Prospects for Applications
based on
Synthetic Biology

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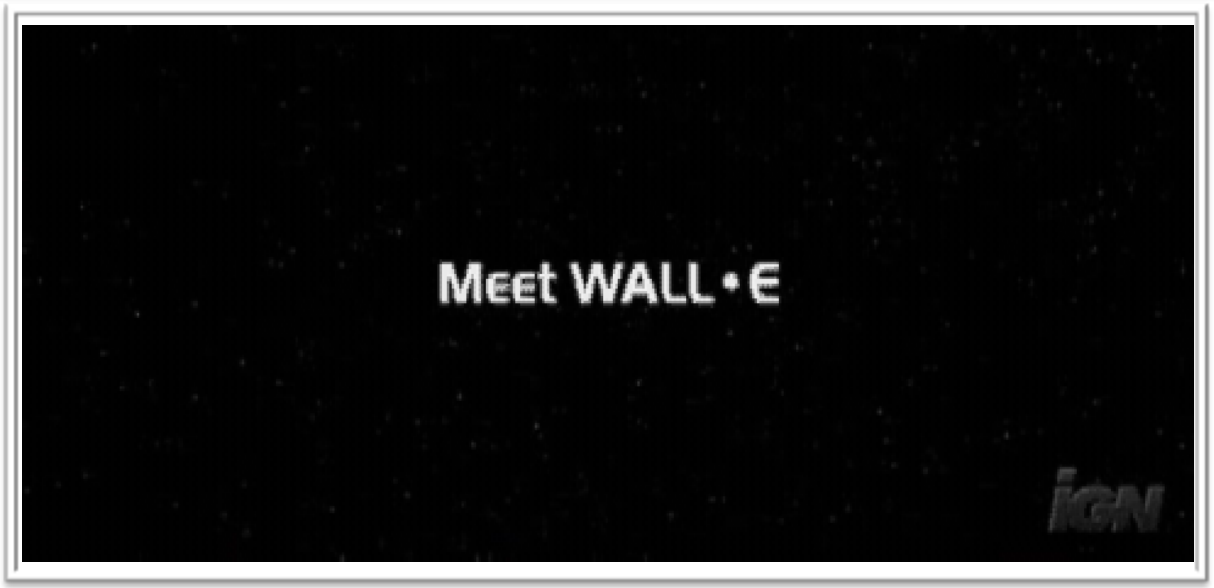
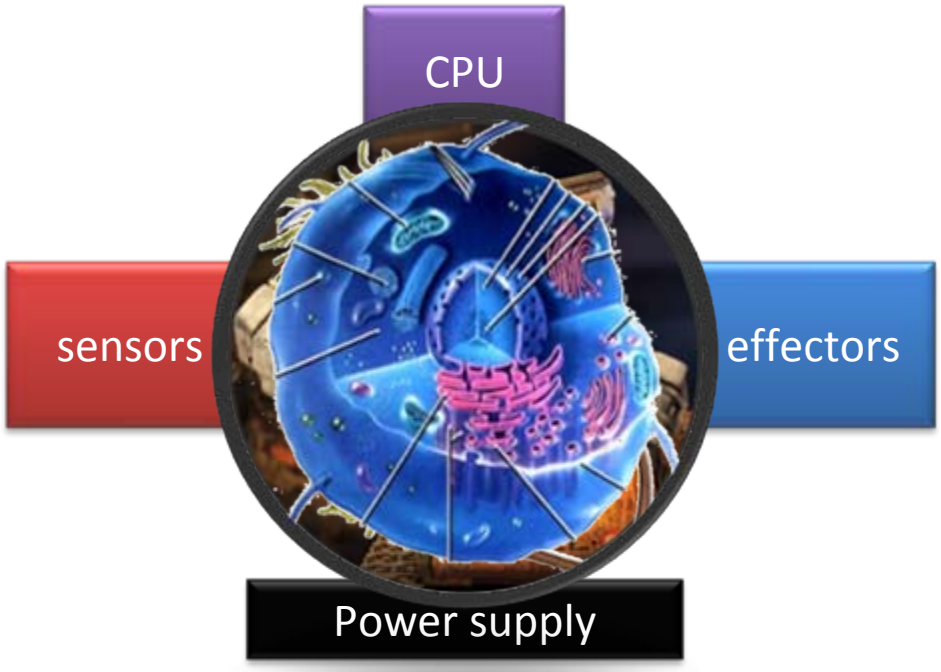
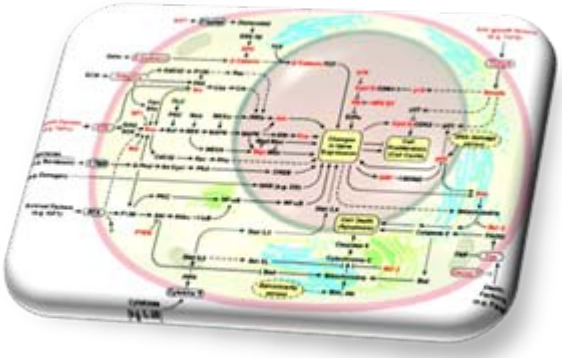
CSAIL

Synthetic biology analogy: bio-bots



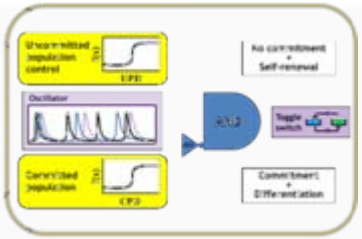


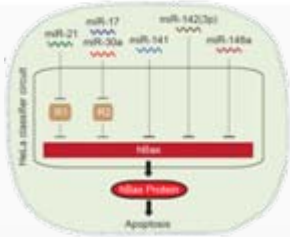
From idea to implementation



Hierarchical organization

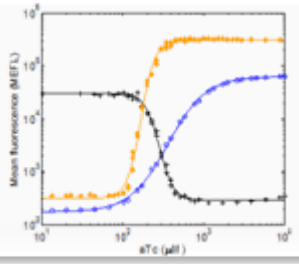
Applications

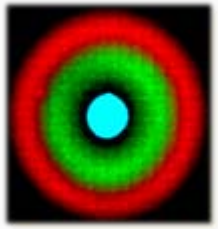




System integration

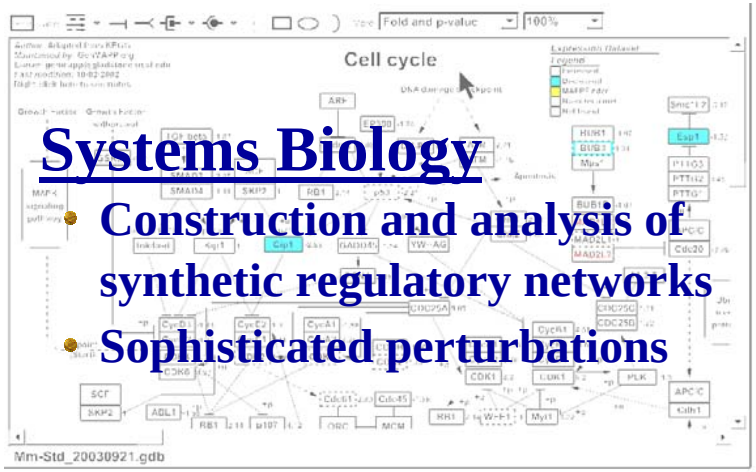
Modules





Genetic parts

Potential applications

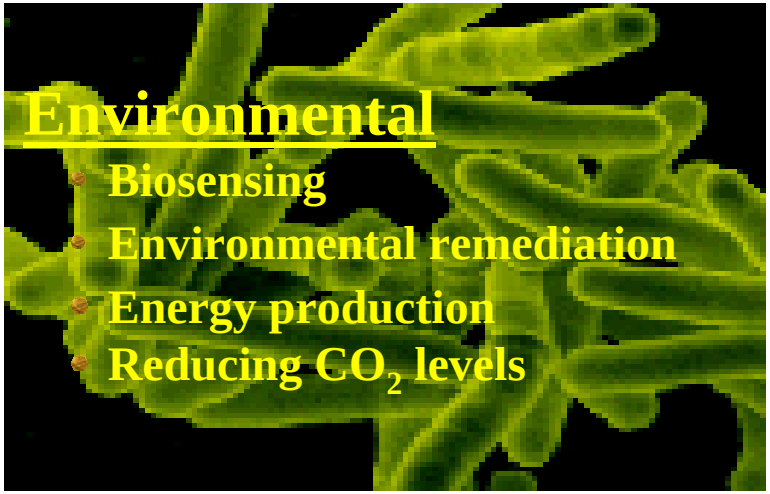


Systems Biology

- Construction and analysis of synthetic regulatory networks
- Sophisticated perturbations

Biomolecular synthesis and fabrication

- Optimized drug synthesis
- Molecular scale device fabrication



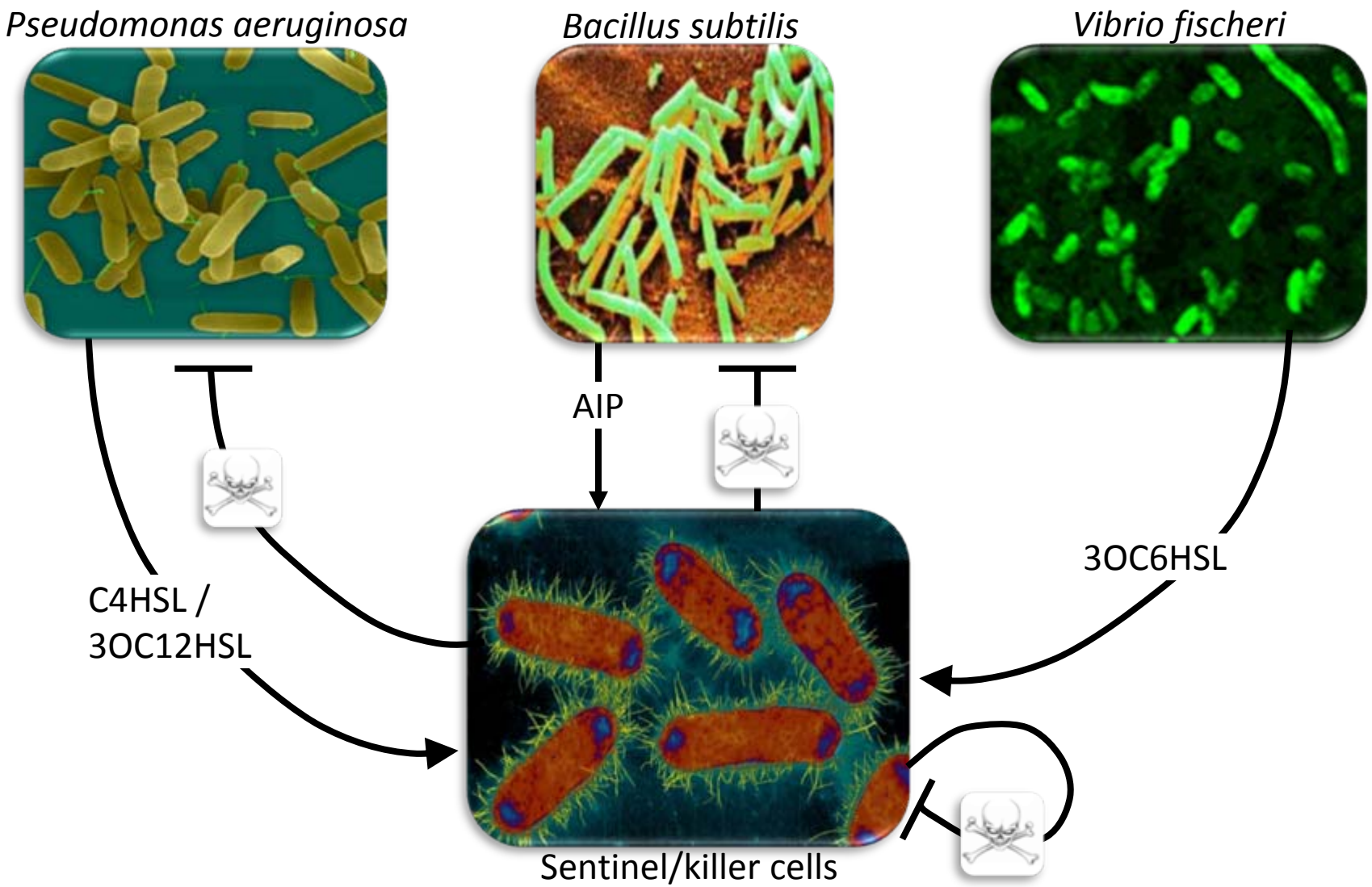
Environmental

- Biosensing
- Environmental remediation
- Energy production
- Reducing CO_2 levels

Biomedical

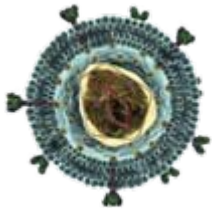
- Artificial immune system
- Cancer therapy
- Tissue regeneration
- Diabetes

Programmed pathogen sense-and-destroy



Cancer therapy: decipher the transcriptome

- **Problem:** Most existing cancer therapies are not specific enough and result in significant collateral damage.
- **Goal:** Develop an adaptable, effective and highly specific cancer therapy that evaluates internal cell state using combinatorial logic
- **Approach:**
  (1) a "smart virus" infects a cell,
  (2) computes whether the transcriptome is indicative of cancer, and if so,
  (3) decides to destroy the cell
- **Main novelty:** A therapeutic agent that carries an RNAi based logic circuit that can respond to a target gene expression profile
- **Note:** Also, non-clinical applications



http://content.hccfl.edu/facultyinfo/ckasper/humanreproduction.html

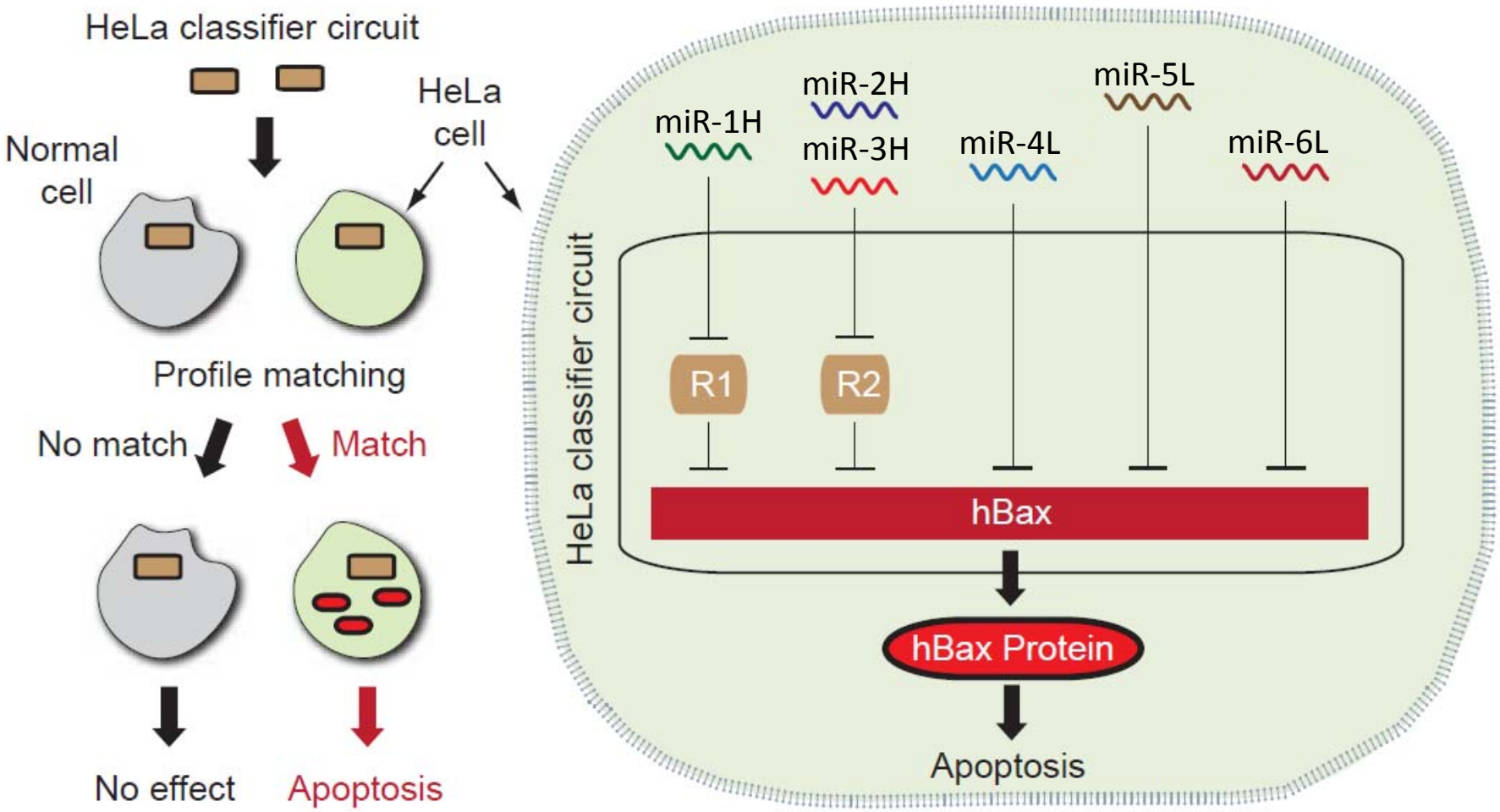
HeLa cell classifier

HeLa = miR-1H ∧ (miR-2H + miR-3H) ∧
¬miR-4L ∧ ¬miR-5L ∧ ¬miR-6L

↑ miR-1H
↑ miR-2H + miR-3H
↓ miR-4L
↓ miR-5L
↓ miR-6L

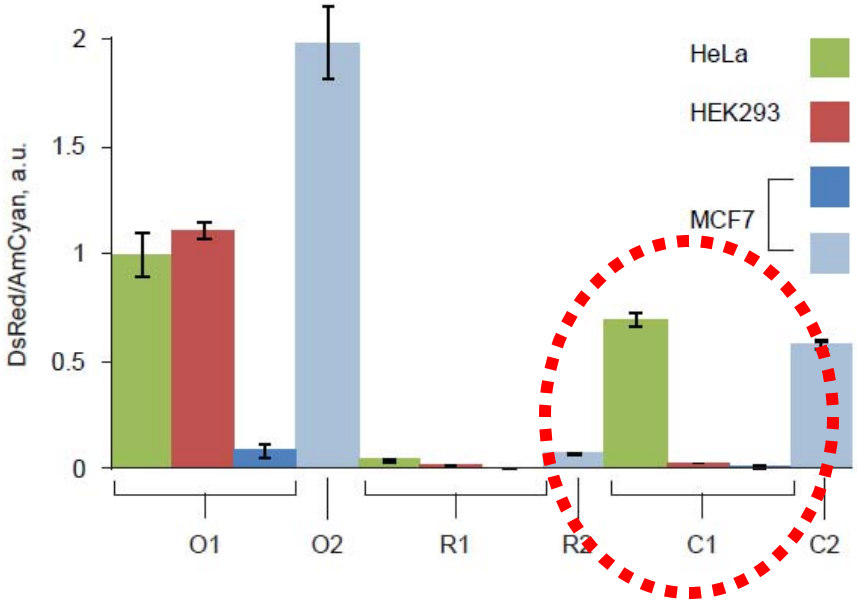
A ∧ B = A and B
¬A = NOT(A)

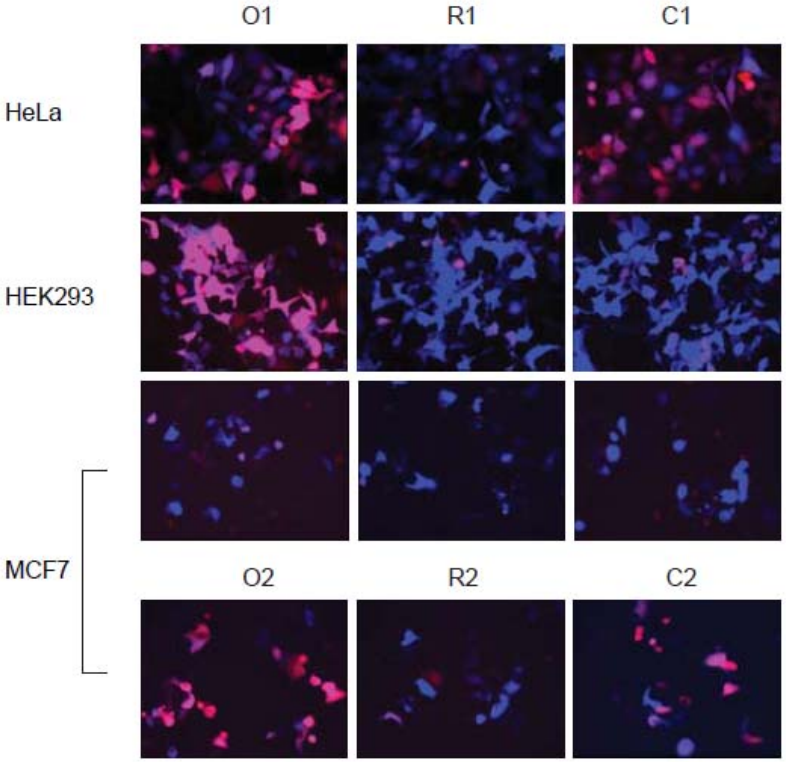
Using microRNA profiles (with Benenson lab)



High expression in HeLa: miR-1H, miR-2H, miR-3H
Low expression in HeLa: miR-4L, miR-5L, miR-6L

Fluorescence output in 3 cell lines

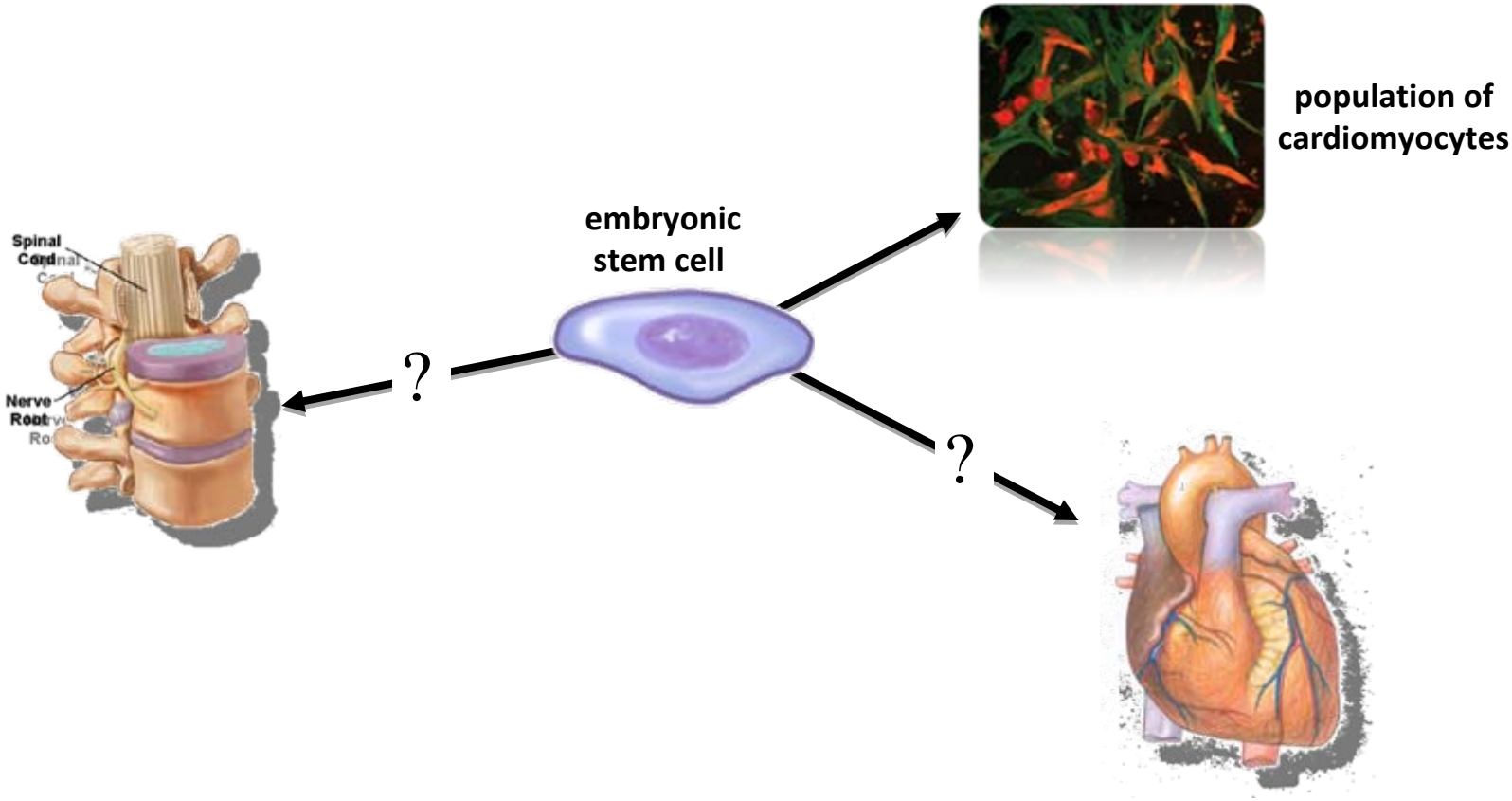




Experimental legend

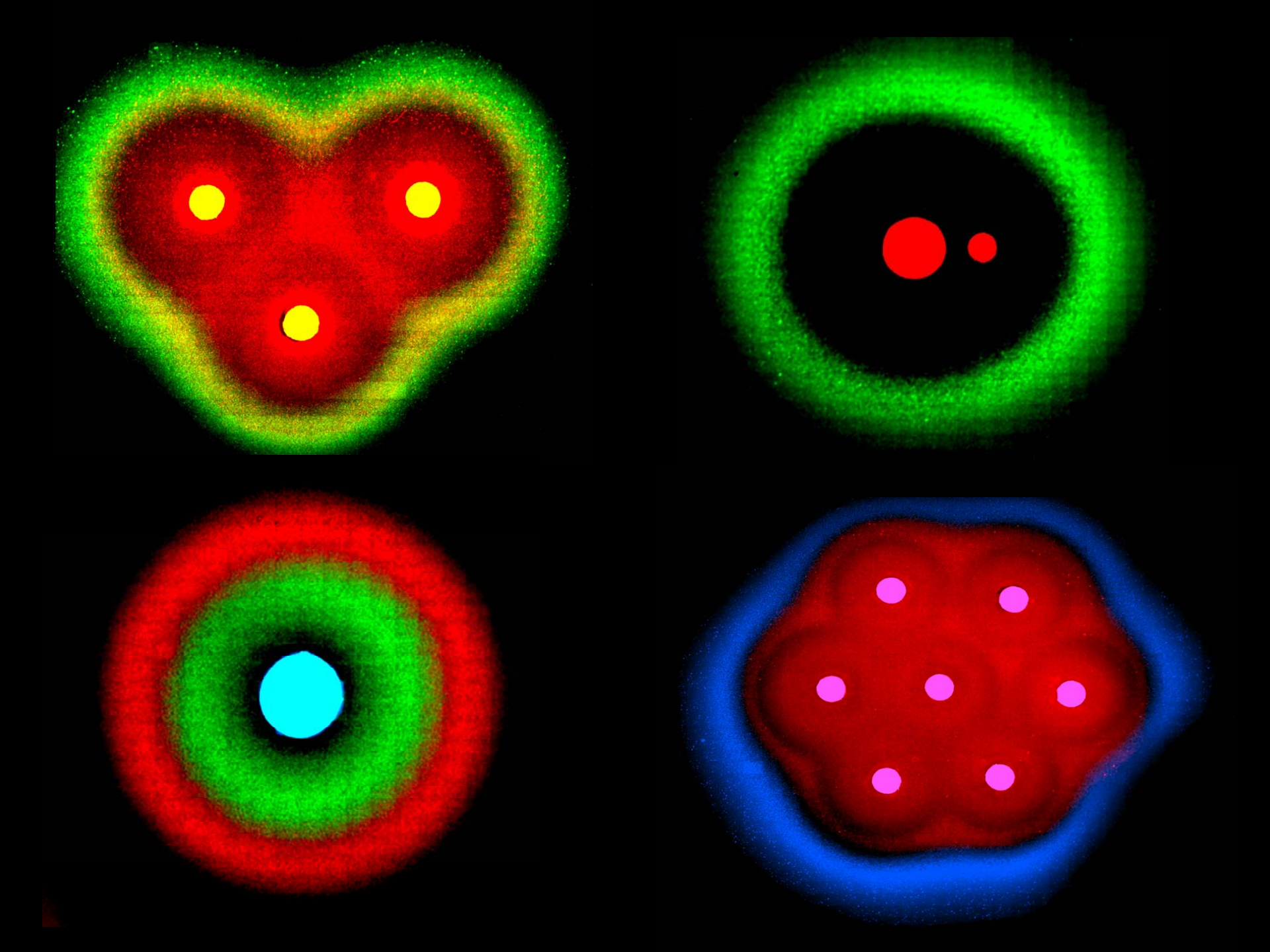
- O1: Just low targets
- O2: No targets
- R1: Low targets + transcriptional repression
- R2: Just transcriptional repression
- C1: Full circuit
- C2: Just high targets

Applying synthetic biology to stem cell research

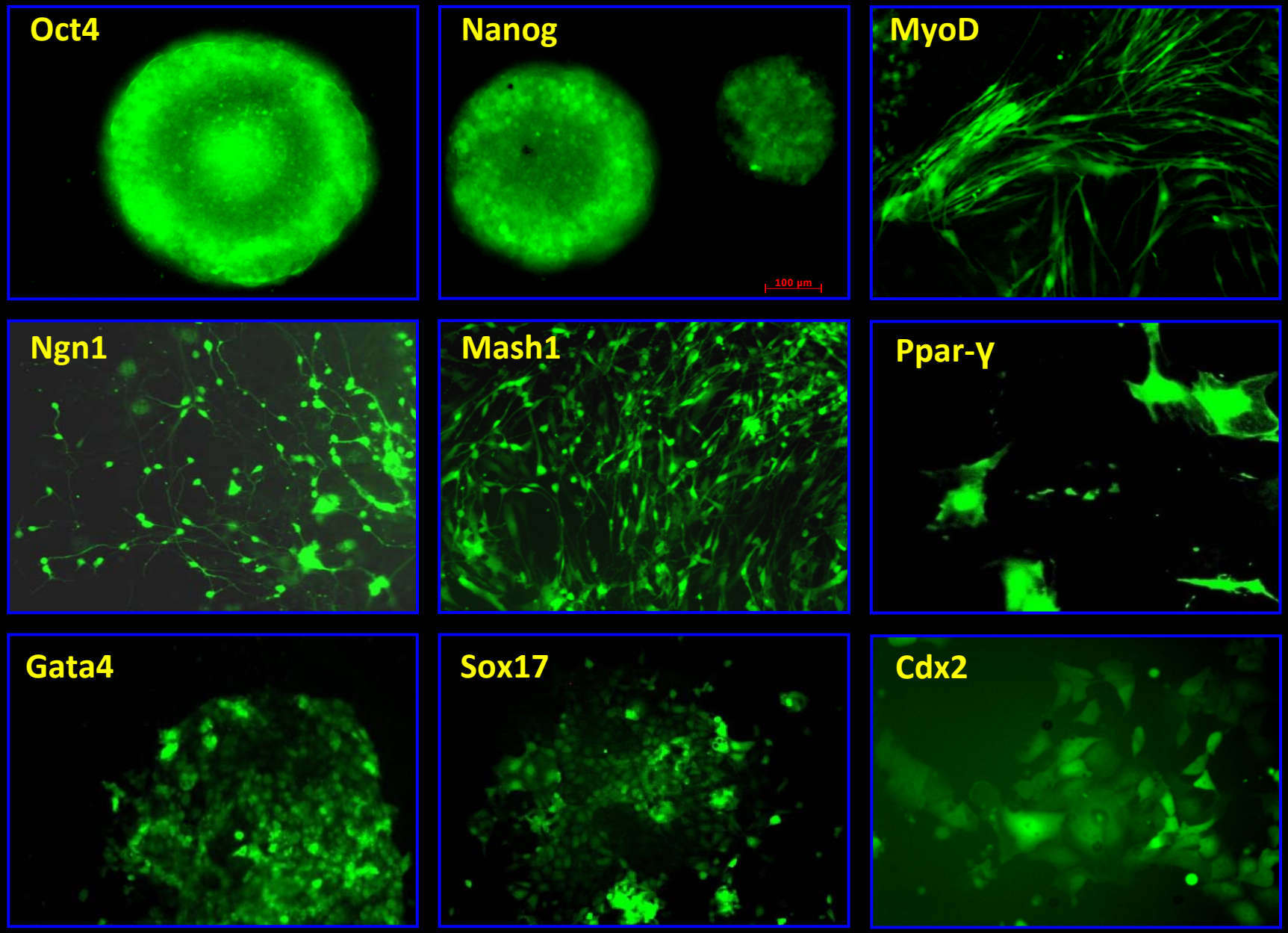


- Fundamental question in tissue engineering:

  Can we <u>create</u> and <u>maintain</u> large scale spatially defined functional tissues?

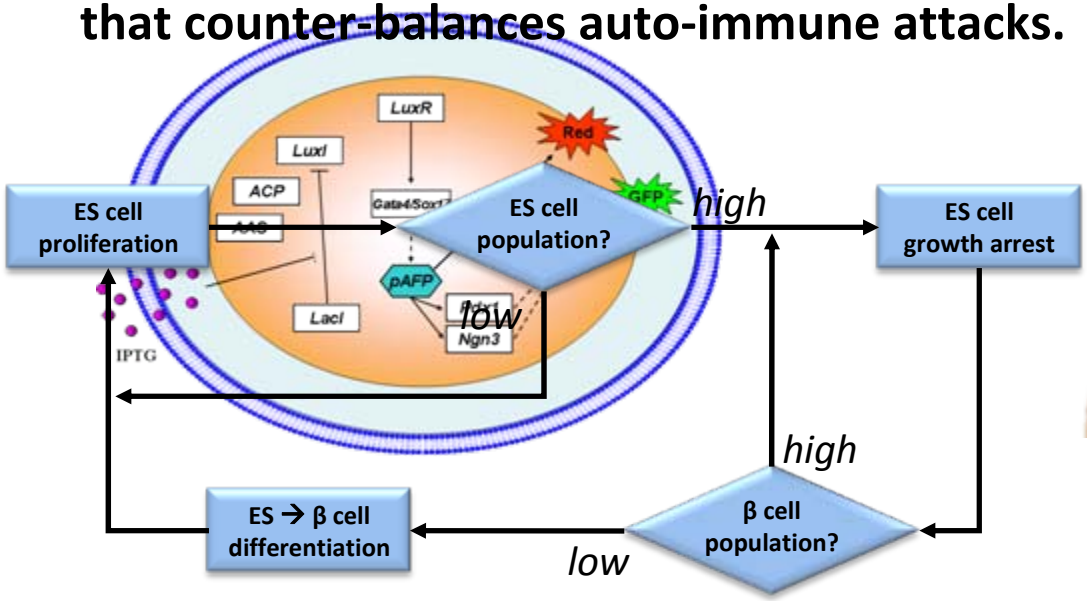


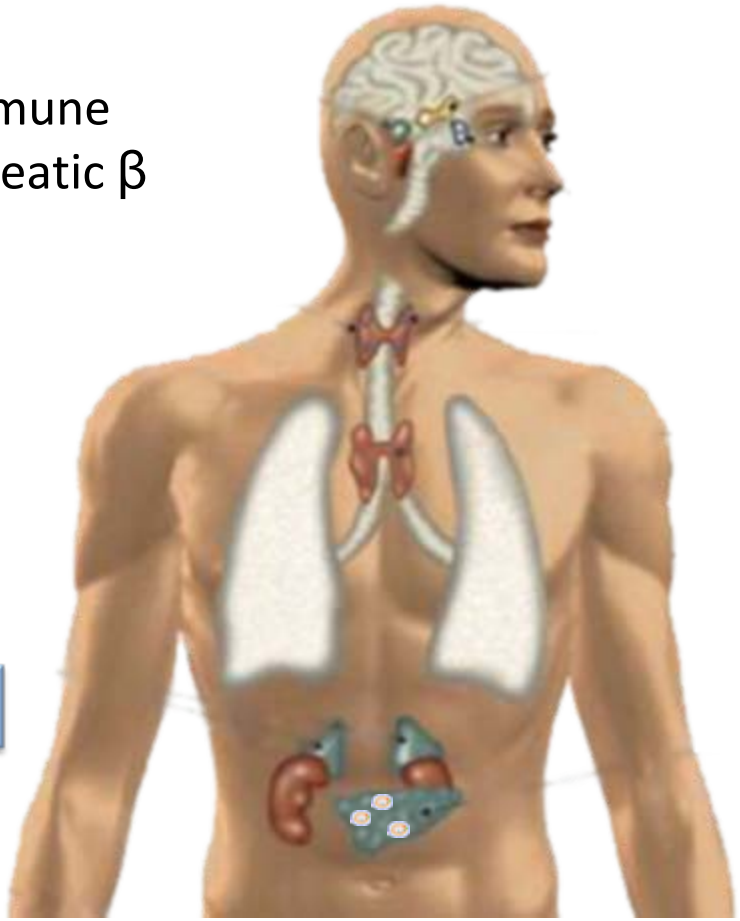
A library of cell fate regulation ‘parts’



Artificial tissue homeostasis for β cells

- 7.8% of the US population has diabetes
- In Diabetes Type I (10% of diabetics), auto-immune response (slowly) kills insulin-producing pancreatic β cells.
- **<u>Goal:</u>**
  Maintain population level of β cells using auto-regulated differentiation of ES cells that counter-balances auto-immune attacks.





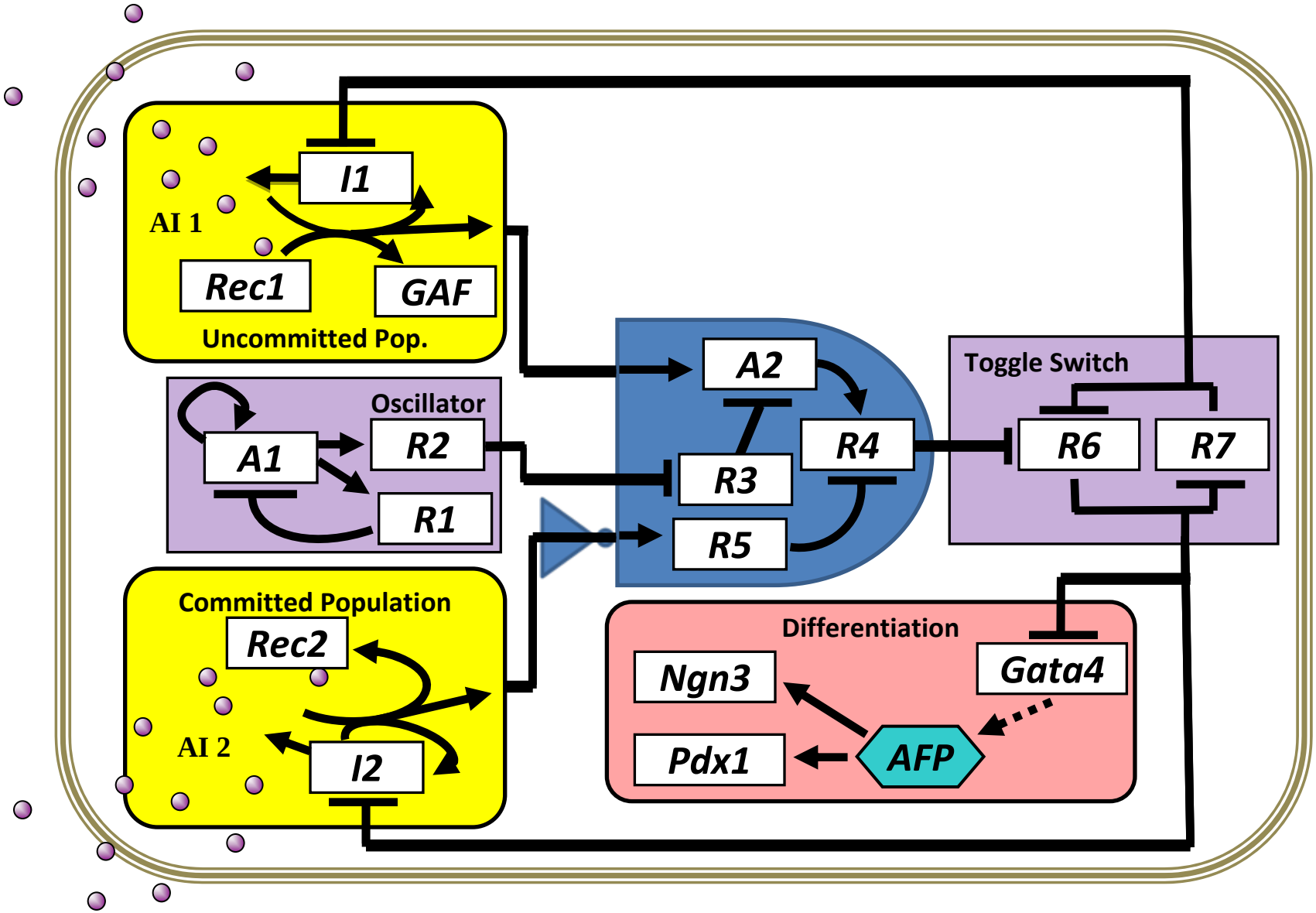
Complex system with 22 components

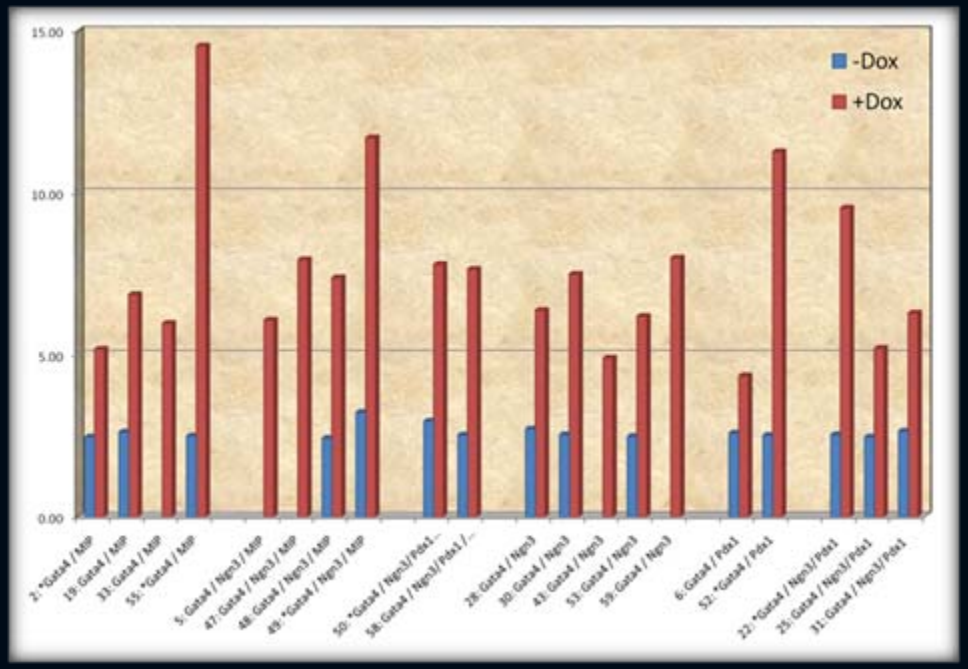
<u>Design with 'known' modules!</u>

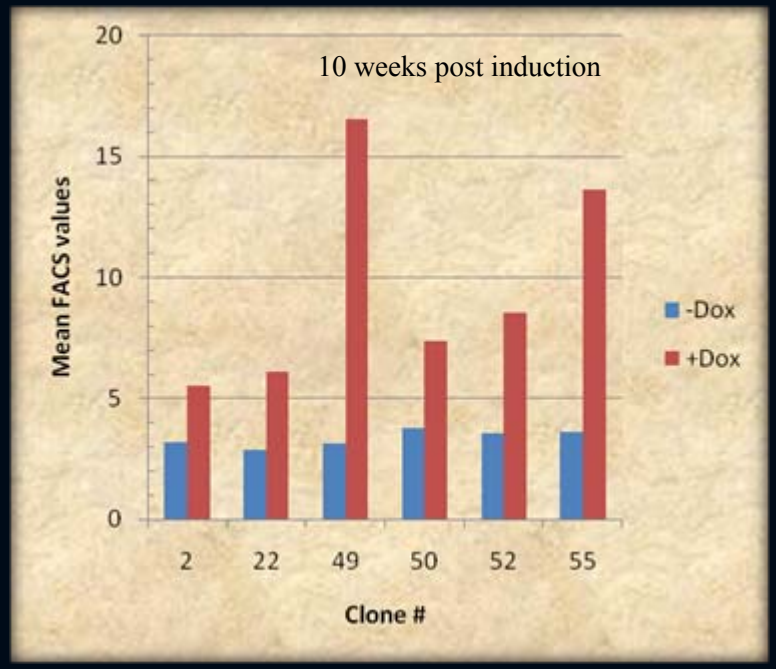
Bio-program: encoding system function

```
Module: population_control()
{
 if (state == uncommitted)
   send(AHL)
 if ((state == uncommitted) &&
   (Tat > thresh_c)          &&
   (AHL > thresh_uc))
   growth_arrest()
}

Module: run_oscillator()
{
 if ((state == uncommitted) &&
    (Tat < thresh_c)         &&
    (oscillator > thresh_osc))
   state = committed
 if (state == committed)
   send(Tat)
}

Module: differentiate()
{
  input: DOX
  if (DOX)
    express(Endo-CFR)
  if (Endoderm)
    express(Islet-CFR)
  if (Islet)
    express(GFP)
}
```

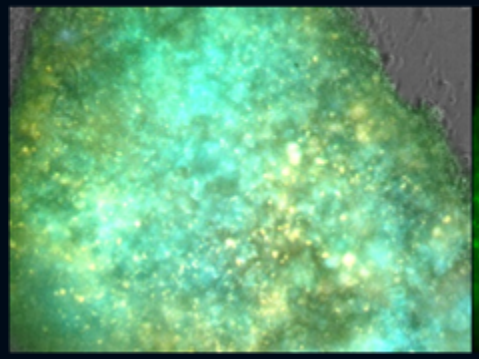
Modular gene network representation



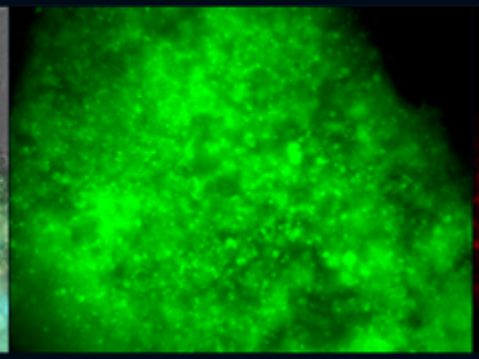




BF + all



MIP



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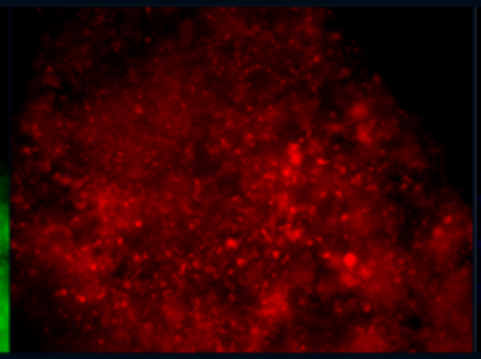
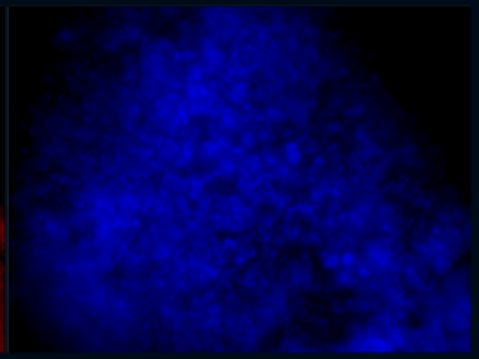
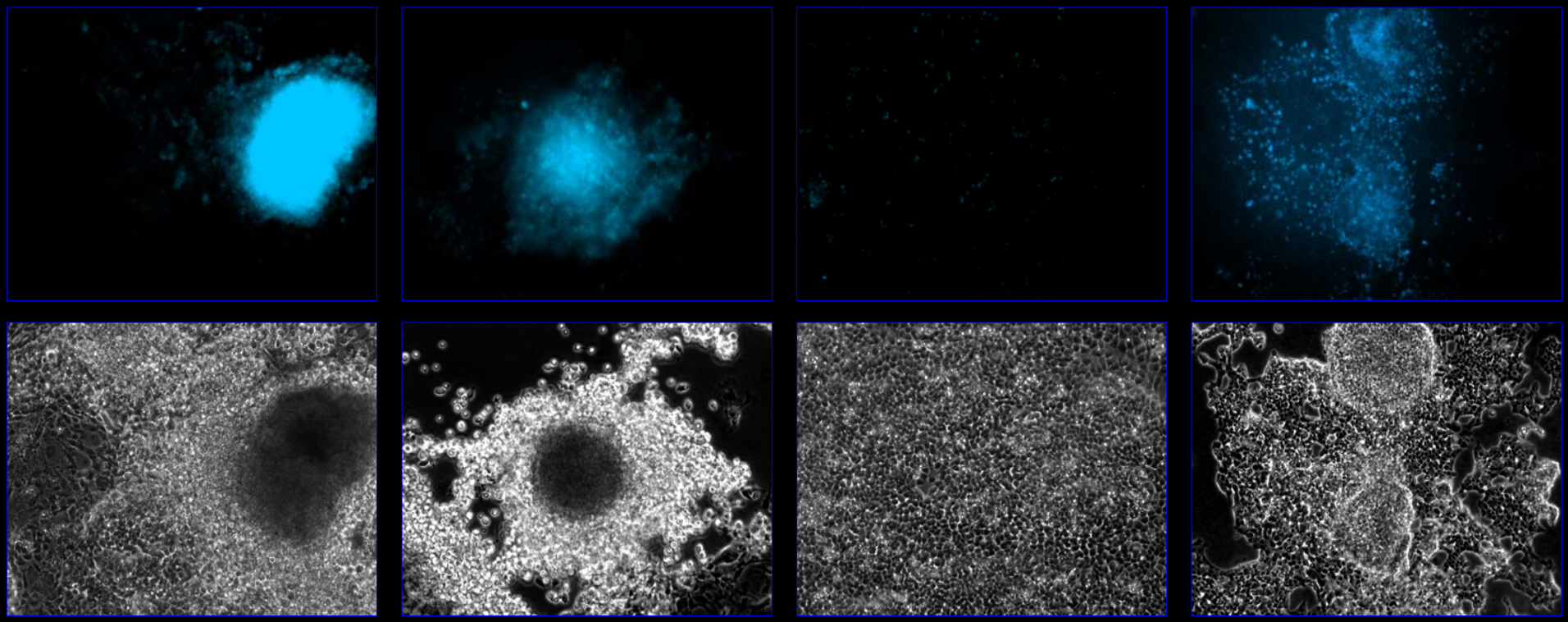


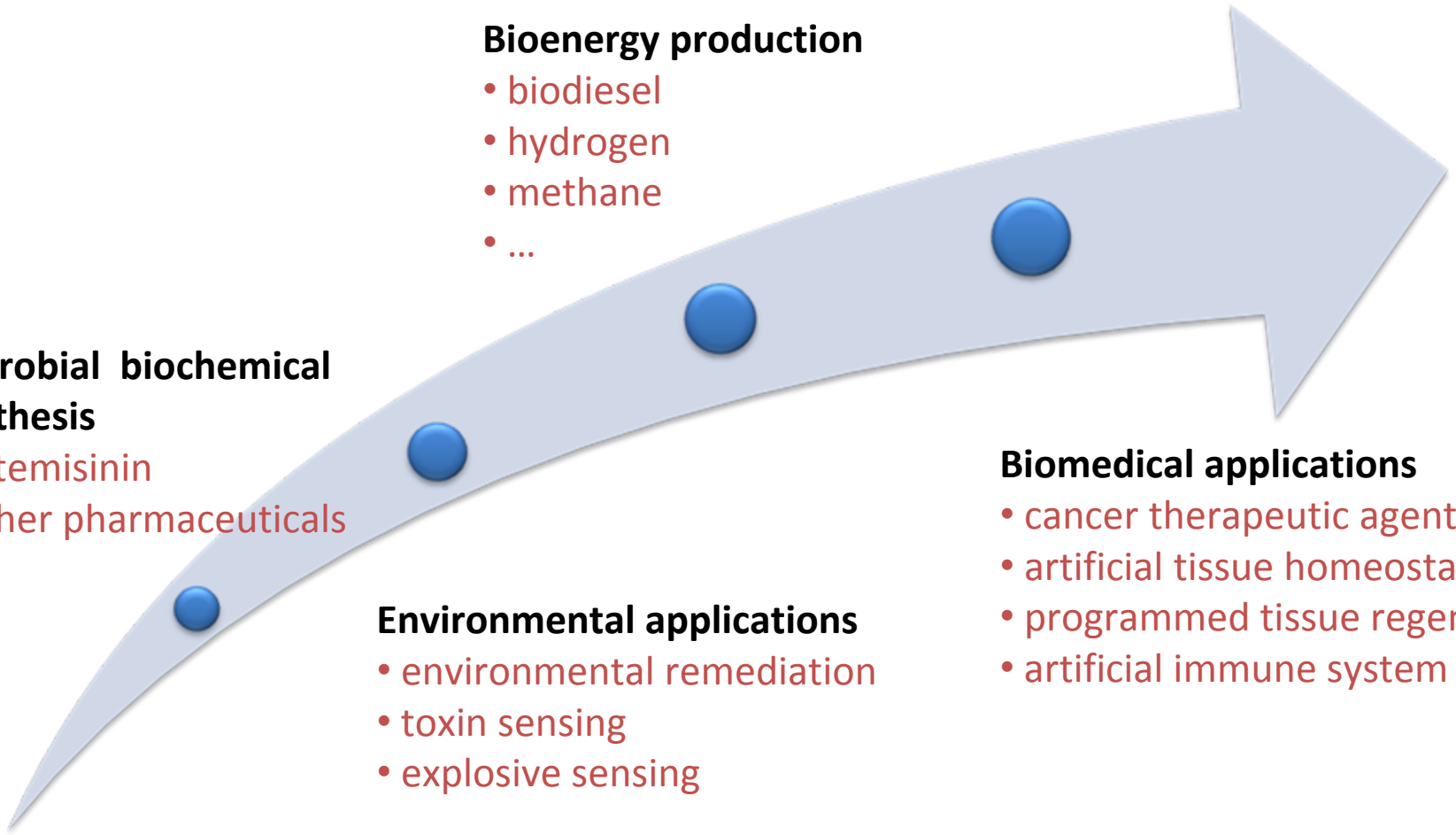
Glut2



Insulin-production assay with C-peptide antibodies



Outlook for applications



Bioenergy production
- biodiesel
- hydrogen
- methane
- …

Microbial biochemical synthesis
- artemisinin
- other pharmaceuticals

Environmental applications
- environmental remediation
- toxin sensing
- explosive sensing

Biomedical applications
- cancer therapeutic agents
- artificial tissue homeostasis
- programmed tissue regeneration
- artificial immune system

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