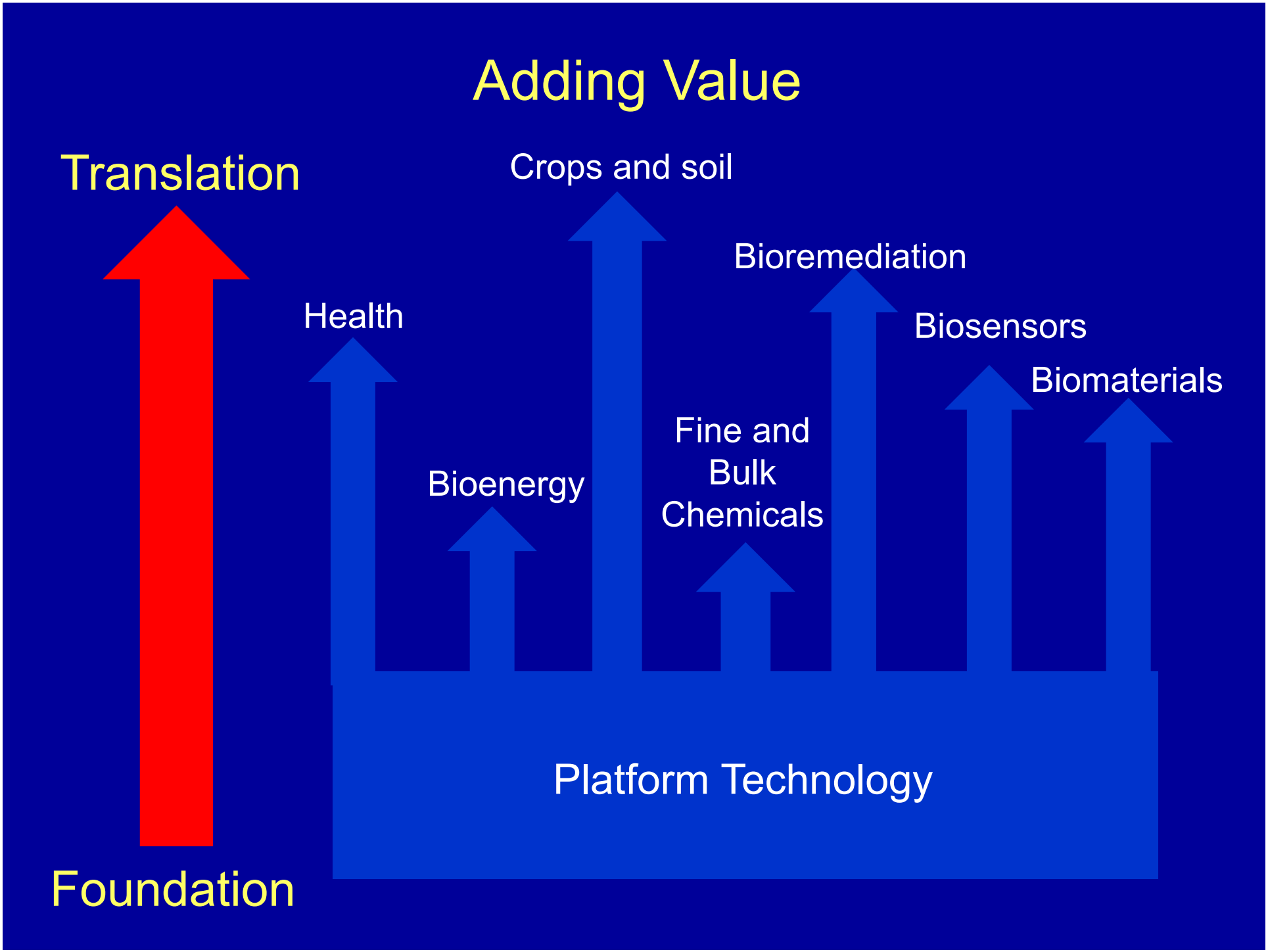
Metrology

Debug/Learn

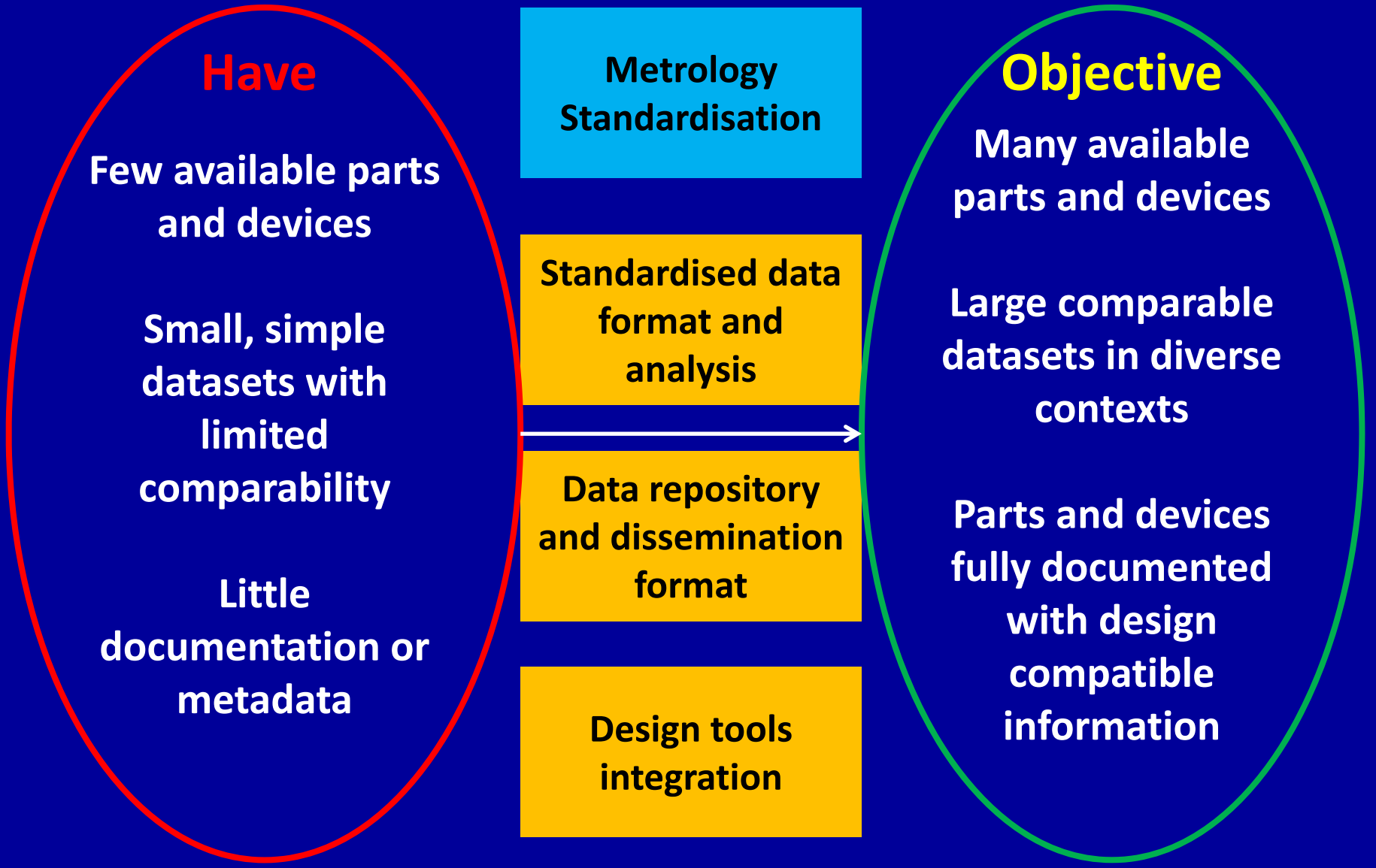


Design, Build, Test and Learn

WET LAB


Adding Value
Translation
Foundation
Crops and soil
Bioremediation
Health
Biosensors
Biomaterials
Bioenergy
Fine and
Bulk
Chemicals
Platform Technology

Using Data for Systematic design



Gathering Knowledge about Bioparts

We need Data

- Large amounts of data
- Reliable Data
- Data on
  - *Fundamental BioParts*
  - *Useful Devices*
  - *Chassis*
  - *Plasmids*
  - *…..*

Characterisation Pipeline

Data Acquisition

- Validated Protocols
  - Reproducible data
  - Minimal Experimental errors
- Automation & High throughput

Data Analysis

- Validated Methods
- Output as populated models

Data must be actionable

Standard BioPart Datasheets

- Minimum Description
- Human readable
- Machine readable

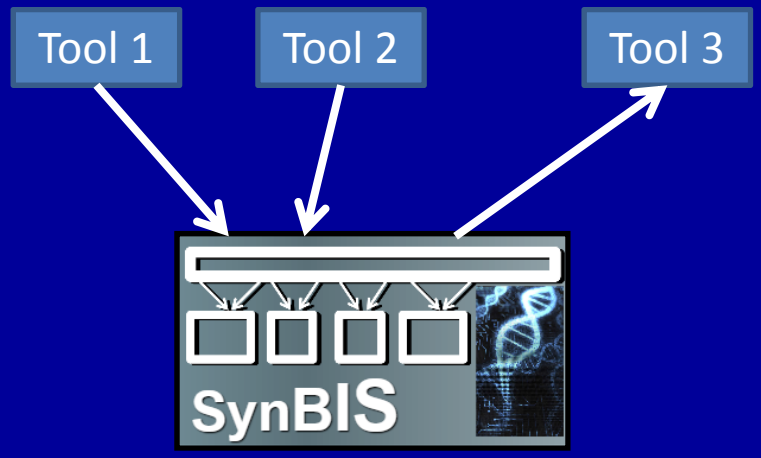
The New IT Infrastructure

A Resource for Data

SynBIS

- Database of BioPart Datasheet
  - BioPart Description
  - Model
  - Raw Data
  - Experiment Description

Interoperability



Integration with CAD Tools

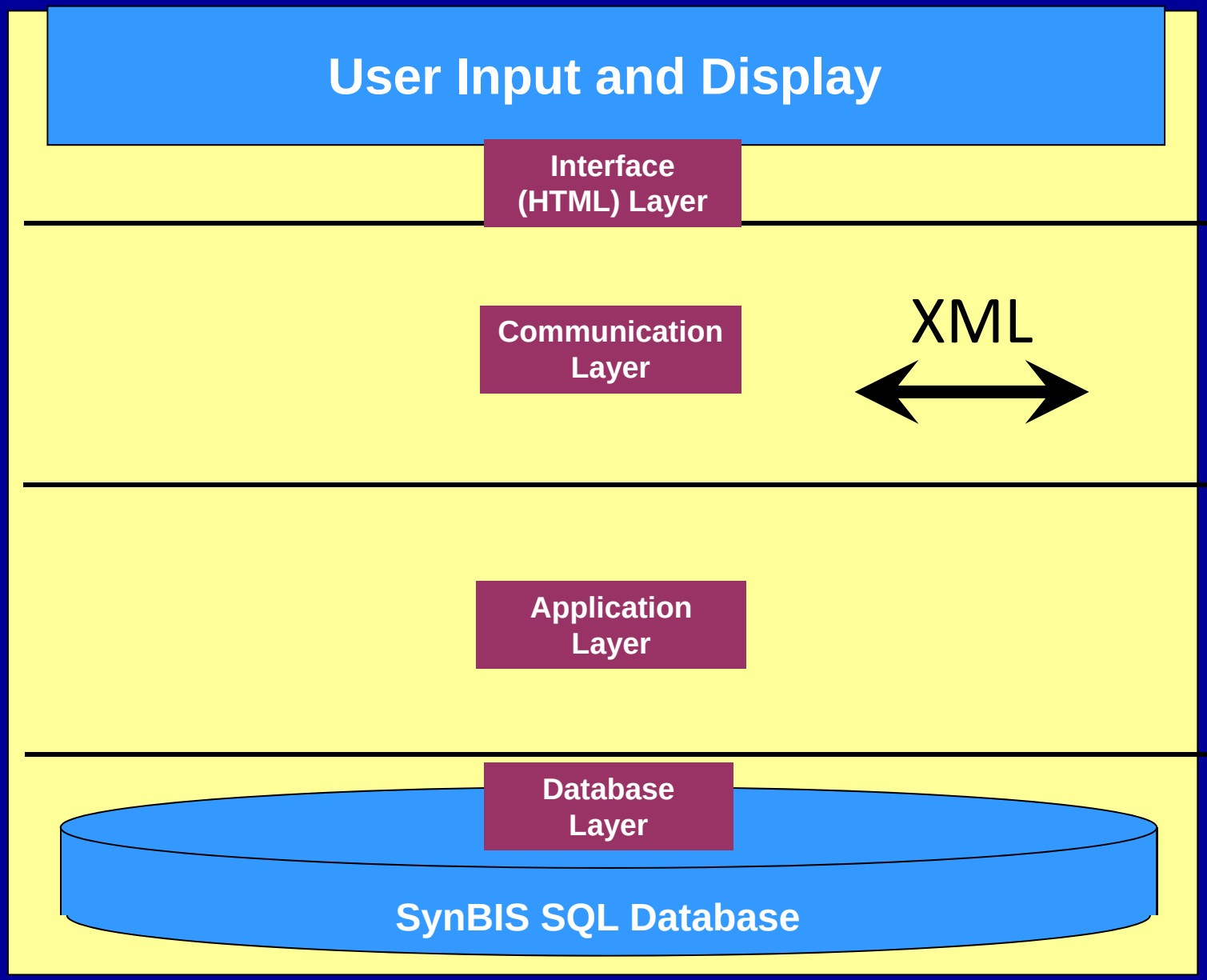
- Import most popular tools
- SynBIS API

Standard Data Formats

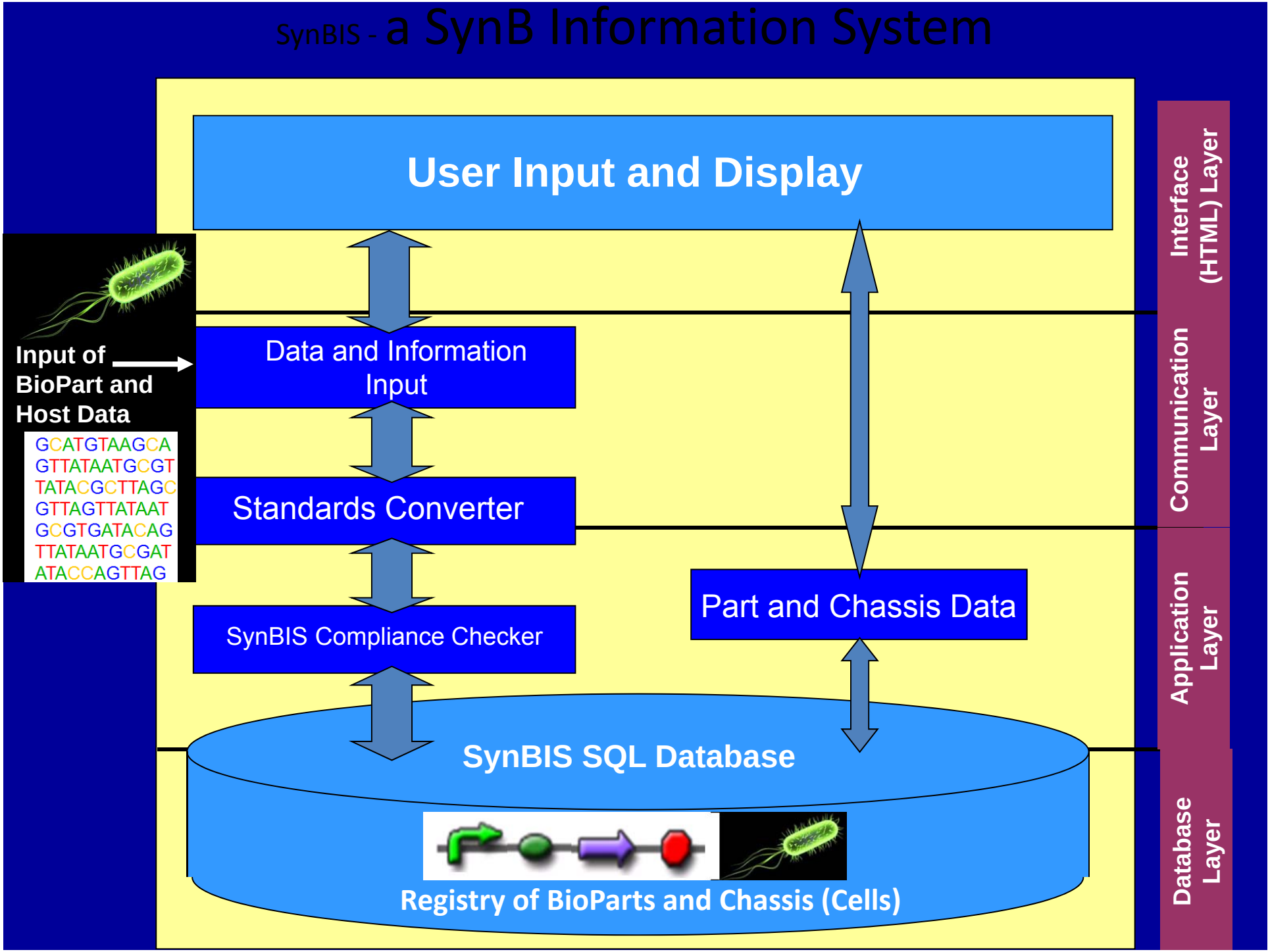
- Enables exchange between tools
- Efficient Storage

Information Systems

SynBIS - a SynBio Information System



SynBIS - a SynB Information System



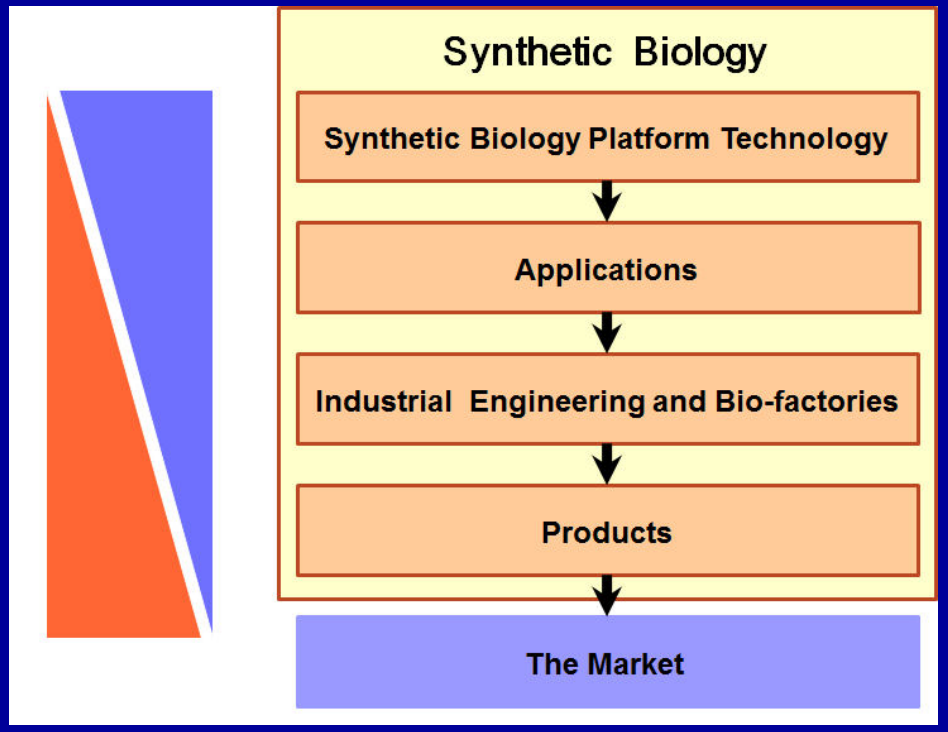
Modularisation

Standardisation

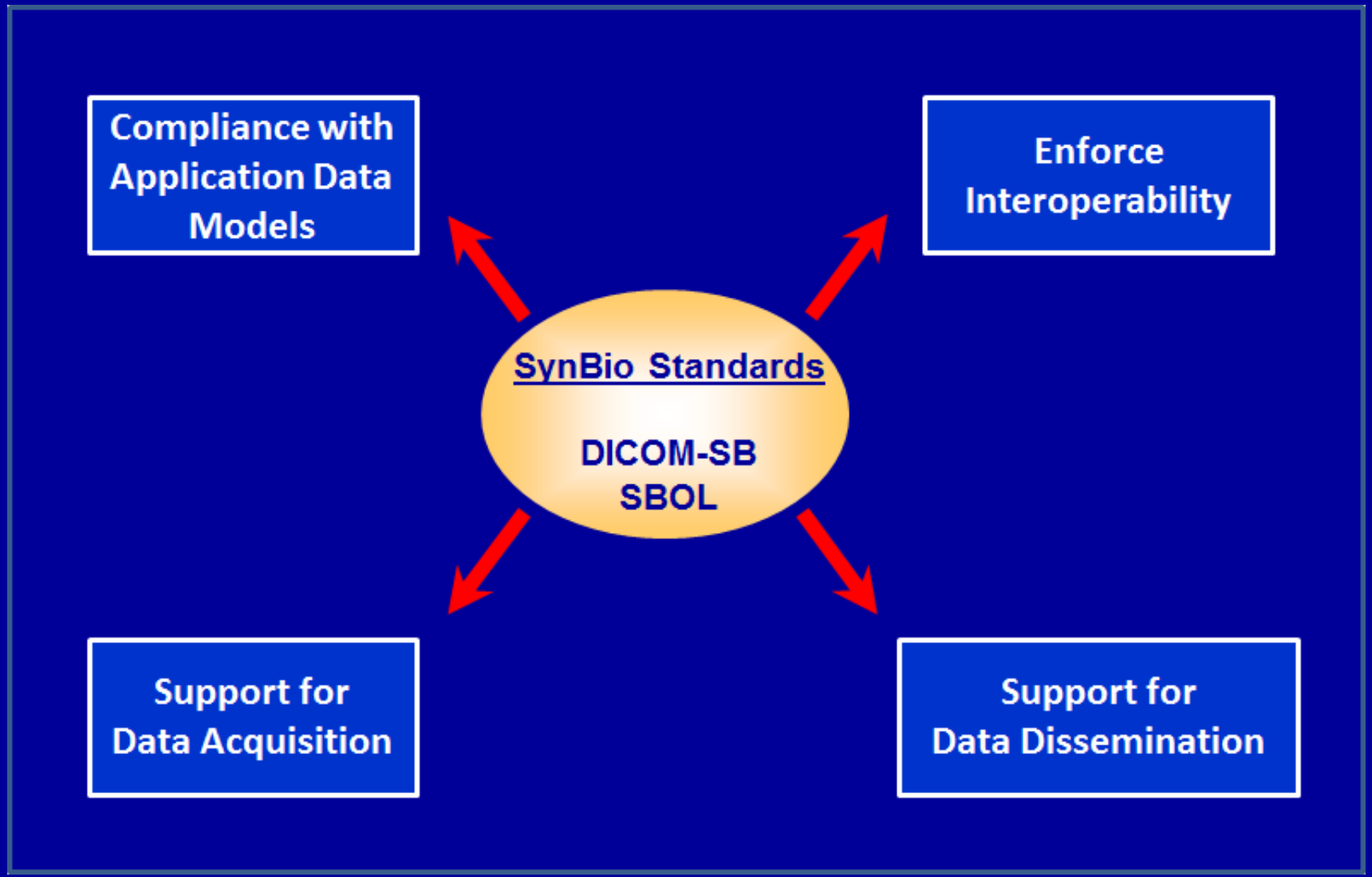
Characterisation


bsi.


ISO


Synthetic Biology
Synthetic Biology Platform Technology
Applications
Industrial Engineering and Bio-factories
Products
The Market

Objectives


Compliance with Application Data Models
Enforce Interoperability
SynBio Standards
DICOM-SB
SBOL
Support for Data Acquisition
Support for Data Dissemination

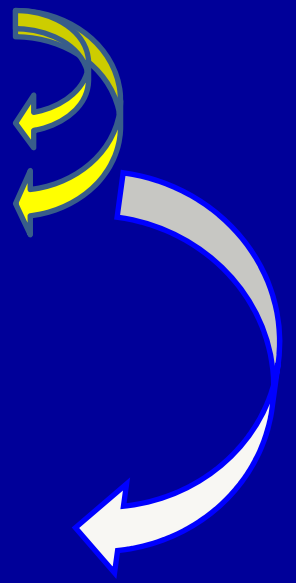
DICOM-SB in SynBIS

DICOM is used and has been modified to:

- Store/send parts & associated metadata
- → " related images
- → " related/collected data

- e.g. BioPart source, design notes, vector resistance, protocols

- Institution name, date, authors



DICOM-SB Data Model

Biopart

Characterisation Experiment

Equipment

Series

Protocol

Modality data

SynBIS
Datasheet model

metadata
- context dependency
measurements

DICOM-SB - Data Model

Biopart	Biopart Name Bipoart ID Biopart Creation Date Biopart Family	J23101 2 20131011 Anderson Collection
Characterisation Experiment	Study UID Study ID Study Date Study Time Study Owner Accession Number	1.3.6.1.4.1.6018.4.888 22 20131011 110000.000000 Chris Hirst 001
Series	Series UID Series Number Series Date Plate Coordinates	1.3.6.1.4.1.6018.5.777 1 20131011 C9
Equipment	Manufacturer Institution Name	BioTek Imperial College London
Protocol	Protocol UID Protocol Name	1.3.6.1.4.1.6018.3.444 Caracterization of const. pr
Modality	Modality Number Channel Number Modality Type (OD,GFP,FC) Modality Metadata Modality data	2 16 OD (optical density) freq=1, bits allowed=16 … 256 300 311 315 325 …

metadata
- context dependency

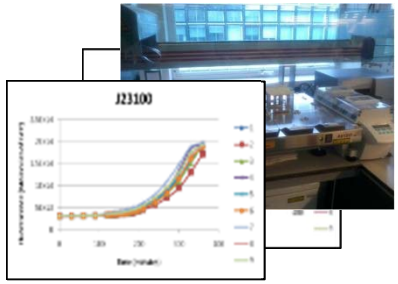
measurements

DICOM-SB supporting Data Acquisition

SynBIS

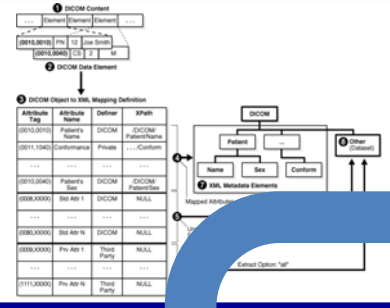
Data preparation

Experimental Data



DICOM-SB IOD generation

DICOM-SB Data



Store service

Storage

Data curation

Compliance check

CSynBI's partners

DICOM-SB will be the **mandatory input format** for data curation

Modularisation

Standardisation

Characterisation

Platform Technologies

SynBIS – integrated BioCAD and modelling suite

CAD

DNA Assembly

Promoters – as an example

- Genes to Pathways

Characterisation (data for SynBIS)

- *In vitro*
- *In vivo*
- Reference parts under different conditions

Chassis (data for SynBIS)

- *E. coli*
- *Yeast*
- *Bacillus subtilis*
- *Geobacillus*

Promoter Measurement Workflow

Starter cultures

Standard media

12-16 hr

growth

Single Cell Data

cell size, age, fluorescence

Identify sub-populations

Single Cell Data

Compare Data

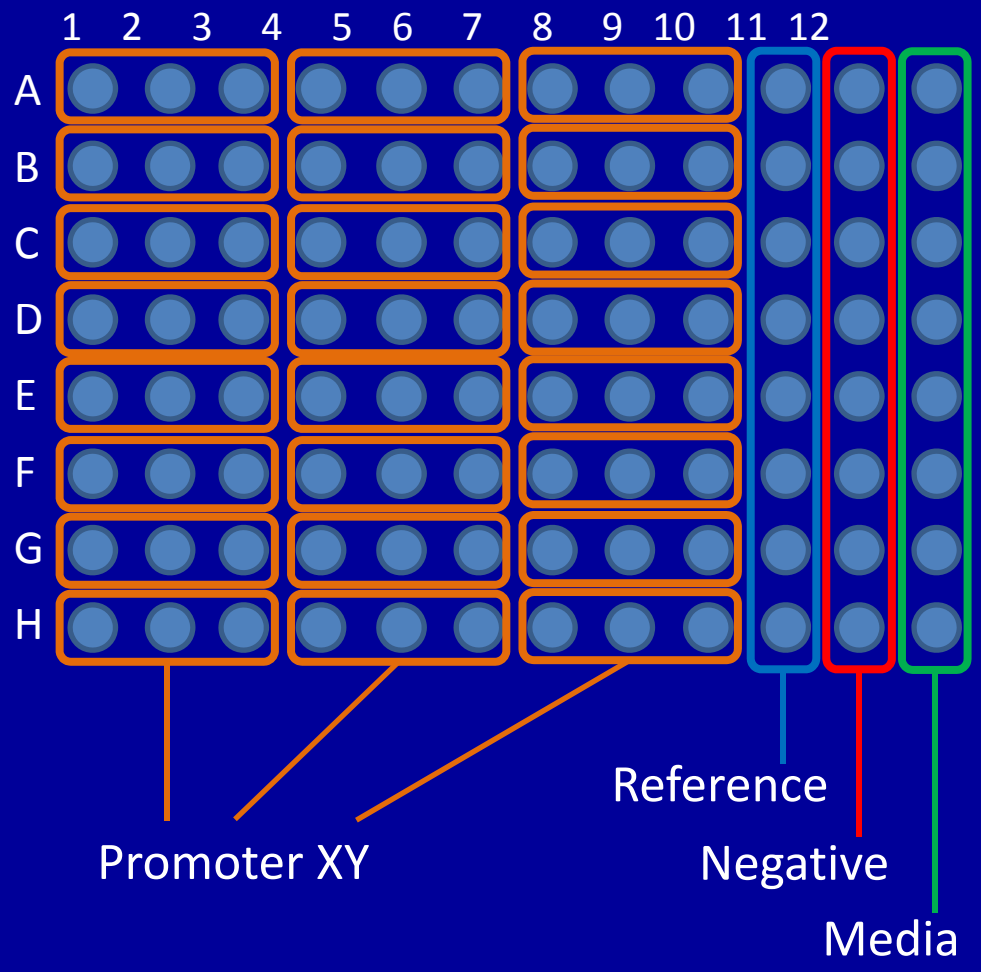
Population Level Data

Population Level Data

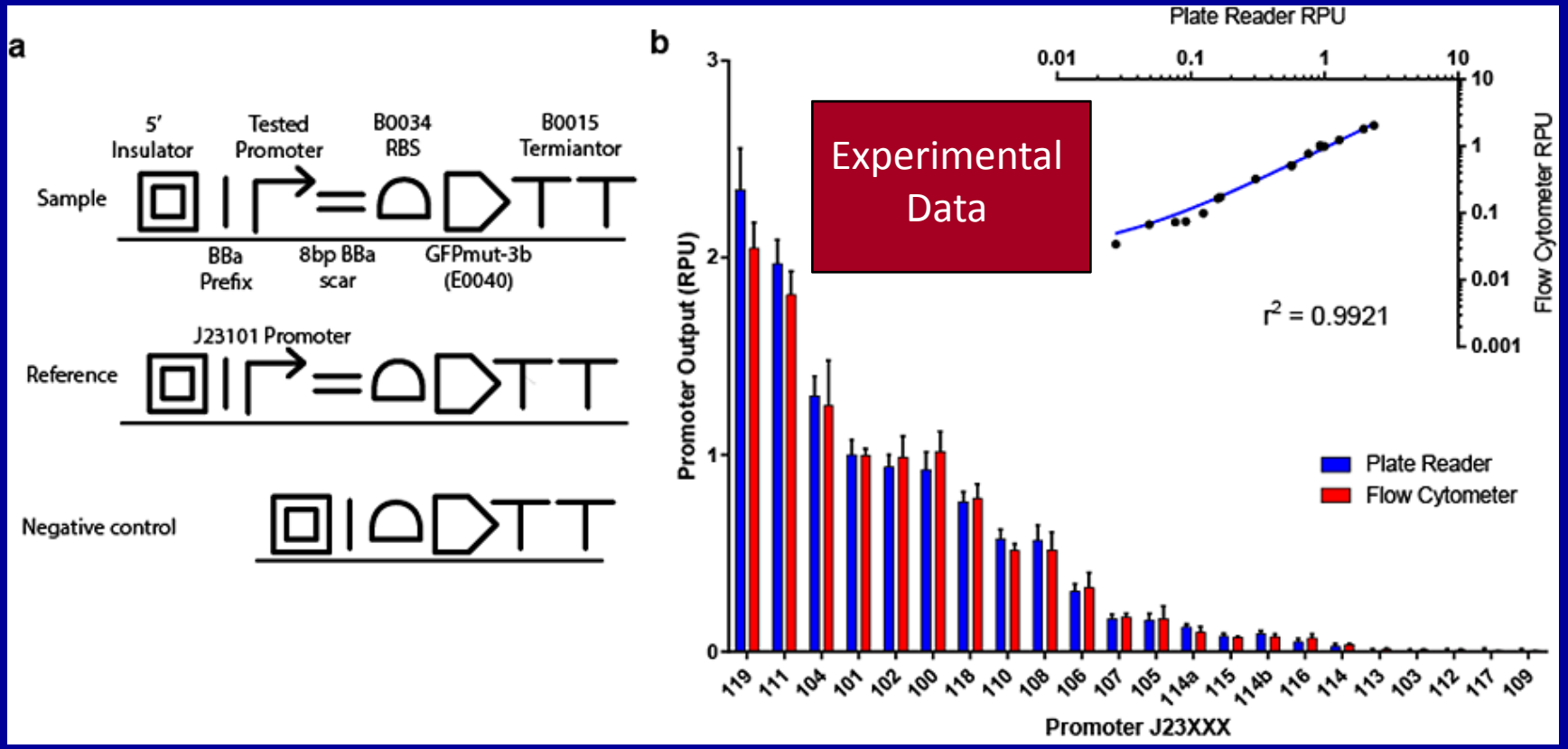
OD, fluorescence

Examplar – Constitutive Promoters

- 12 x 8 plates are used
- Each promoter is assigned 3 plates.
- Last 3 columns are controls.
- Each plate is analysed in two different equipments:
  - OD and GFP reader (1 Series each).
  - Flow Cytometer (2 Series).
- The measurements are repeated during 3 days, creating one Characterisation Experiment per day.



Constitutive Promoters



High level of agreement between plate reader and flow cytometry data and low levels of error

Handling the amount of data becomes tricky and requires data analysis automation

SynBIS

Experimental Data | Compliance Checking | Curation (Semi-automatic) | Data Processing | Final Curation | Dissemination

Automatic

Checks that
- All data files (fields) supplied
- Files properly formatted
- Compulsory Metadata supplied

Basic Checks on Data Quality

Automatic/Semi-automatic

Data Analysis
- Algorithms tailored to the BioPart
- Algorithms validated

Constitutive Promoters
- Calculate RPUs
- Calculate Synthesis Rate
- Calculate Growth Rate

Quality Control

Data Files
- All data files (fields) supplied
- Files properly formatted
- Compulsory Metadata supplied

Data Quality
- Controls successful
- Calibration of raw numbers
- Remove failed experiments

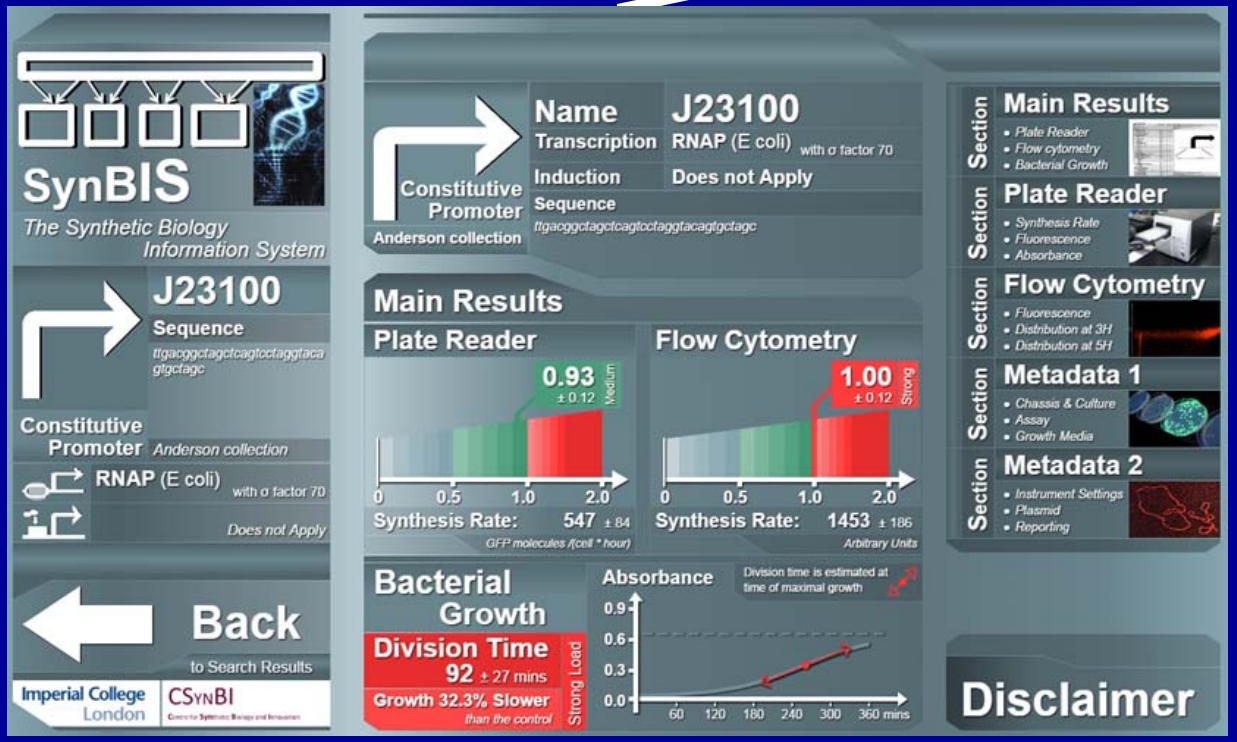
Curator's Word Final

Human Step – moving to automation

Curator confirms/corrects output of data processing Step
- Experiments flagged as incorrect, checked before removal
- Model fits confirmed to be accurate

SynBIS

Experimental Data | Compliance Checking | Curation (Semi-automatic) | Data Processing | Final Curation | Dissemination



SynBIS

The Synthetic Biology Information System

SynBIS

SynBIS

The Synthetic Biology Information System

CSynBI
Centre for Synthetic Biology and Innovation

Imperial College, London

CSynBI *develops foundational tools for Synthetic Biology and uses them to generate innovative biological applications for cutting edge research, healthcare and industry.*

Along *with our research and development of Synthetic Biology, we combine our science with emerging ethical, legal and societal issues - so this novel, powerful technology may be matured in a responsible way.*

Click here to learn more
(the link will open in a new tab)

Imperial College London | CSynBI Centre for Synthetic Biology and Innovation

Welcome to SynBIS

SynBIS is a web-based resource open to the whole Synthetic Biology community. Its aim is to make available high-quality characterisation data for the most commonly used bio-parts, in order to support the development of Synthetic Biology worldwide.

All data stored on SynBIS have been collected and analysed according to stringent, validated protocols - specifically developed for bio-part characterisation.

Contact Us

We have placed the greatest care to the collection,processing and curation of our data.

We would therefore be grateful if you could report any issue you may encounter at:

Bioeng-synbis @imperial.ac.uk

SynBIS v2.0

August 2014

All Data Courtesy of CSynBI

Centre for Synthetic Biology and Innovation
Imperial College, London

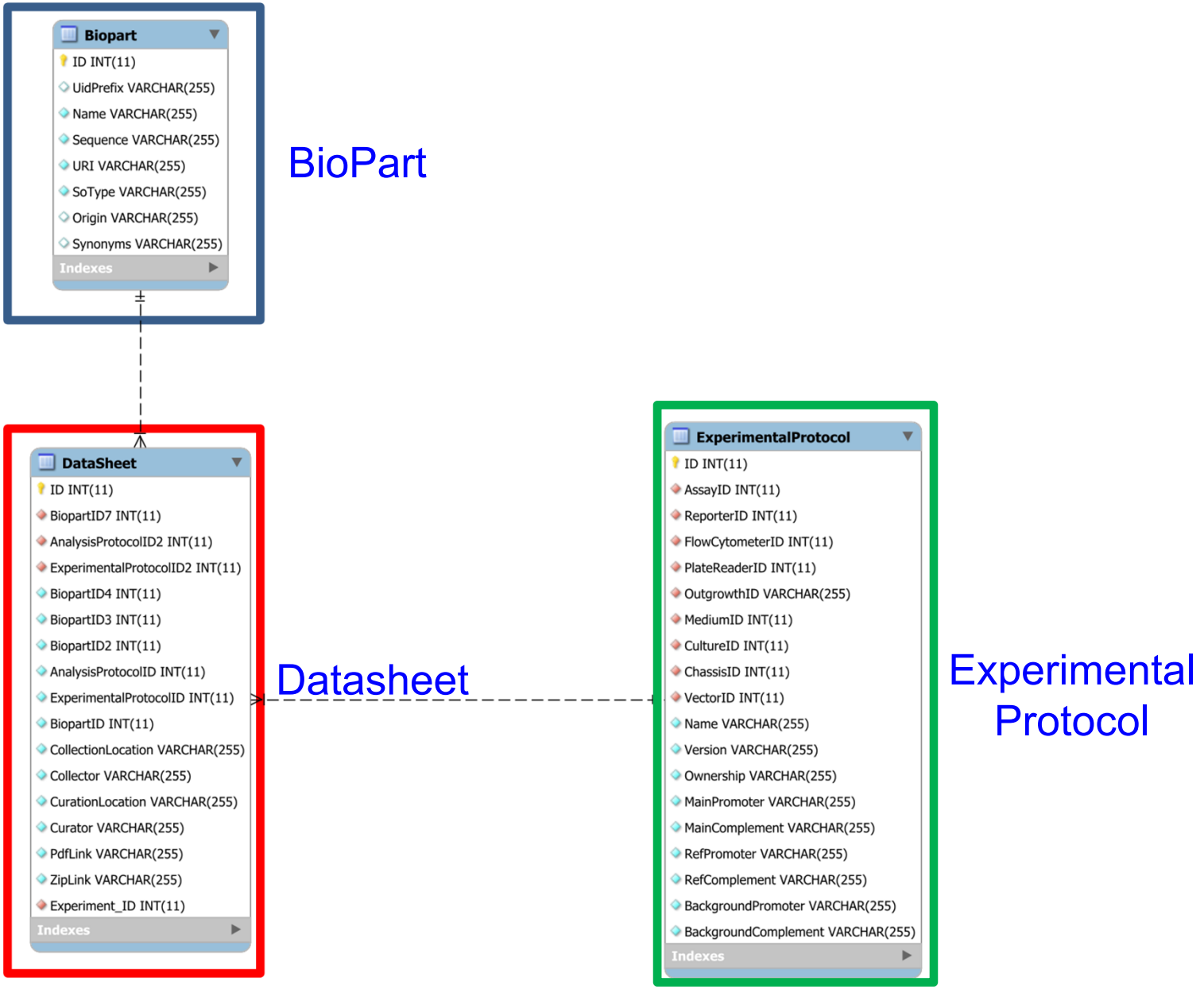
Our Protocols

Check here for all the protocols used for the collection and analysis of the data stored on SynBIS.

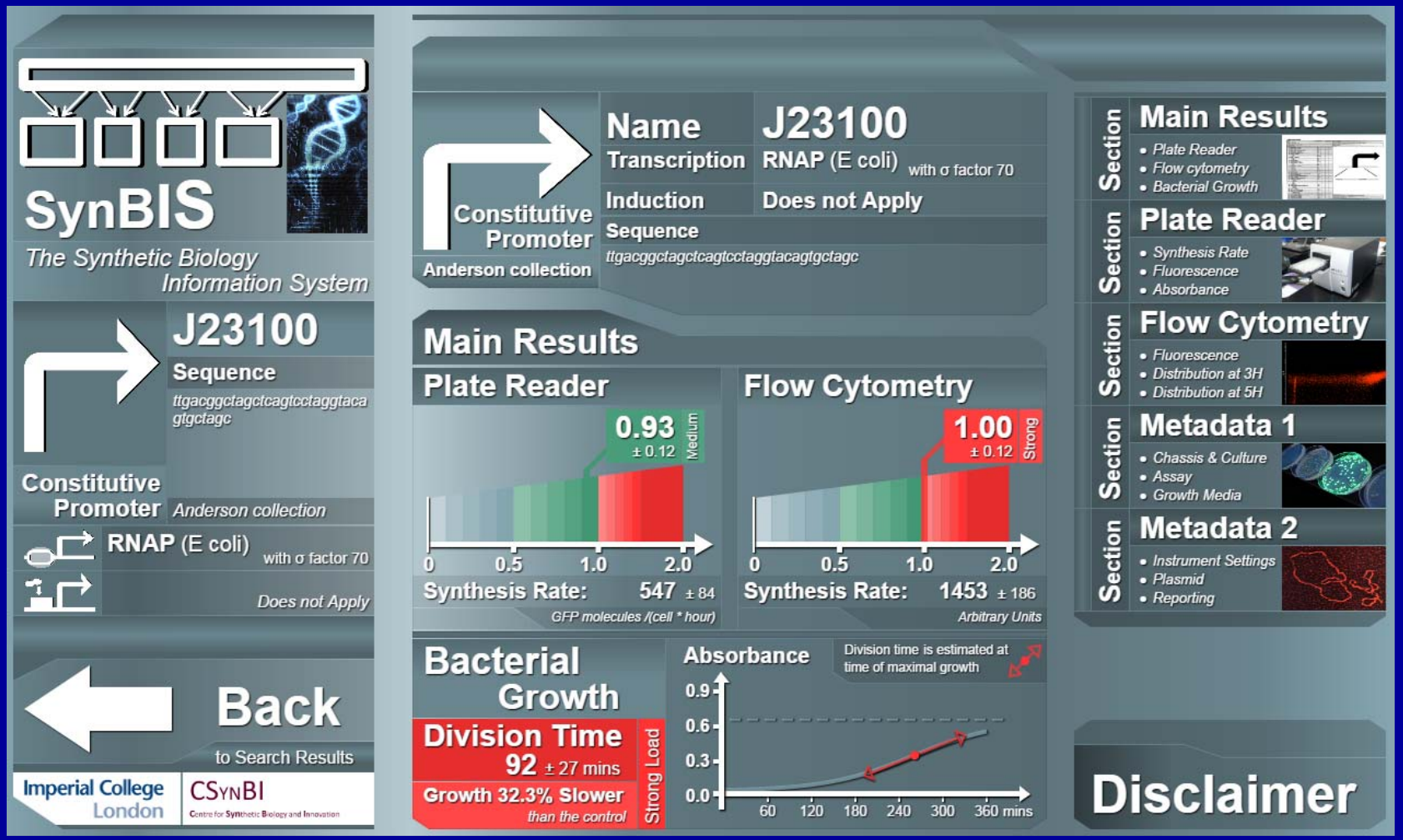
Available Data

- **Constitutive** *Promoter*
- **Inducible** *Promoter*
- **Ribosome** *Binding Site*
- **Riboswitch**
- **Degradation Tag**

SynBIS Schema – Basic Schema



Datasheet - Main Results



J23100 First Element of the Anderson Collection

Datasheet – Modality Sections

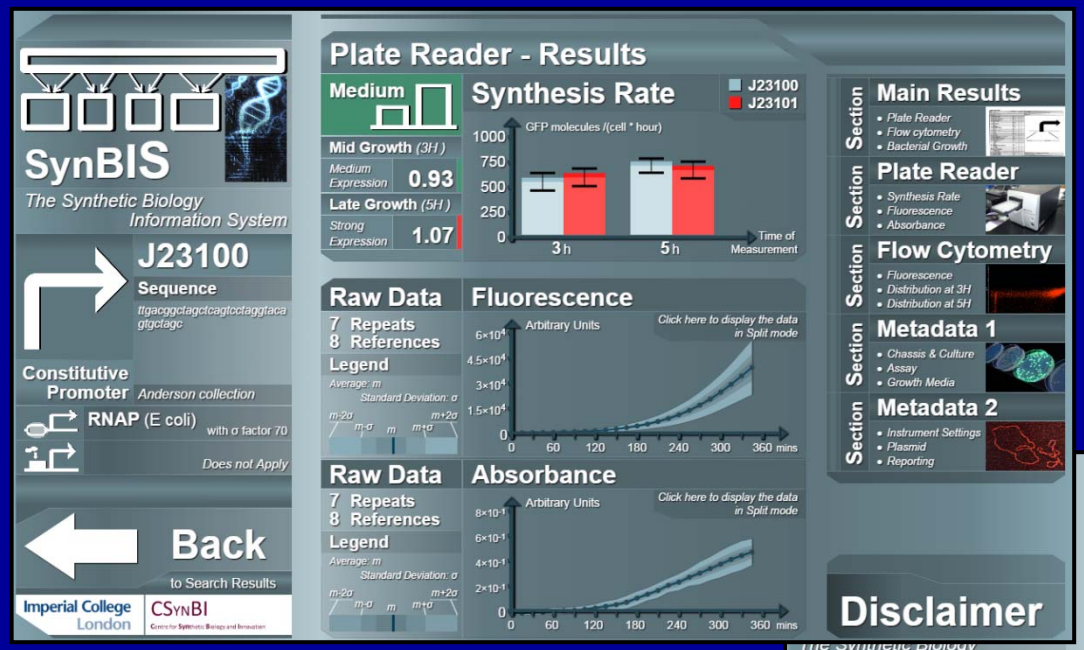
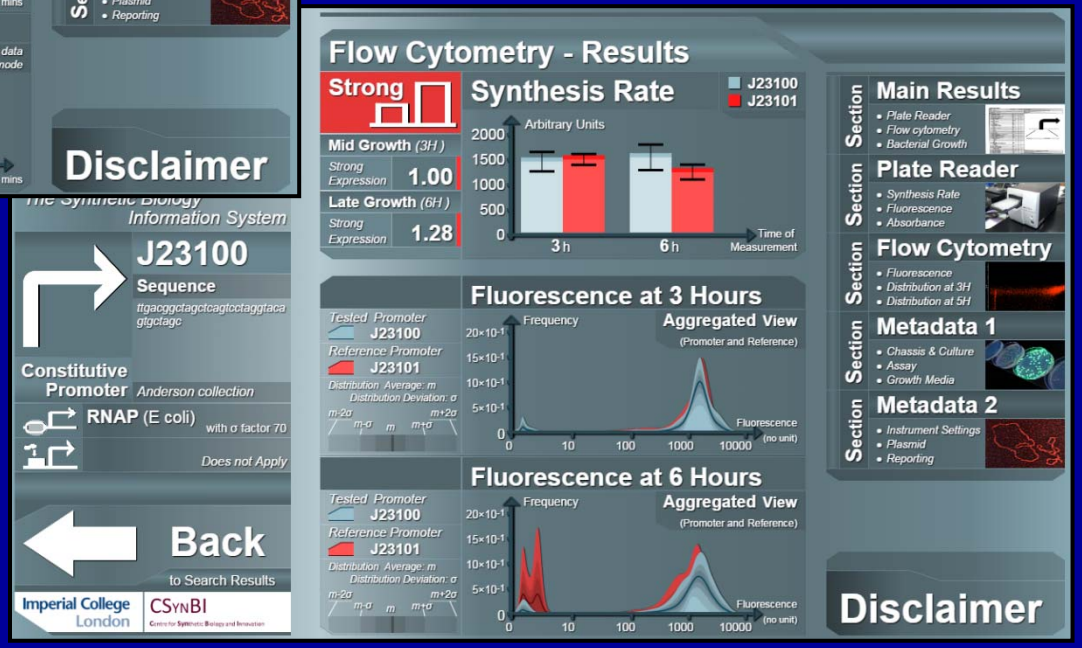
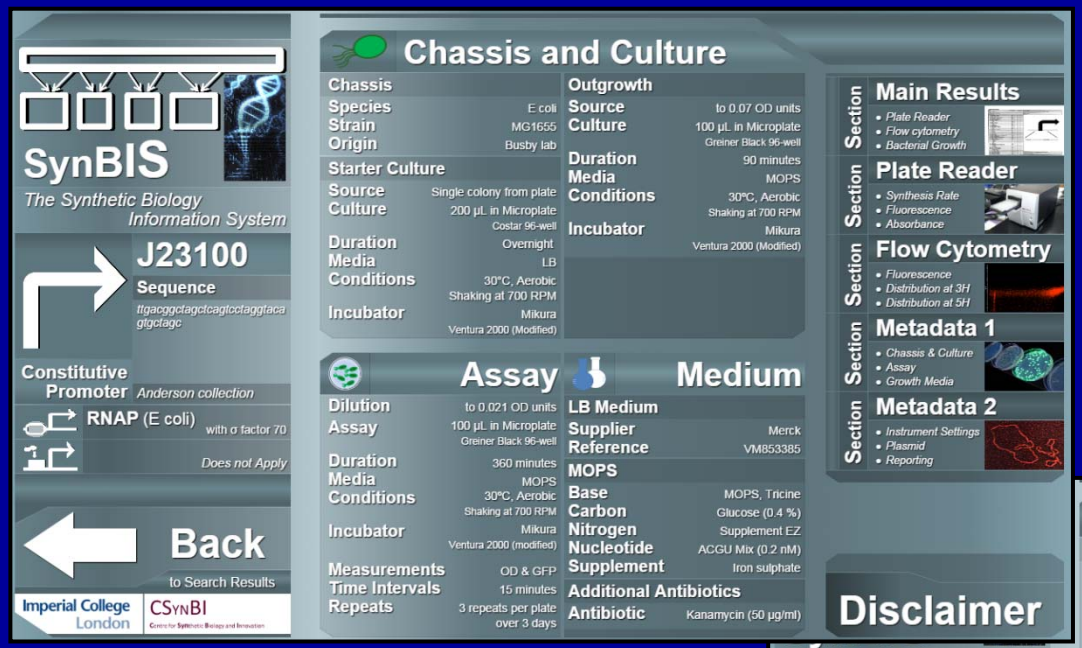


Plate Reader



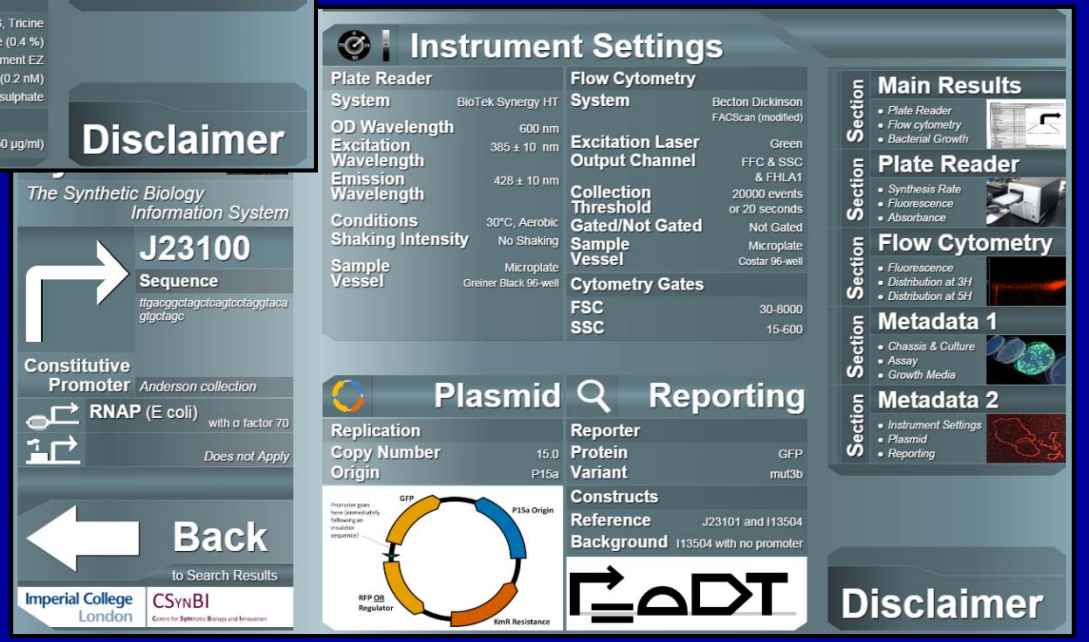
Flow Cytometry

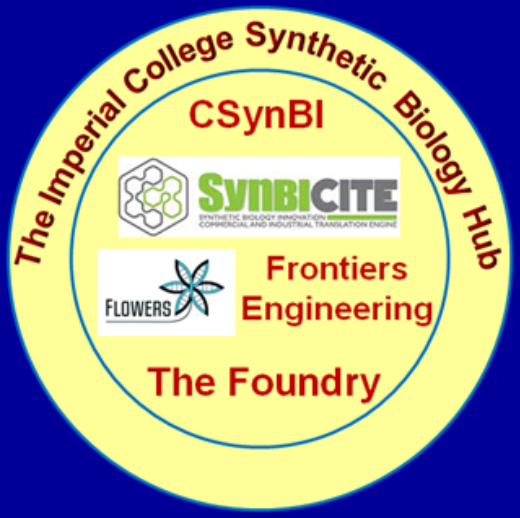
Datasheet – Metadata



Chassis
Assay
Medium

Instrument Settings
Plasmid Details
Reporter Details

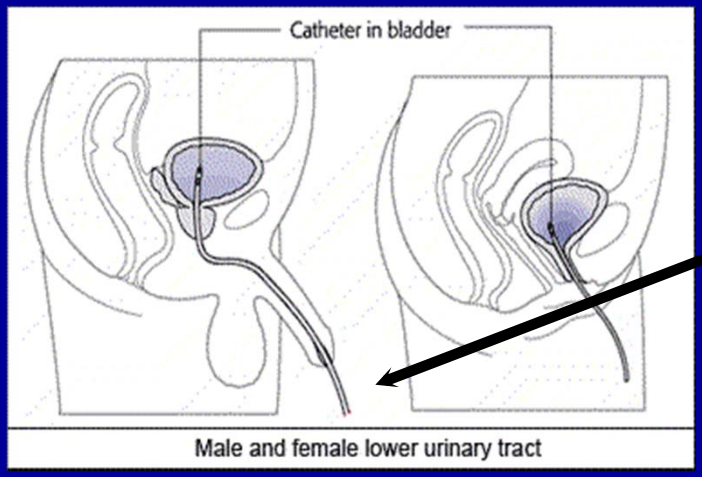




Examples of Applications

Biofilms and Urinary Tract Infections

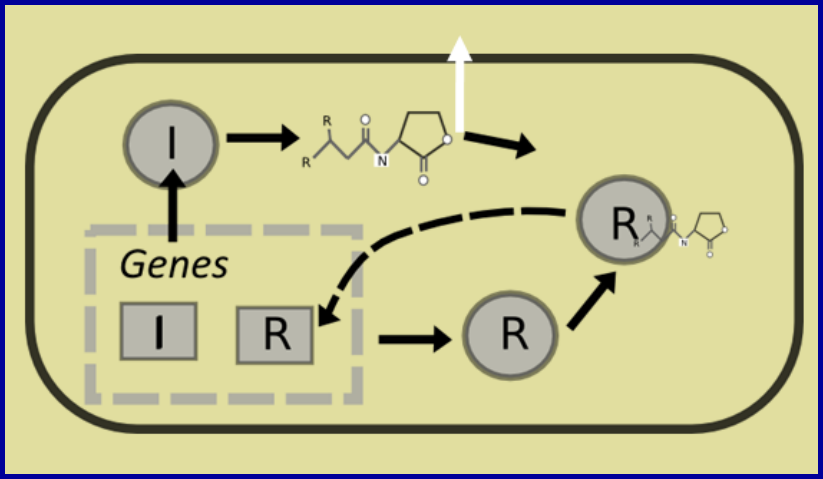
- The infection takes 24-36 hours to spread to the bladder and causing a major bacterial infection
- Treatment - “industrial strength” antibiotics over many days
- The catheter has to be replaced – which can be extremely painful



Infection starts on the outside of the catheter

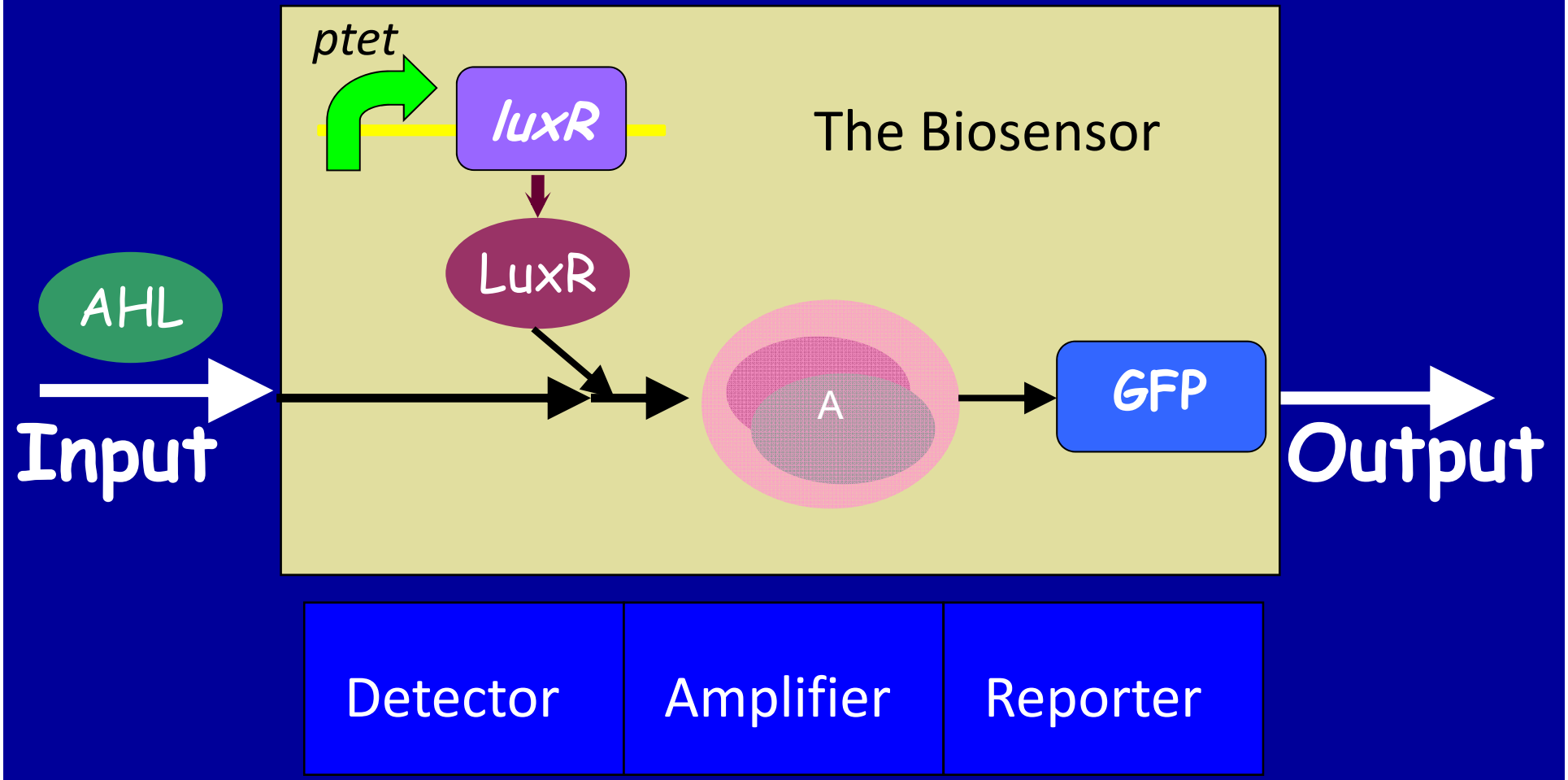
Detection of Pathogenic Biofilms - Using Nature's Toolbox

- When **AHL** reaches a key threshold concentration, a
- transcription factor (*luxR* homologues) is activateBiofilm formation depends on the ability of cells to communicate by **quorum-sensing**
- Quorum sensing involves production of **AHL** by enzymes (*luxI* homologuesd
- AHL can be used as the input to a biosensor to detect biofilms

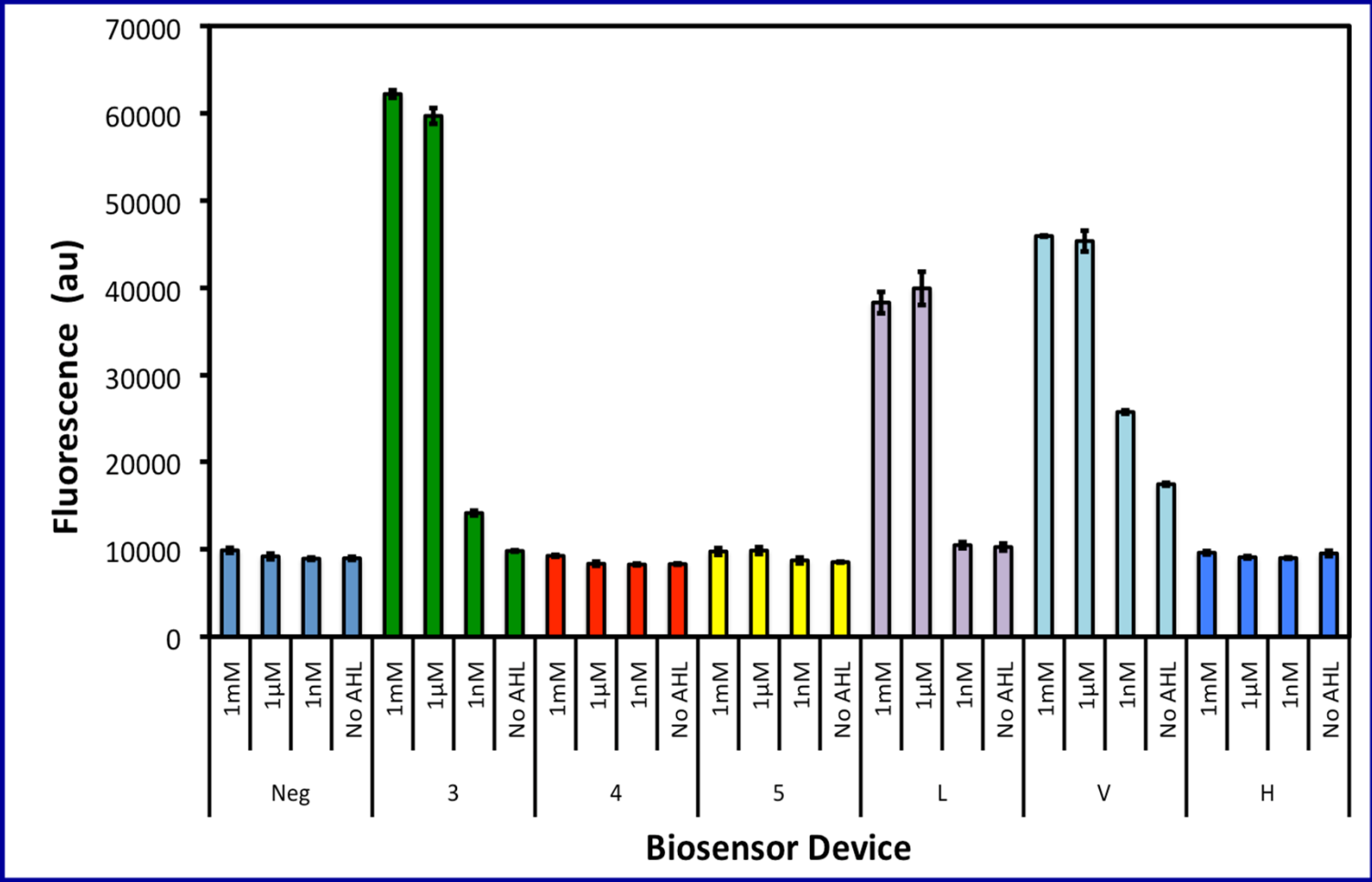


P.aeruginosa

Urinary Tract Infection Detector – a three stage device

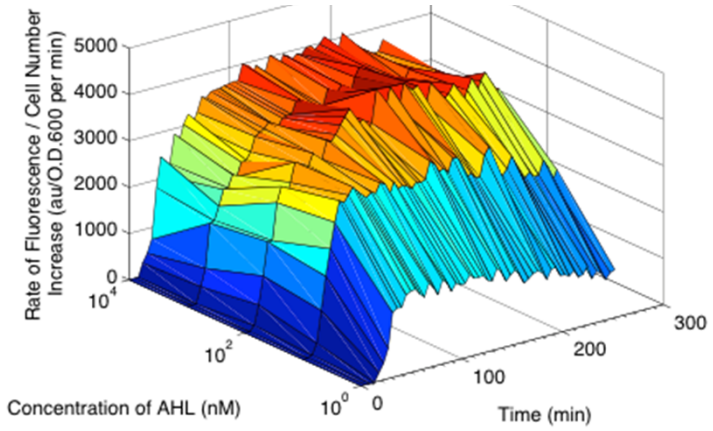


Initial Screening of Functional Devices - performed *in vivo* in E. coli

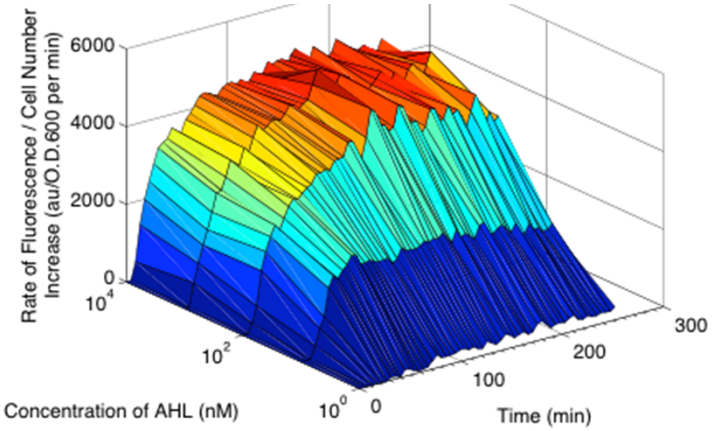


Biosensor – Characterisation of Devices

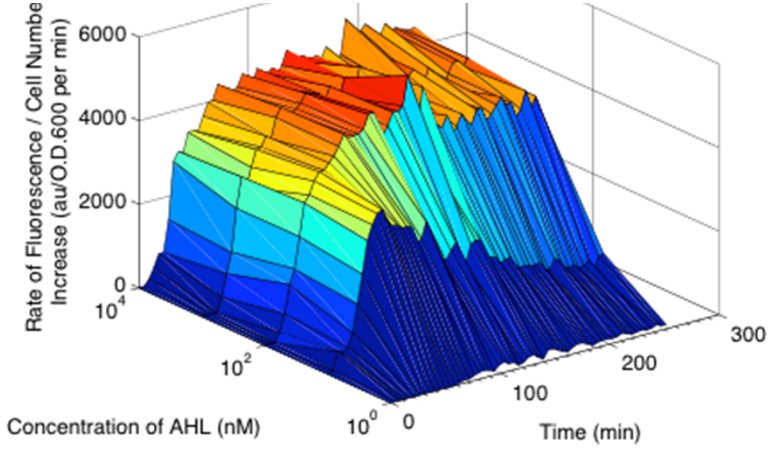
A. Biosensor V



B. Biosensor 3



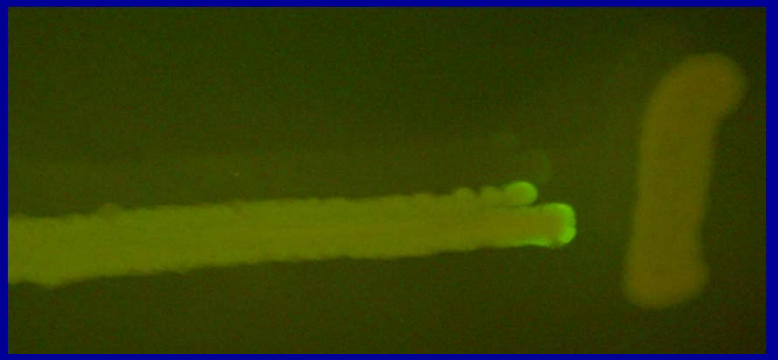
C. Biosensor L



The Biosensor

Testing

After 1 hour – can be seen with the eye



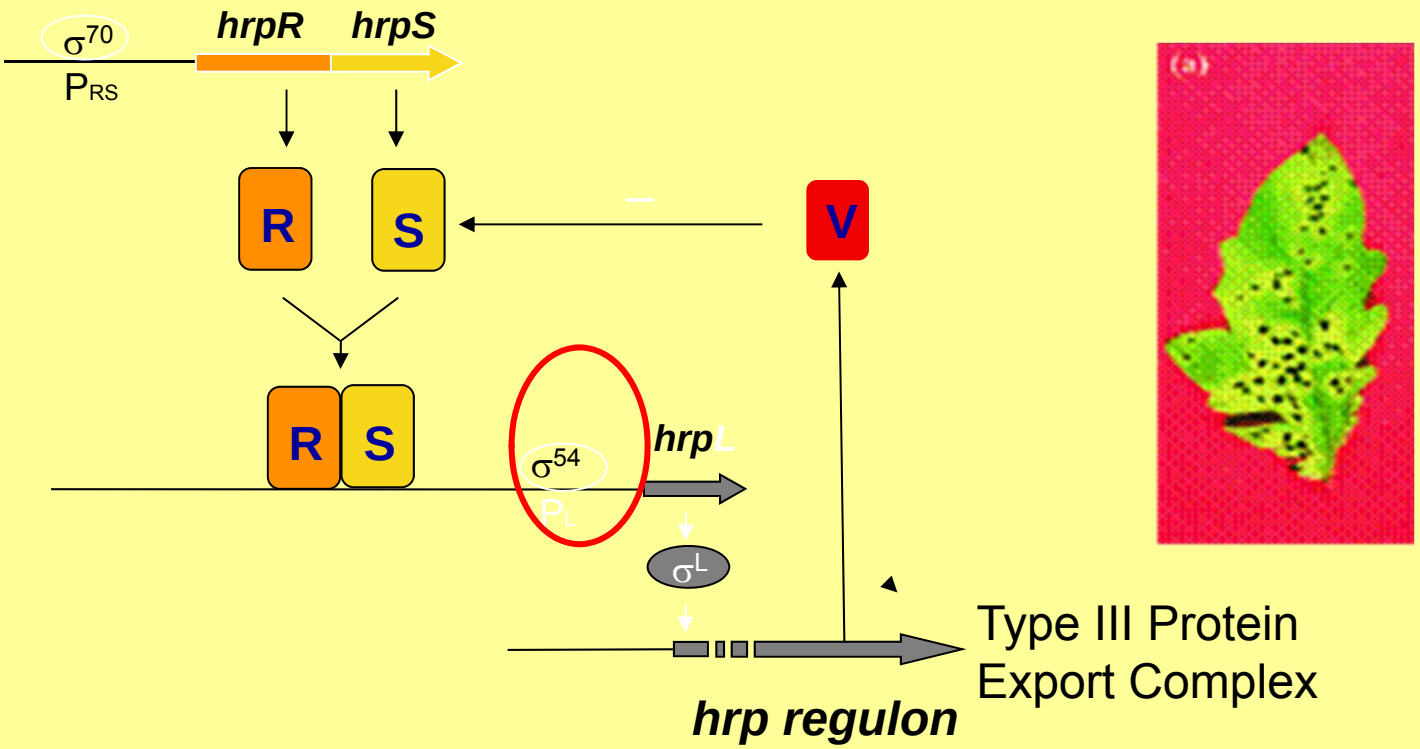
P.aeruginosa PA14 + *E.coli* BS L

Biologically-based Logic Gates

- Gates are the basis of almost all digital devices
  - Counters
  - Calculators
  - Microprocessors
- Near term applications
  - Biosensors of various kinds
- Longer term
  - Intracellular control and signalling

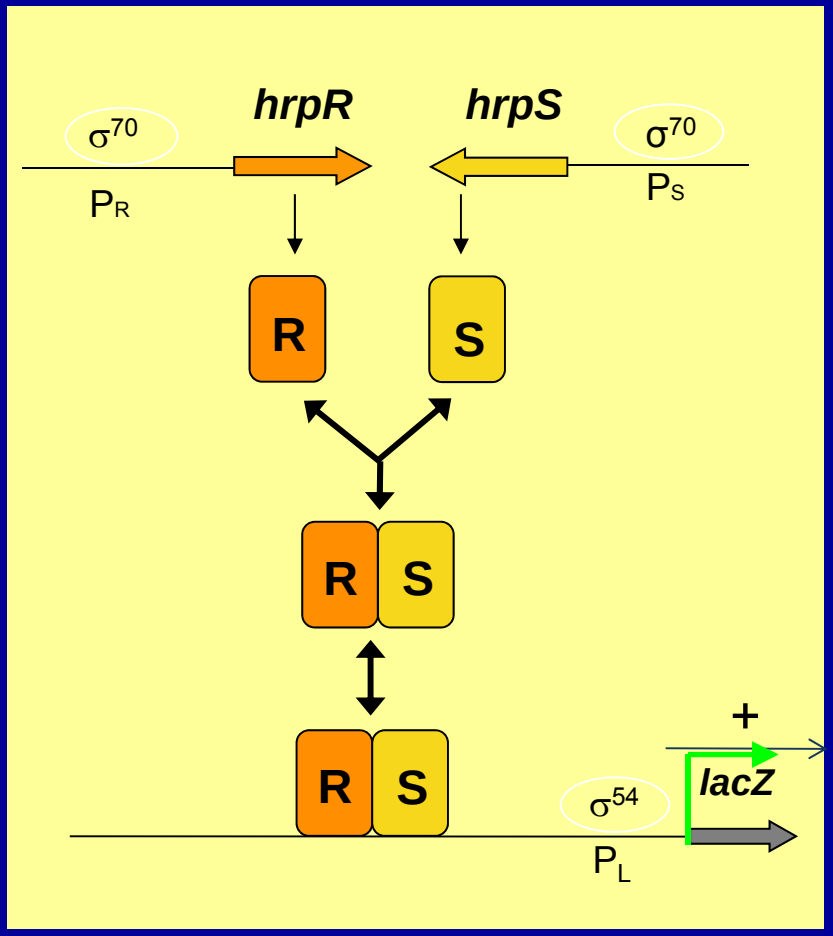
The hrp gene regulation system – a great system for modular biologically-based logical devices

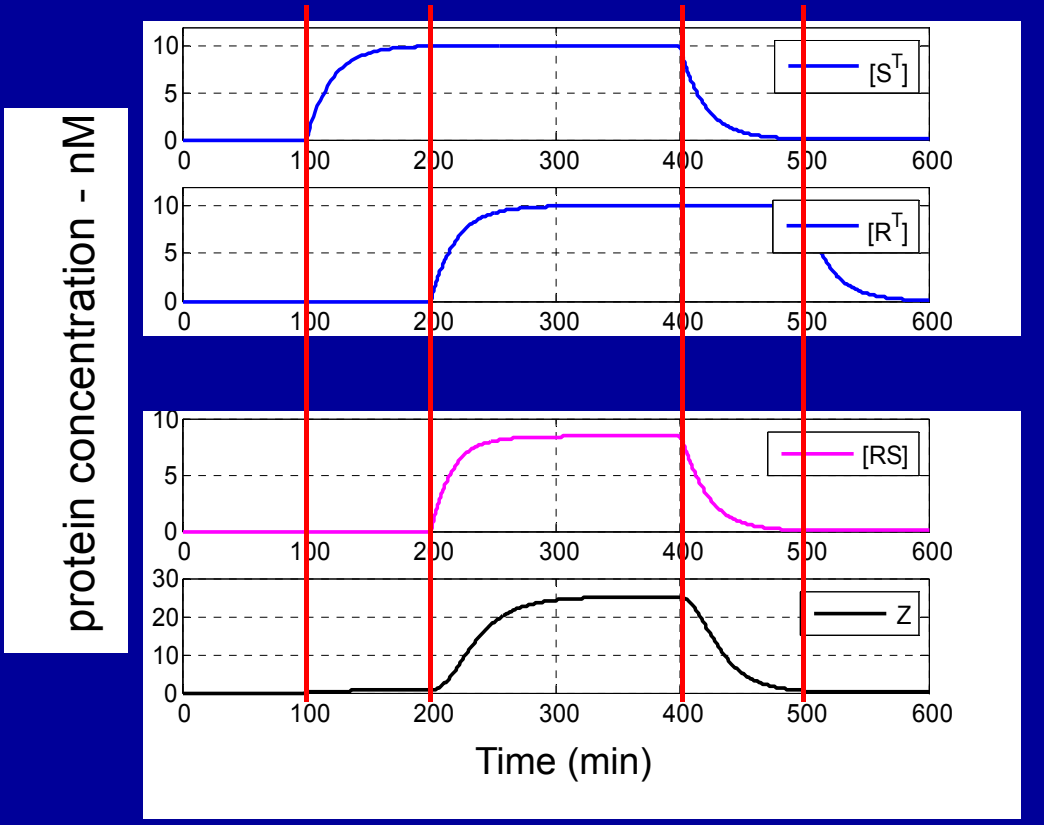
hrp (hypersensitive response and pathogenicity)



Pseudomonas syringae hrp regulatory system

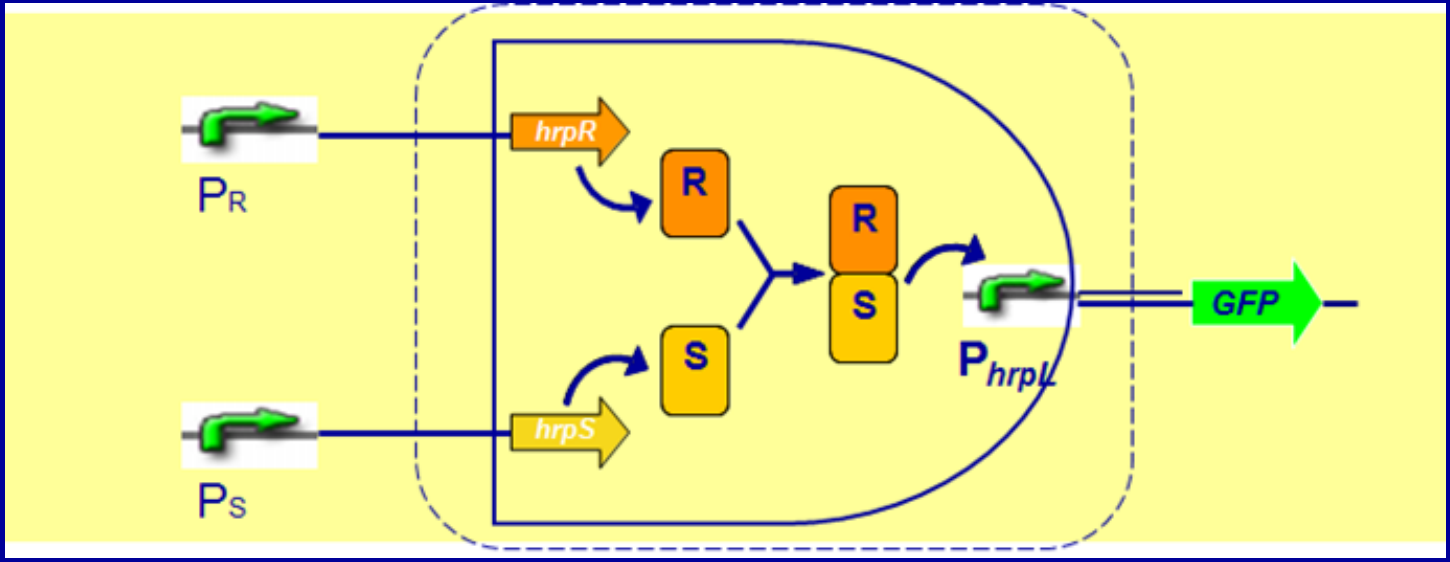
Modelling Case: *hrpL* regulated by 2 factors

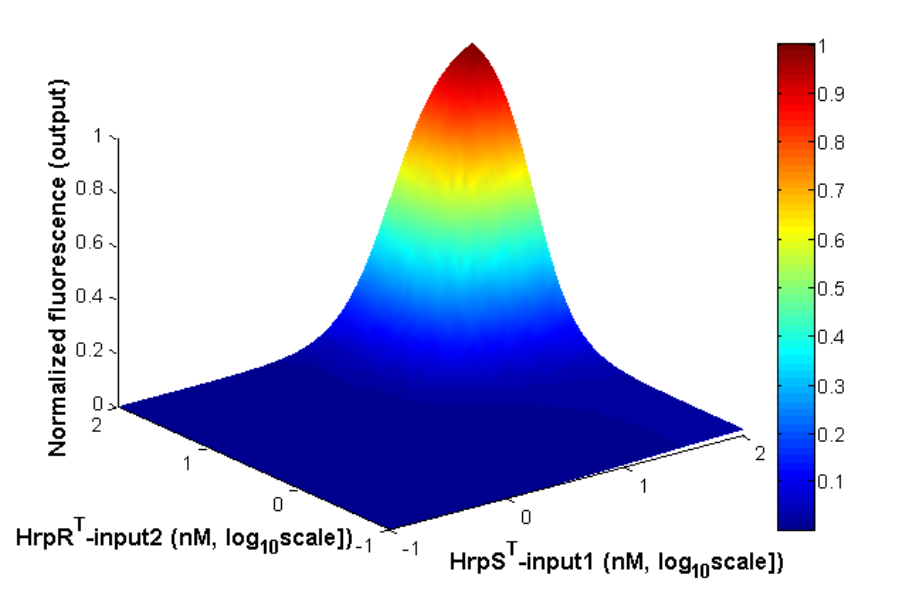




Simulation results: the dynamic evolution of protein concentrations

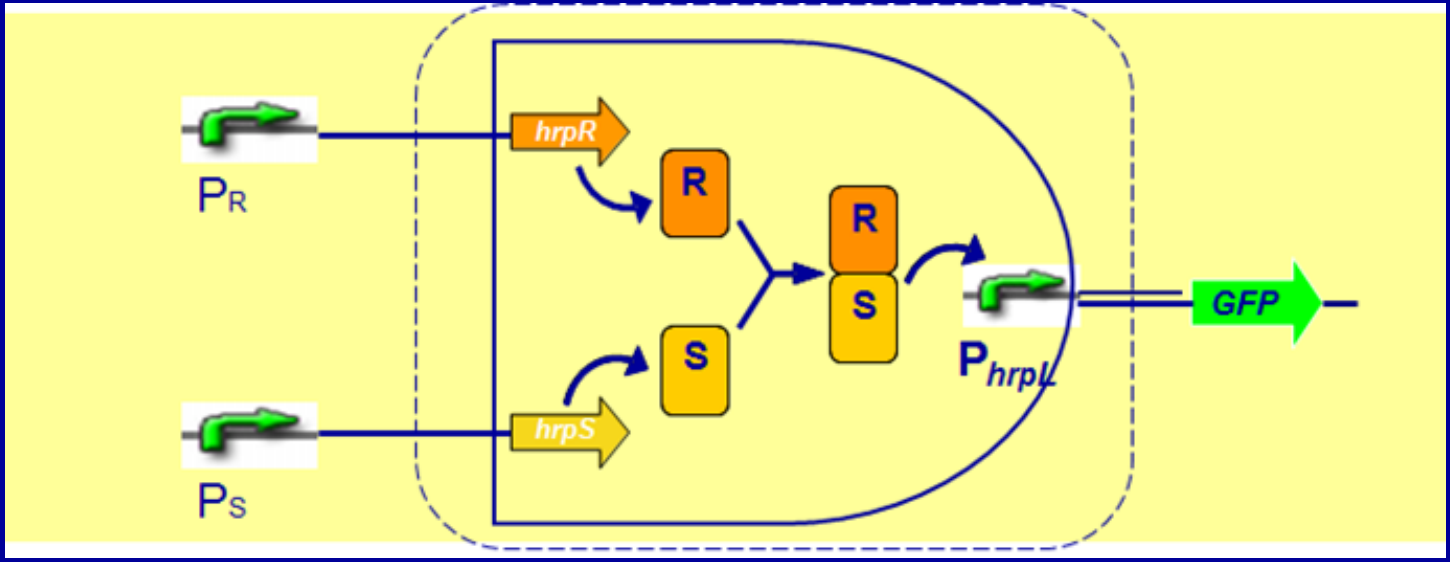
A Modular AND Gate

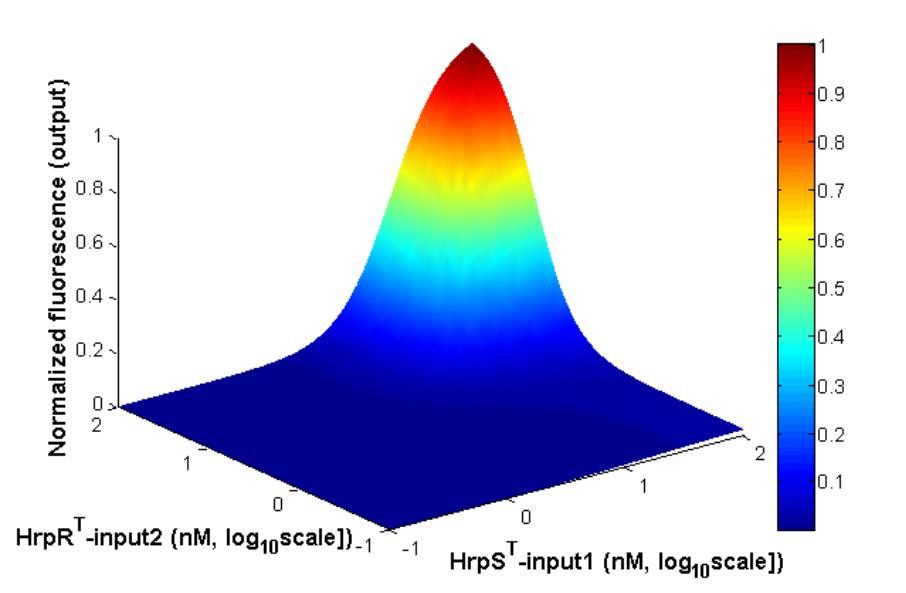


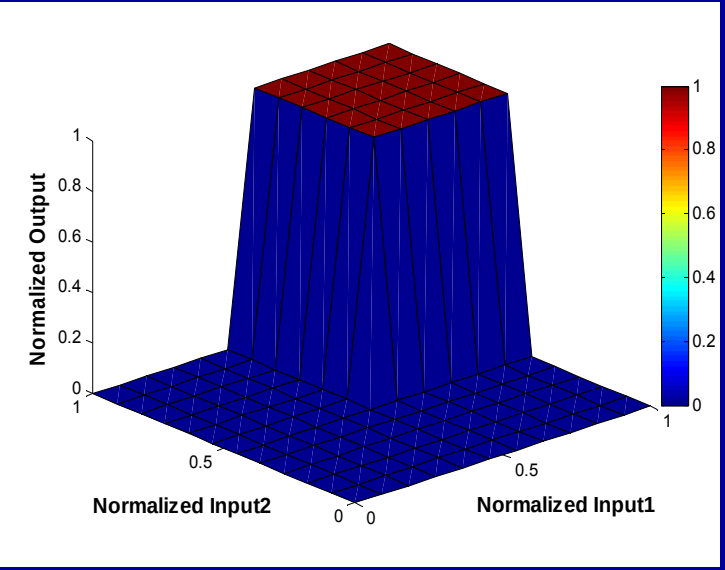


P_R	P_S		pHrpL
0	0		0
0	1		0
1	0		0
1	1		1

A Modular AND Gate

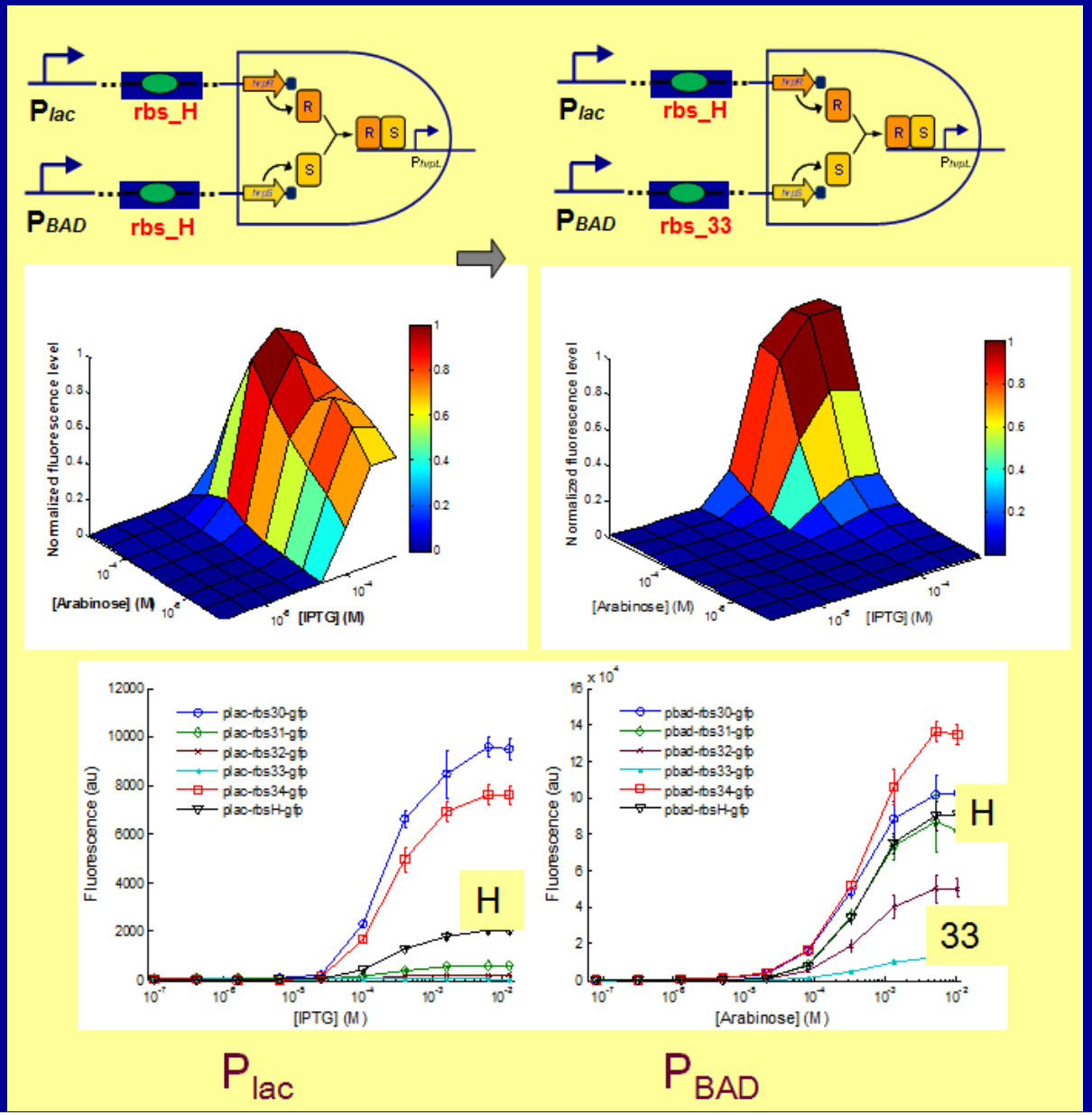






Ideal AND Gate

AND gate characterisation using P_{lac} and P_{BAD} as the 2 driving inputs



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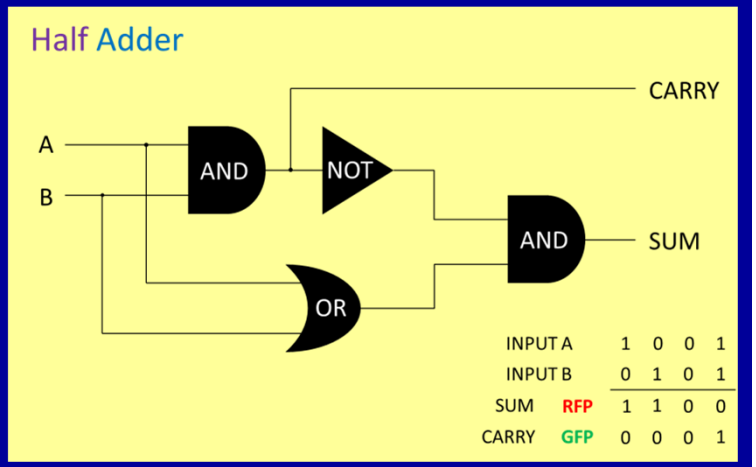
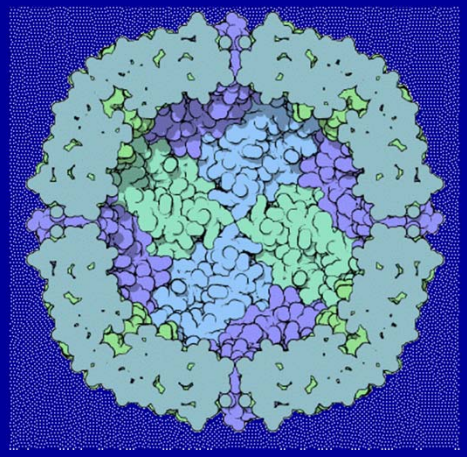
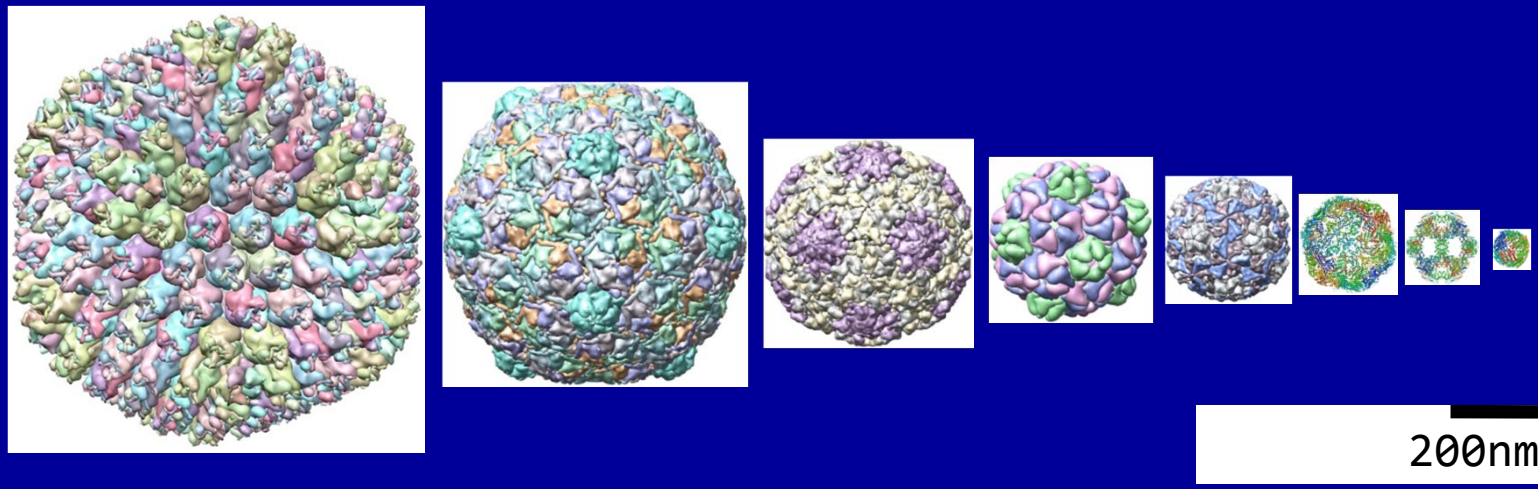


The Vision

Biosensors that ‘permanently’ reside in the body to detect particular types of abnormally; for example arterial disease and cancer

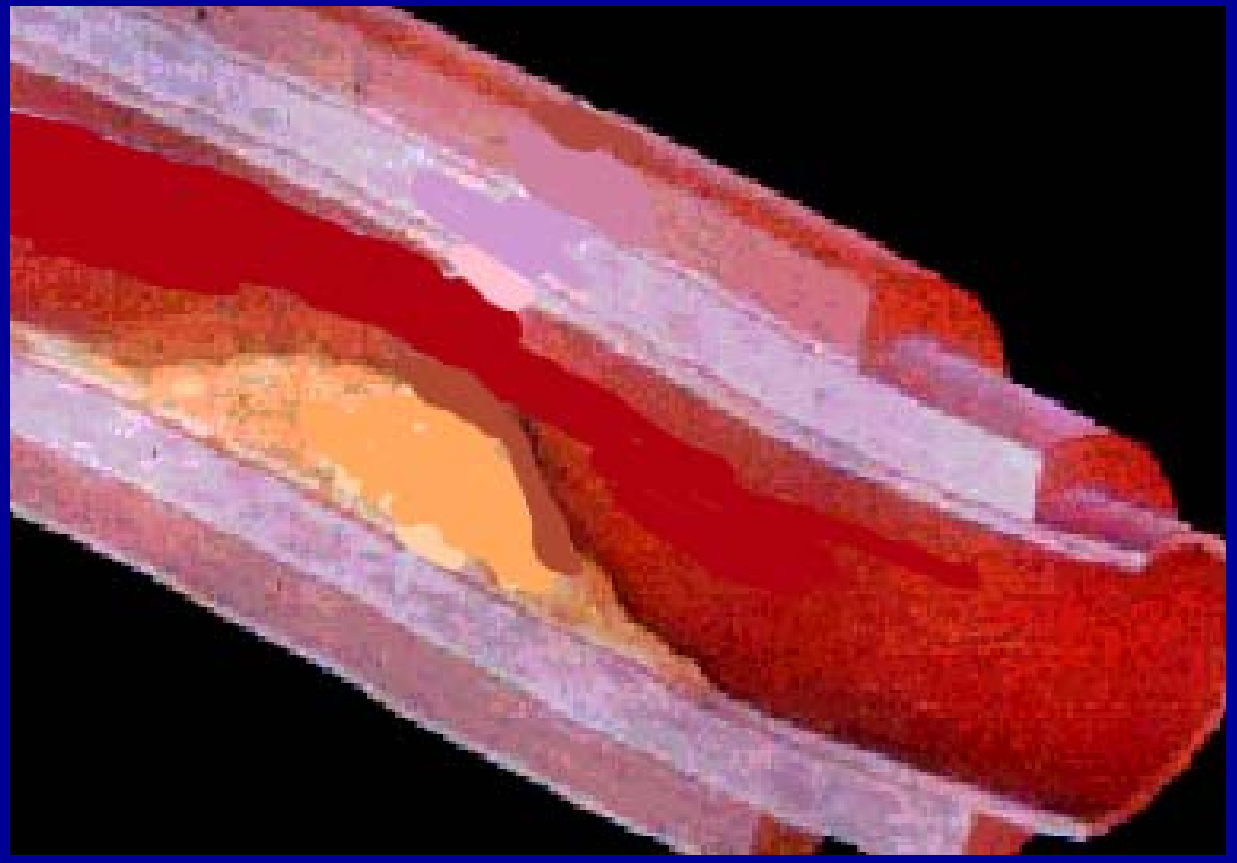


Biological Nanodevices

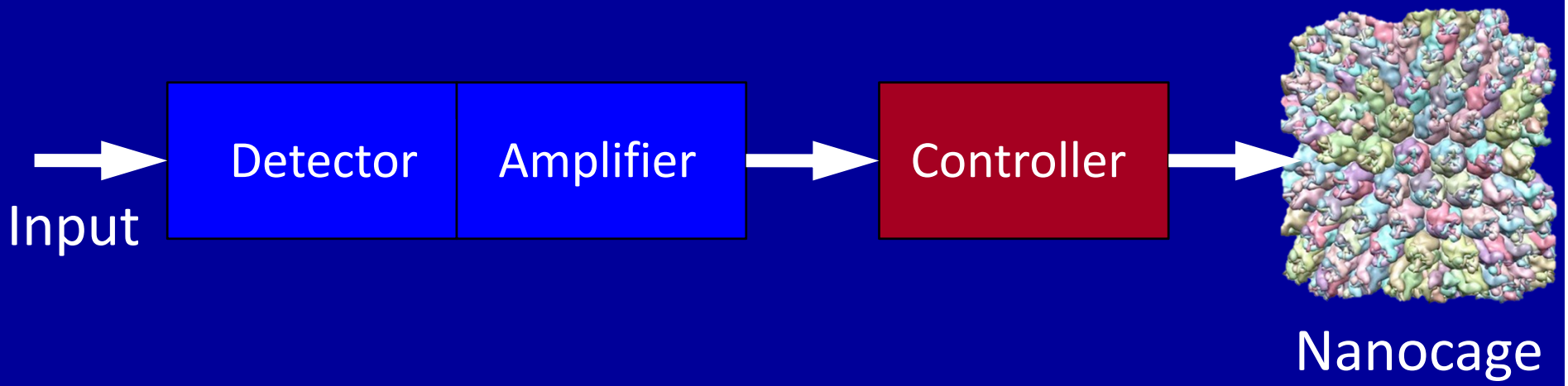


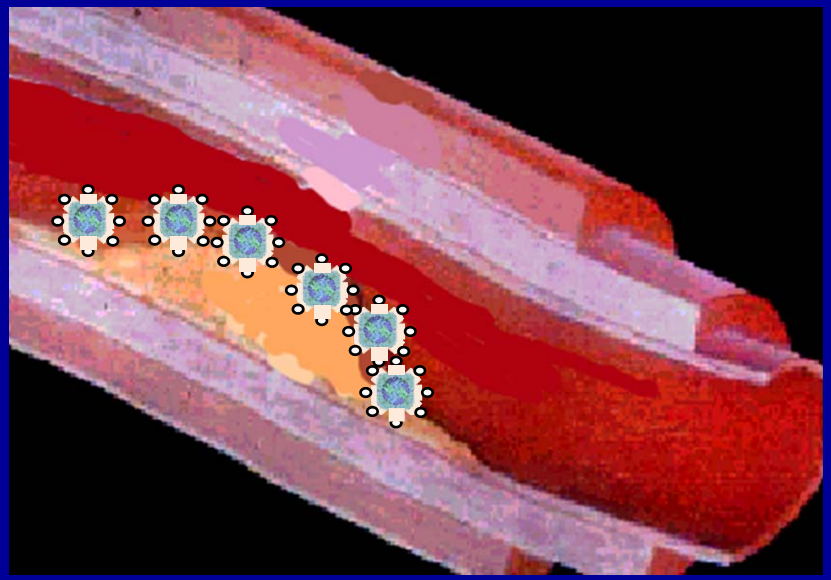
Protein nanocages are naturally occurring spherical proteins that can be SYSTEMATICALLY ENGINEERED to fight disease at the cellular level

Arterial Disease – a major killer in Western Society

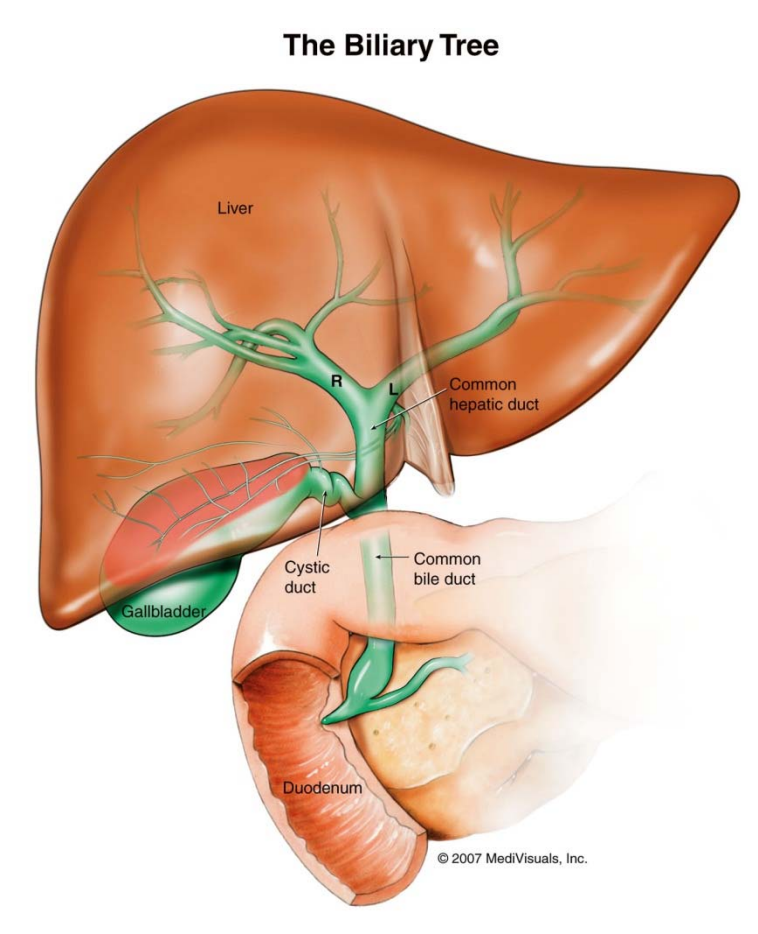


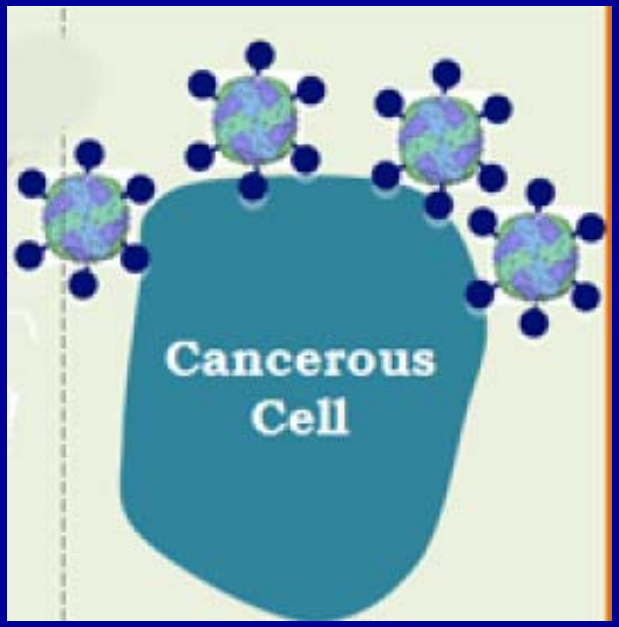
Biosensor/Drug Delivery System

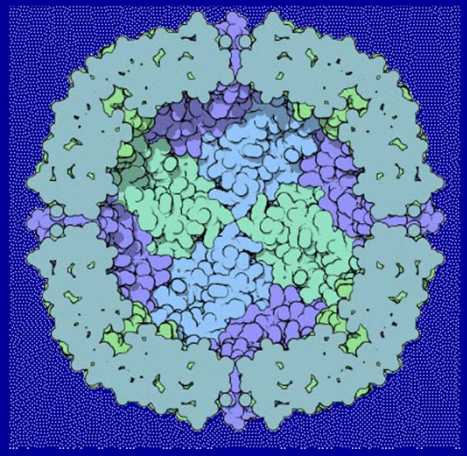




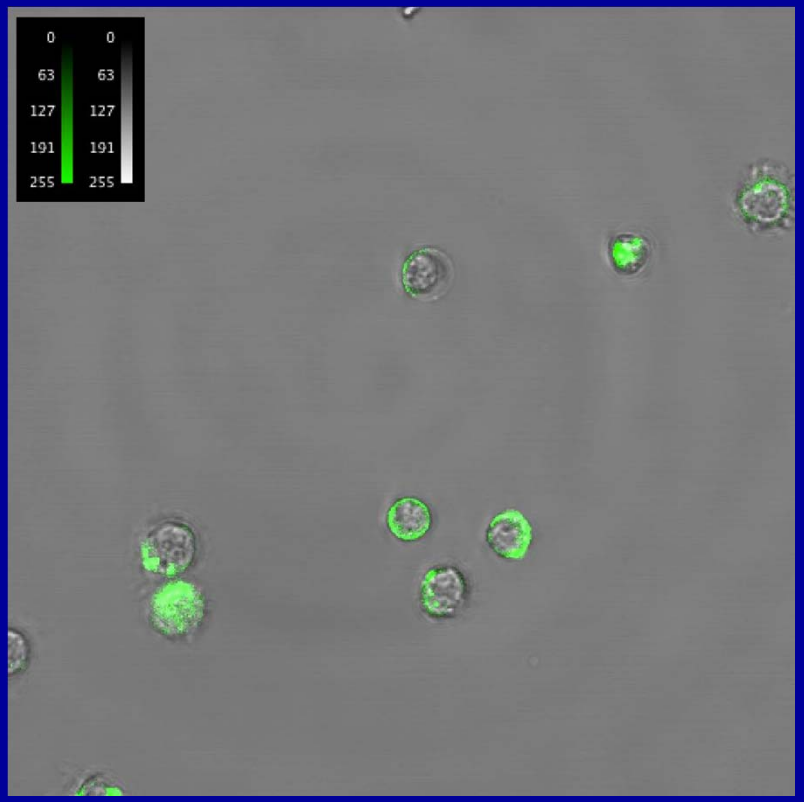
Synthetic Biology Device for the Early Detection of Cholangiocarcinoma



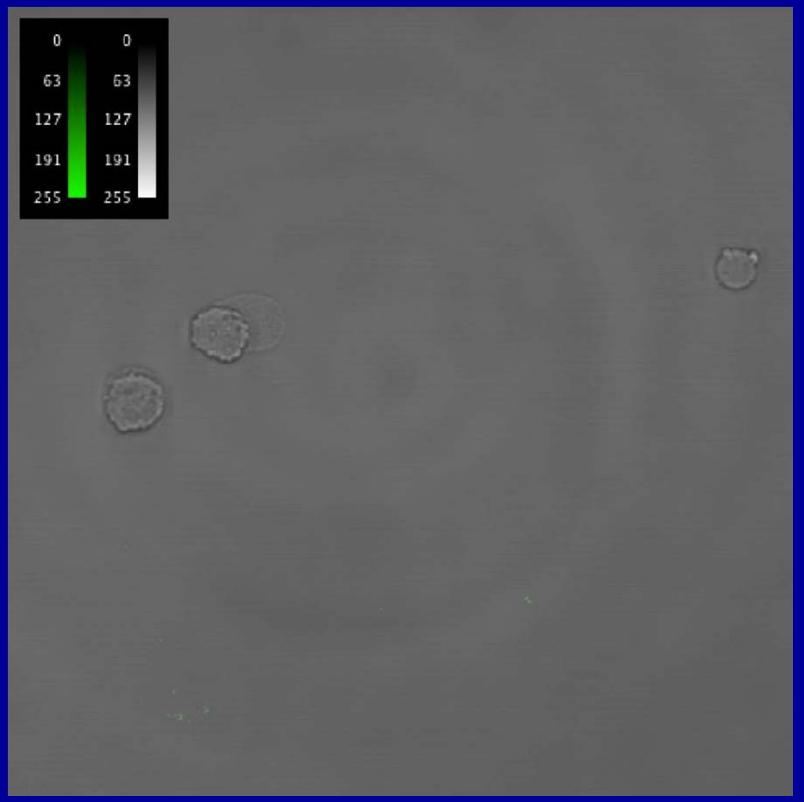




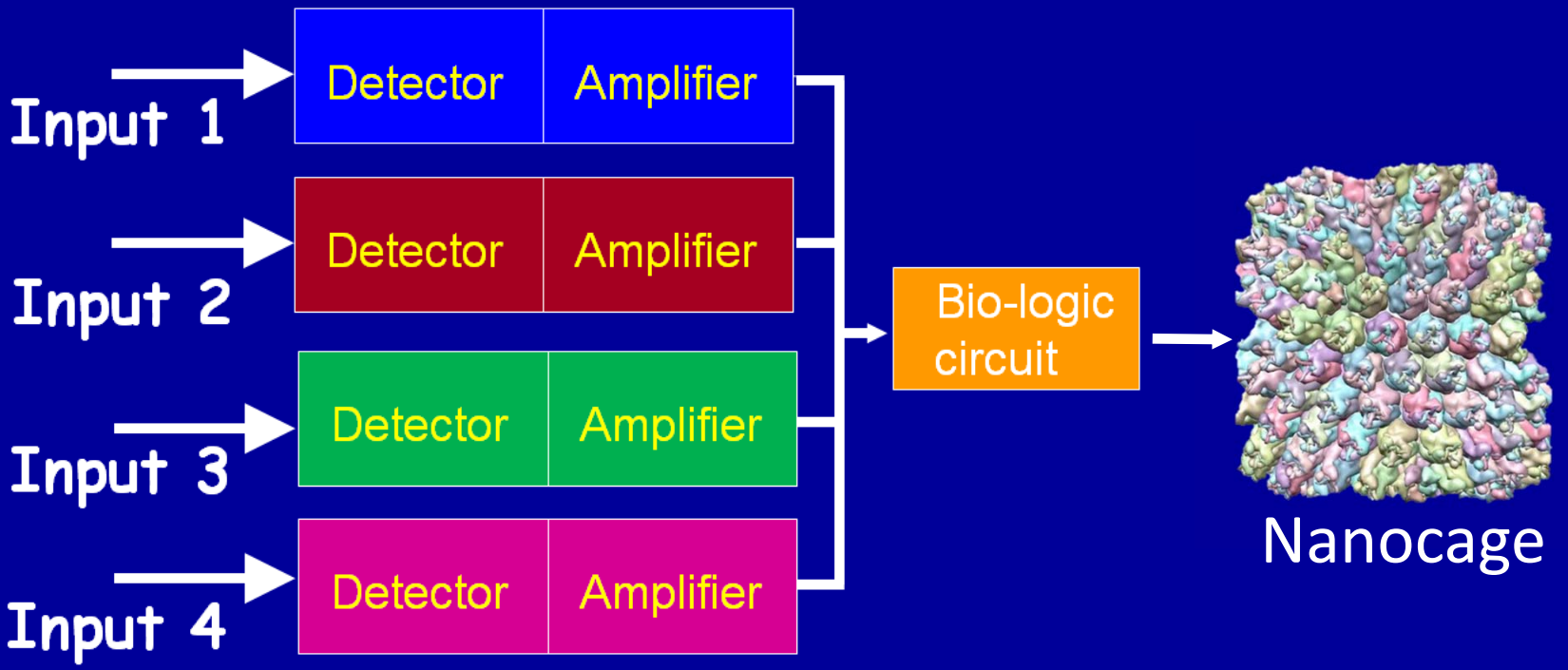
Cells + Targeted Nanocages



Cells + Untargeted Nanocages



Multi-channel Biosensor/Drug Delivery System for specific malignant cell types



SynbiCITE
SYNTHETIC BIOLOGY INNOVATION COMMERCIAL AND INDUSTRIAL TRANSLATION ENGINE

Imperial College London

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Developing new synthetic biology products and processes

Prof. Richard Kitney describes why Synthetic Biology is one of the 8 Great Technologies for our time

read more >

KEY FACTS & FIGURES

20%

Of all medicines are now estimated to be biopharmaceuticals (derived from using biotechnology)

SynbiCITE

has been formed by a collaboration between industry, academia and government organisations

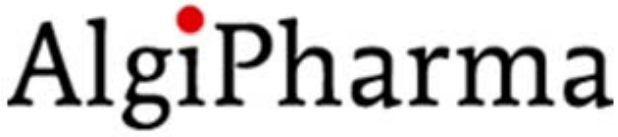
Synthetic Biology

aims to design and engineer biologically based parts, novel devices and systems as well as redesigning existing, natural biological systems

Thirty Three

companies are currently involved in SynbiCITE

Start-up & SME Partners



The

SynBICITE

SYNTHETIC BIOLOGY INNOVATION
COMMERCIAL AND INDUSTRIAL TRANSLATION ENGINE

Foundry

Design Objectives

- Industrial Facing
- Not Integrated
- Modular
- Scalable

The

SYNBICITE

SYNTHETIC BIOLOGY INNOVATION COMMERCIAL AND INDUSTRIAL TRANSLATION ENGINE

Foundry

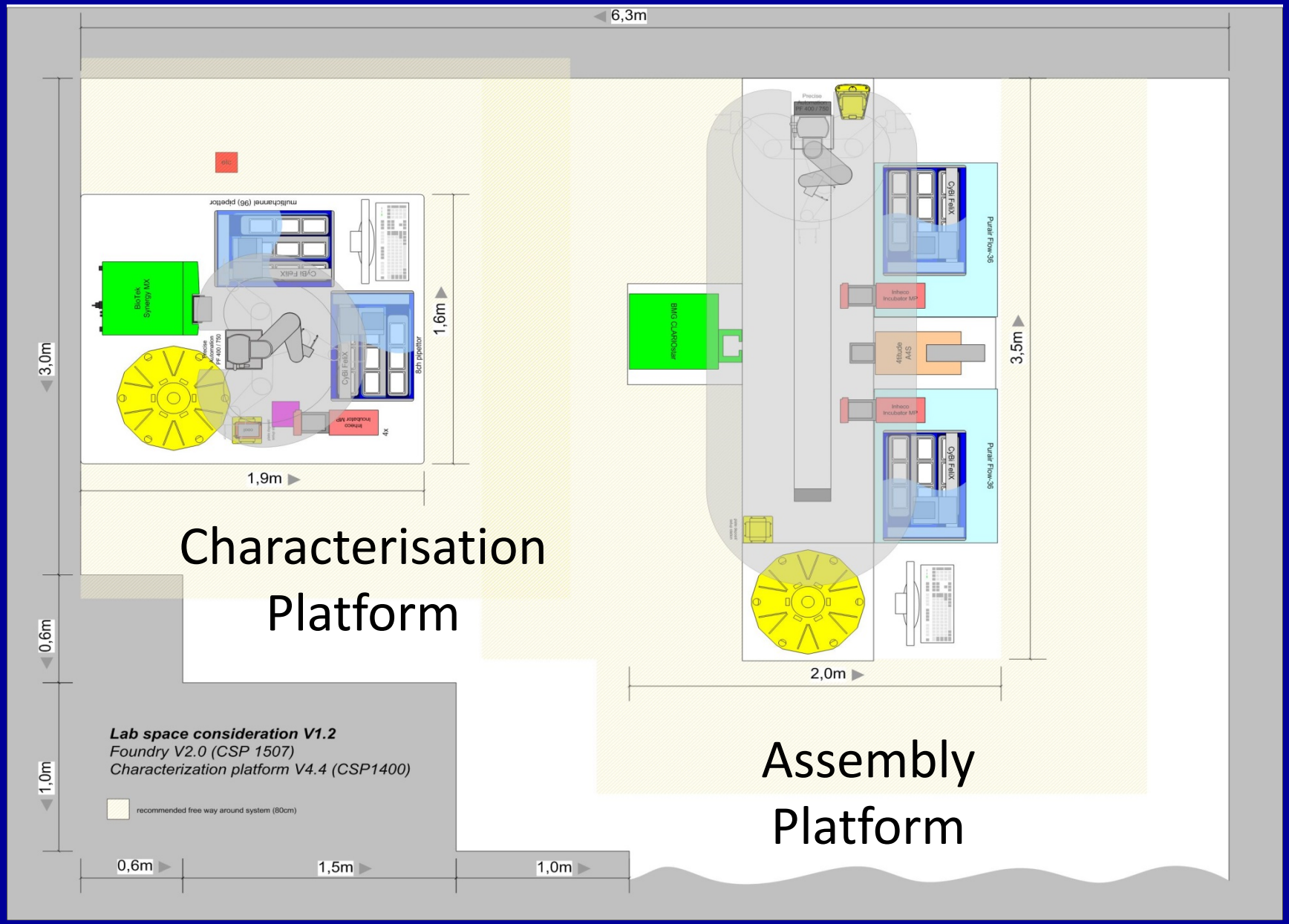
Integrated SynBio Technology Platform

- Computational Modelling
- Structure-based Modelling
- Assembly Design

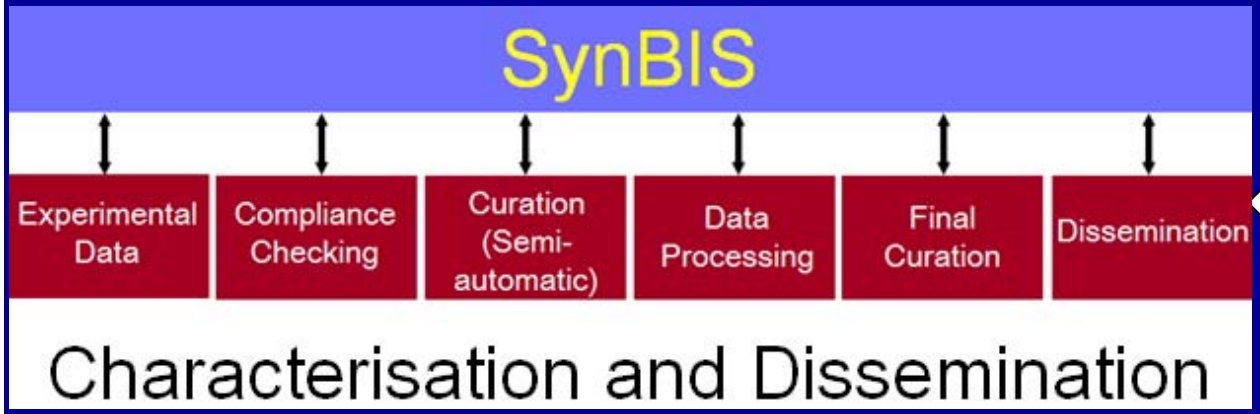
- DNA Synthesis
- DNA Sequencing
- DNA Optimisation
- Gene Assembly

- Characterisation
- Testing & Trials

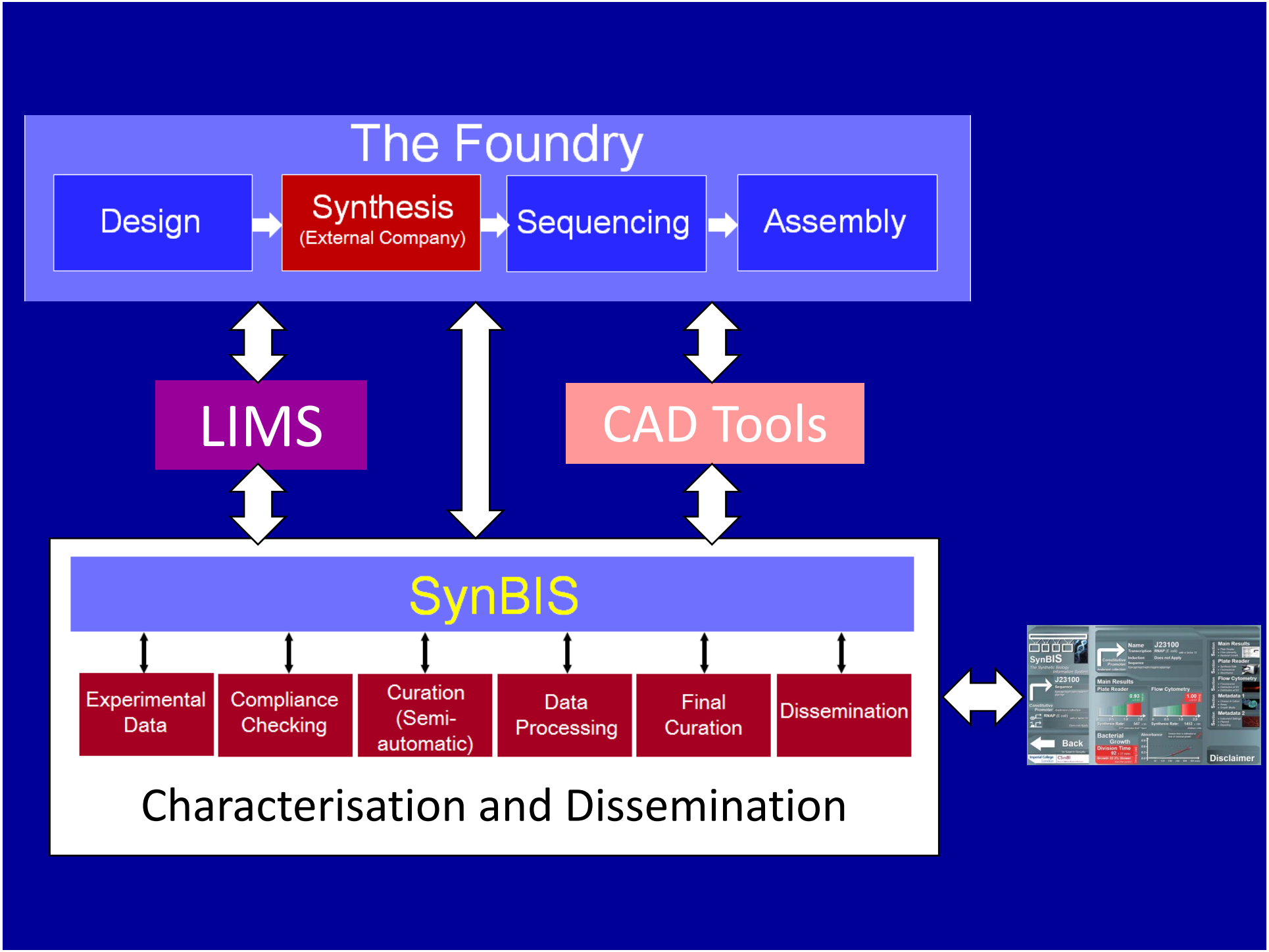
- Prototype/POC
- Pilot/Demo
- Scale-up
- Production model
- Commercialisation & Production


6,3m
3,0m
0,6m
1,0m
1,6m
1,9m
BioTek Synergy MX
CyBi FelX
8ch pipettor
multichannel (96) pipettor
Characterisation Platform
BMG CLARIOstar
Purair Flow-36
Inheco Incubator MP
4titude AMS
3,5m
2,0m
Assembly Platform
Lab space consideration V1.2
Foundry V2.0 (CSP 1507)
Characterization platform V4.4 (CSP1400)
recommended free way around system (80cm)
0,6m
1,5m
1,0m

Characterisation Platform


SynBIS
Experimental Data
Compliance Checking
Curation (Semi-automatic)
Data Processing
Final Curation
Dissemination
Characterisation and Dissemination


SynBIS
The Synthetic Biology Information System
J23100
Sequence
Constitutive Promoter
Anderson collection
RNAP (E coli)
Does not Apply
Back
Name
Transcription
Induction
Main Results
Plate Reader
Flow Cytometry
Synthesis Rate:
Bacterial Growth
Division Time
Growth 32.3% Slower
Absorbance
Metadata 1
Metadata 2
Disclaimer


The Foundry
Design
Synthesis
(External Company)
Sequencing
Assembly
LIMS
CAD Tools
SynBIS
Experimental Data
Compliance Checking
Curation (Semi-automatic)
Data Processing
Final Curation
Dissemination
Characterisation and Dissemination

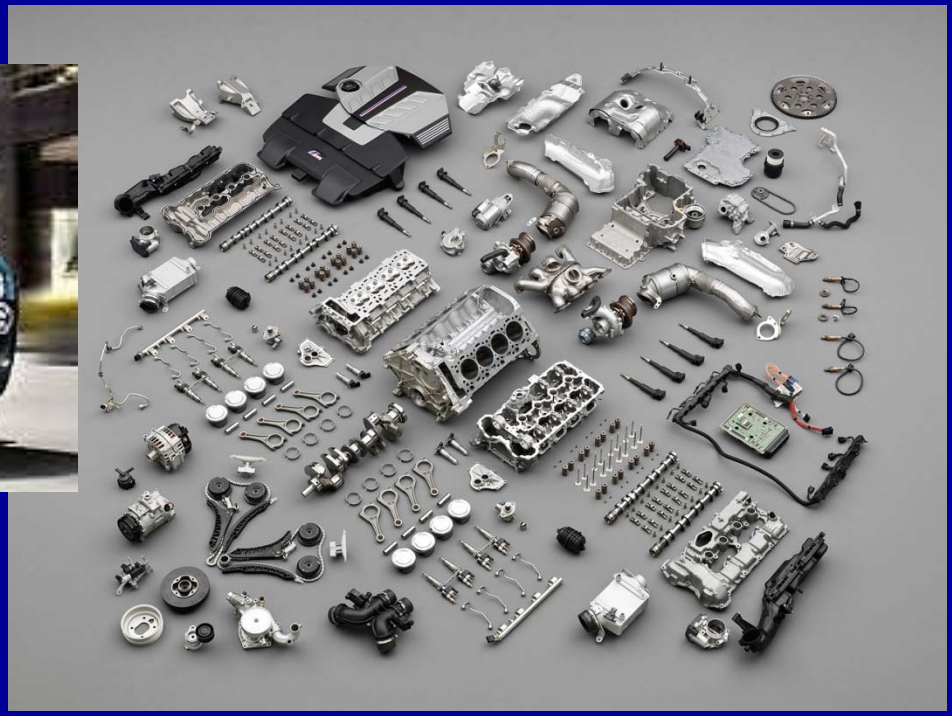
Translational

The Pipeline

The Pipeline - Added Value

Foundational

Some comments on the future



Suppliers to the new BMW 3 series

Automotive News Europe

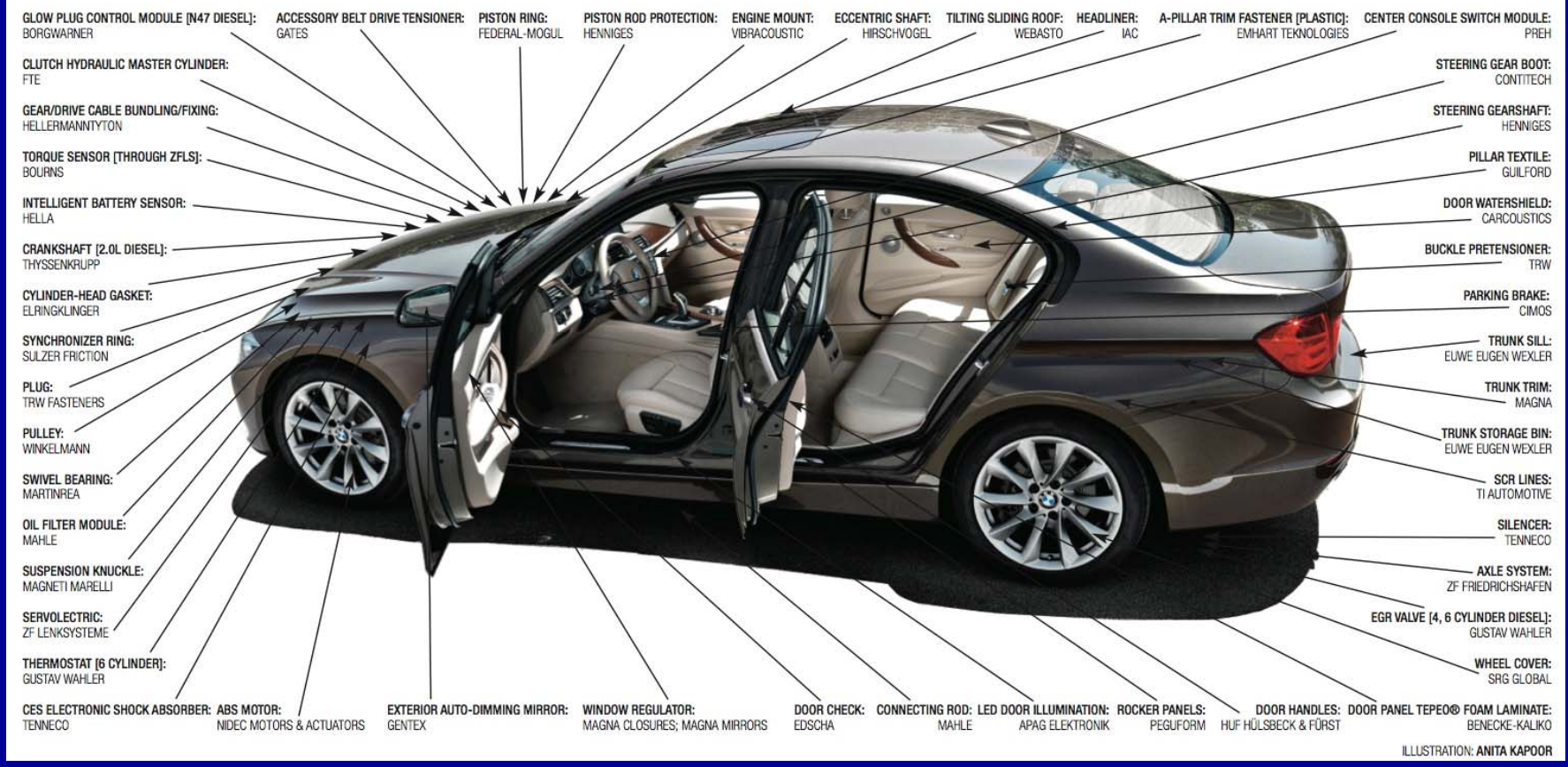
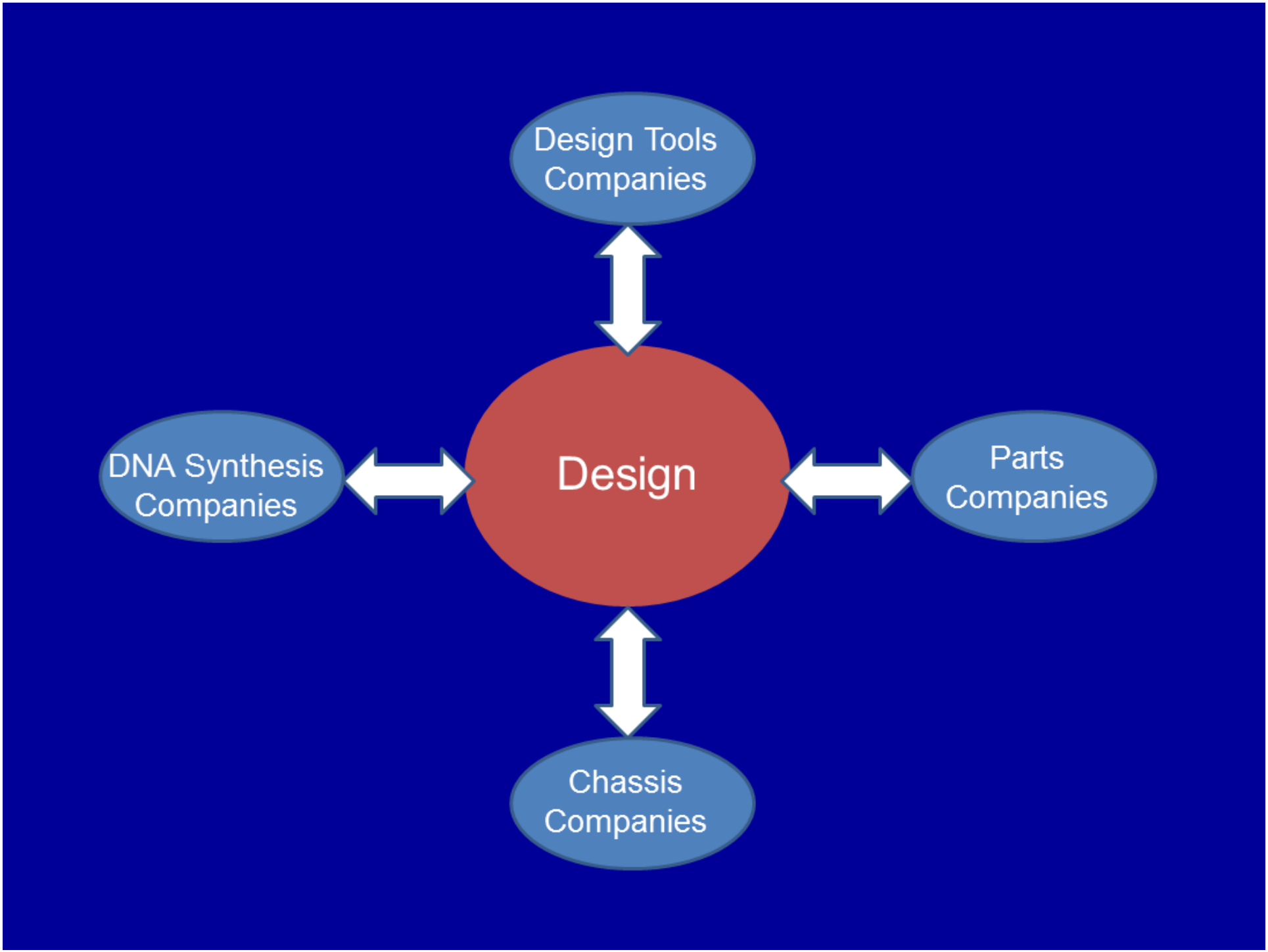


ILLUSTRATION: **ANITA KAPOOR**


Design Tools Companies
DNA Synthesis Companies
Design
Parts Companies
Chassis Companies

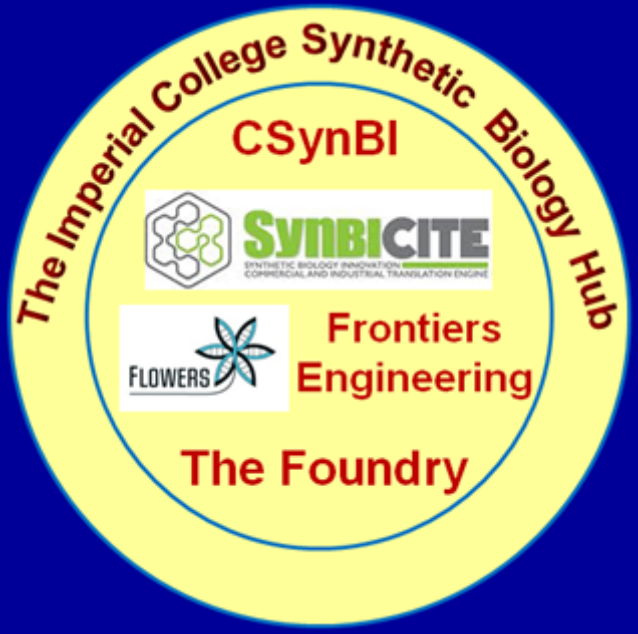
Acknowledgements

Paul Freemont

Steve Chambers
John Collins

ST-Flow

The Hub Funding Agencies



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