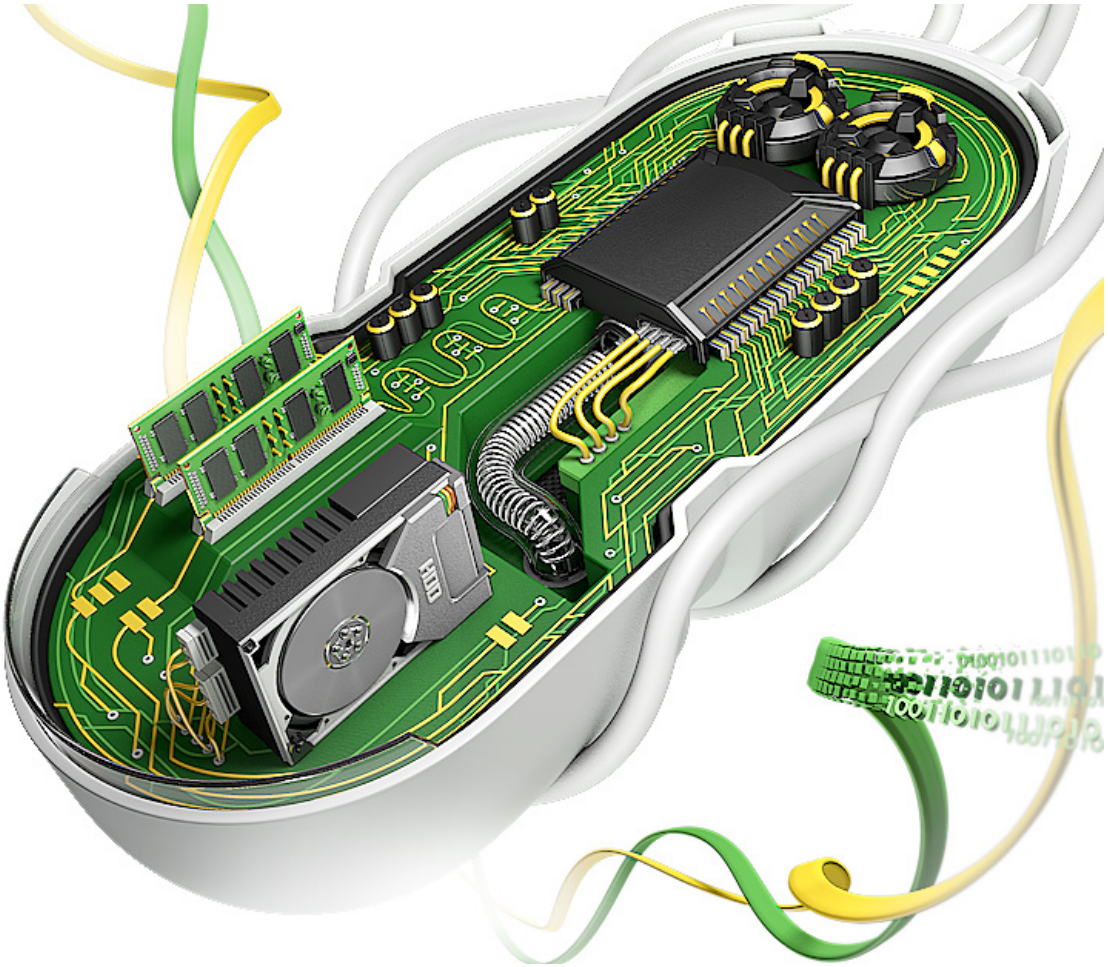
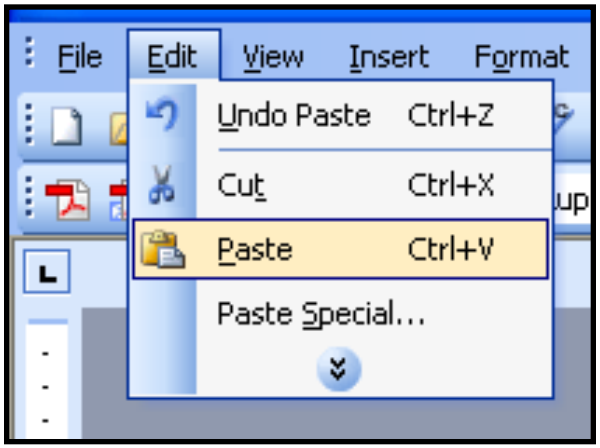
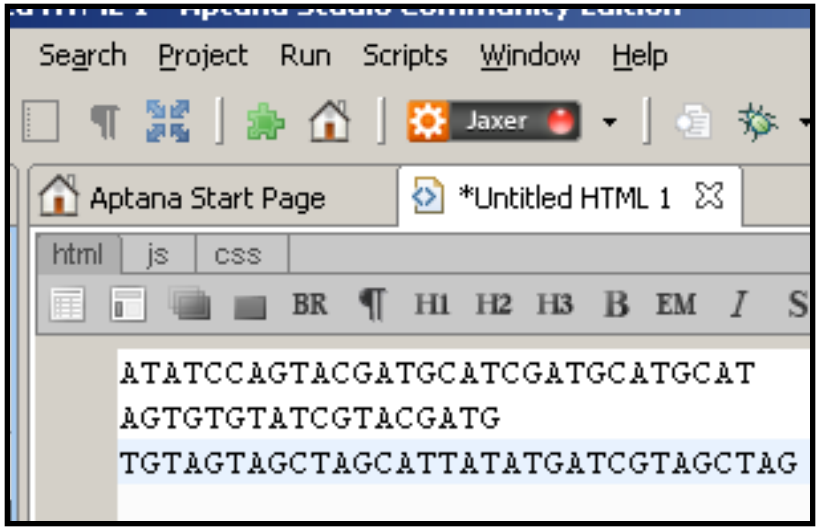
Closed-Loop Therapies as Adaptive Medicines

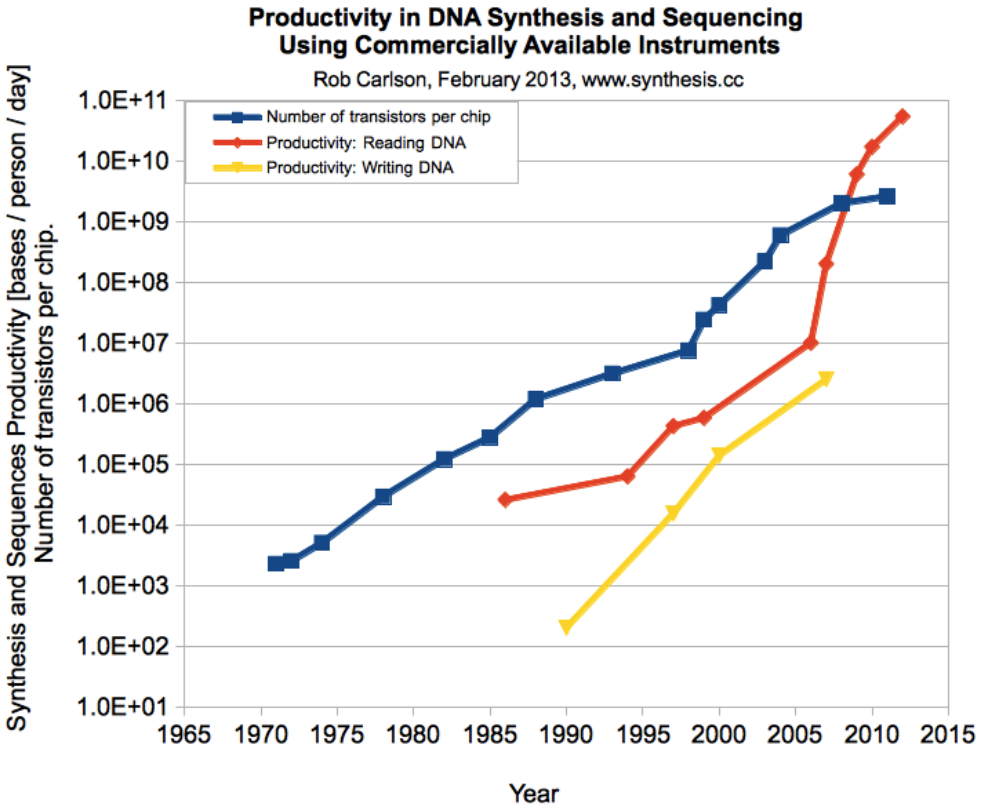


Timothy Lu, M.D., Ph.D.
Associate Professor
MIT EECS and BioEng
February 22, 2016

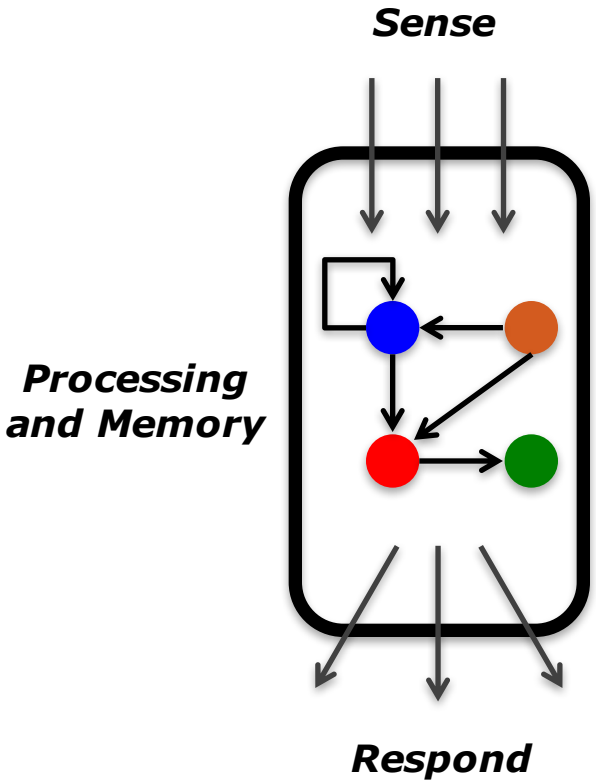
Synthetic Biology – From Cut & Paste to Programming DNA

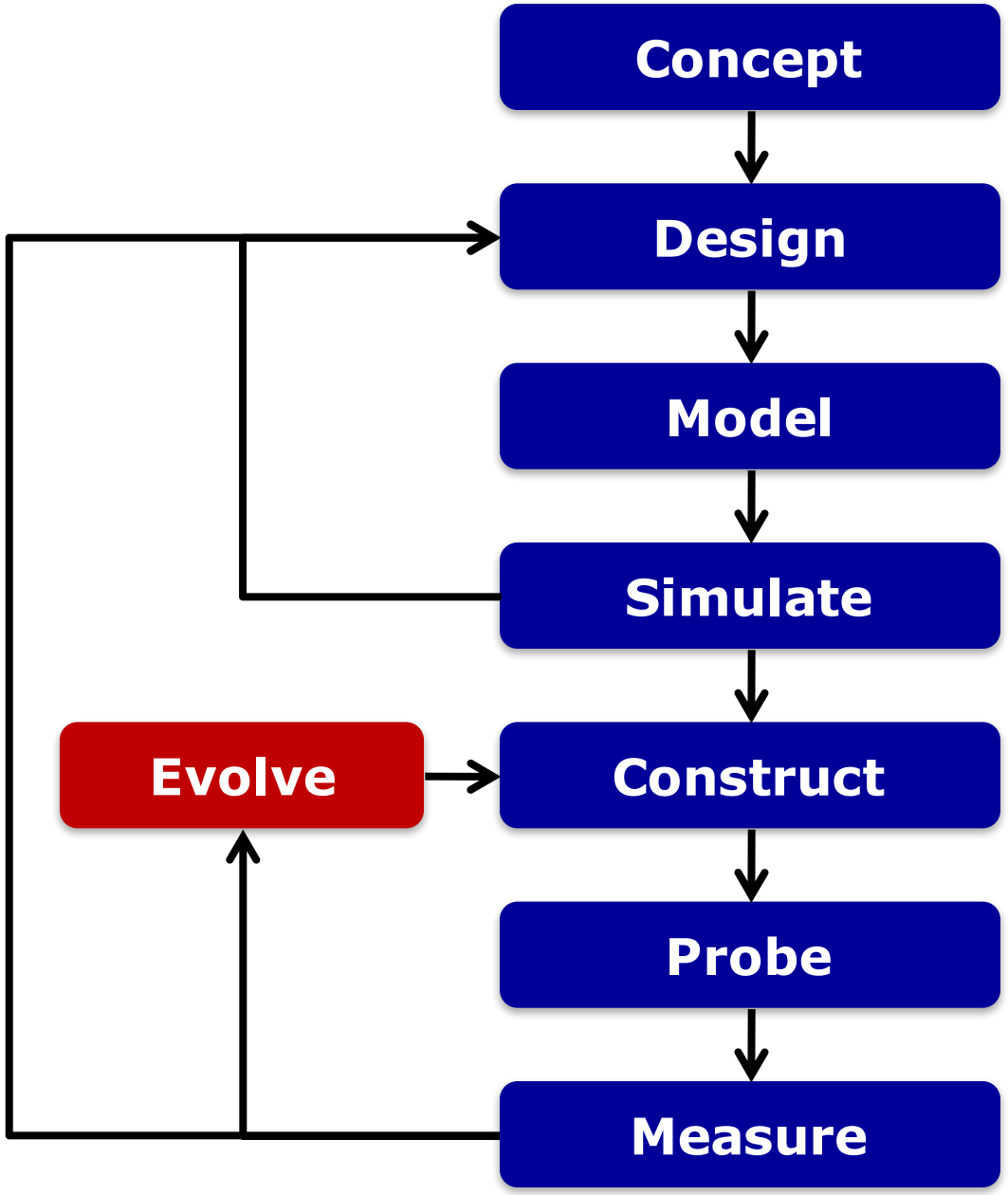




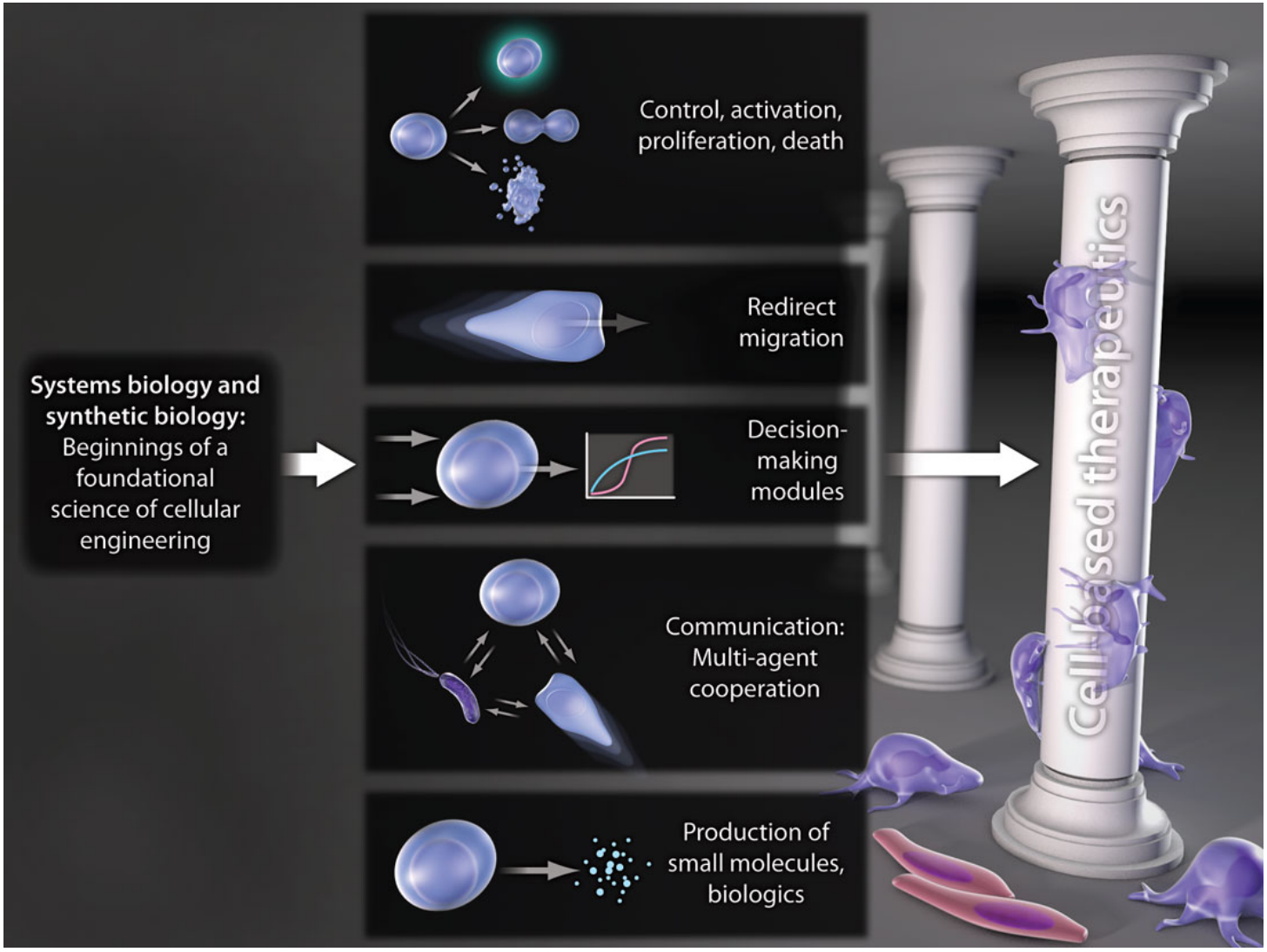


Programming Adaptive Medicines with Synthetic Biology



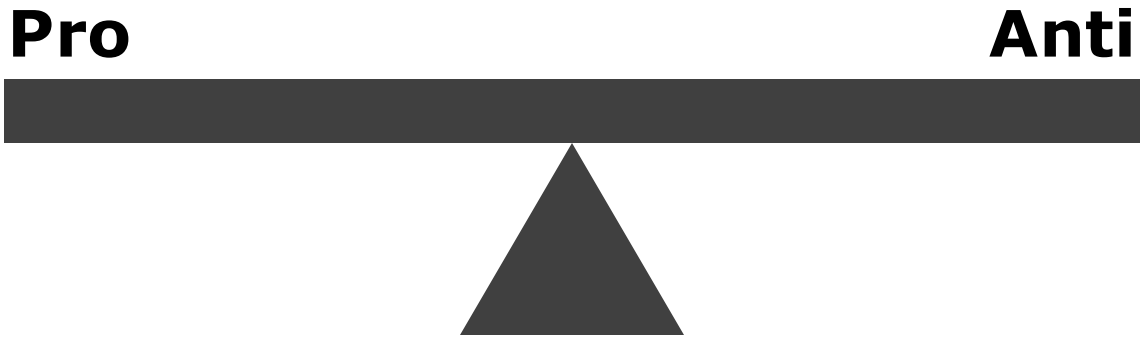


Engineering Sense-and-Respond Circuits for Cell Therapies

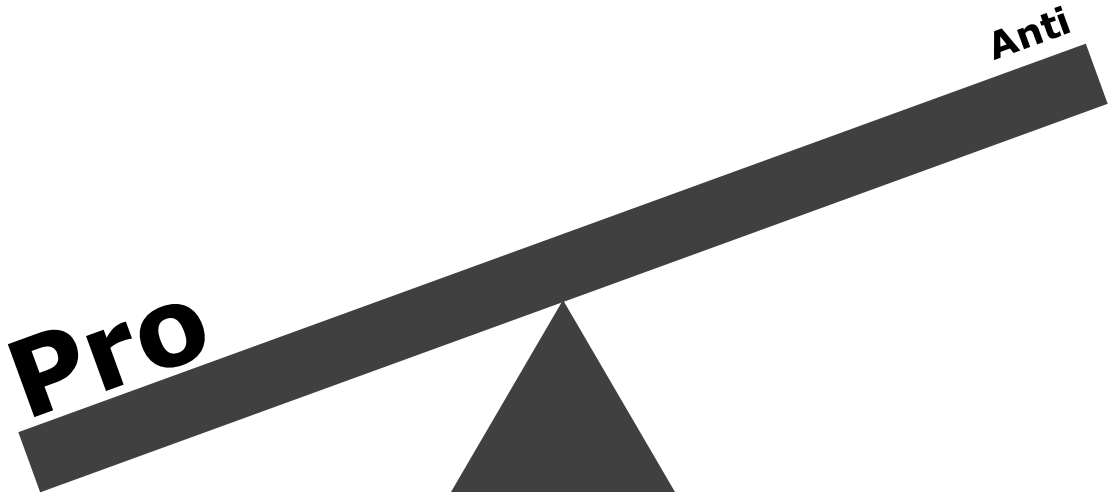


Fischbach, Bluestone, Lim

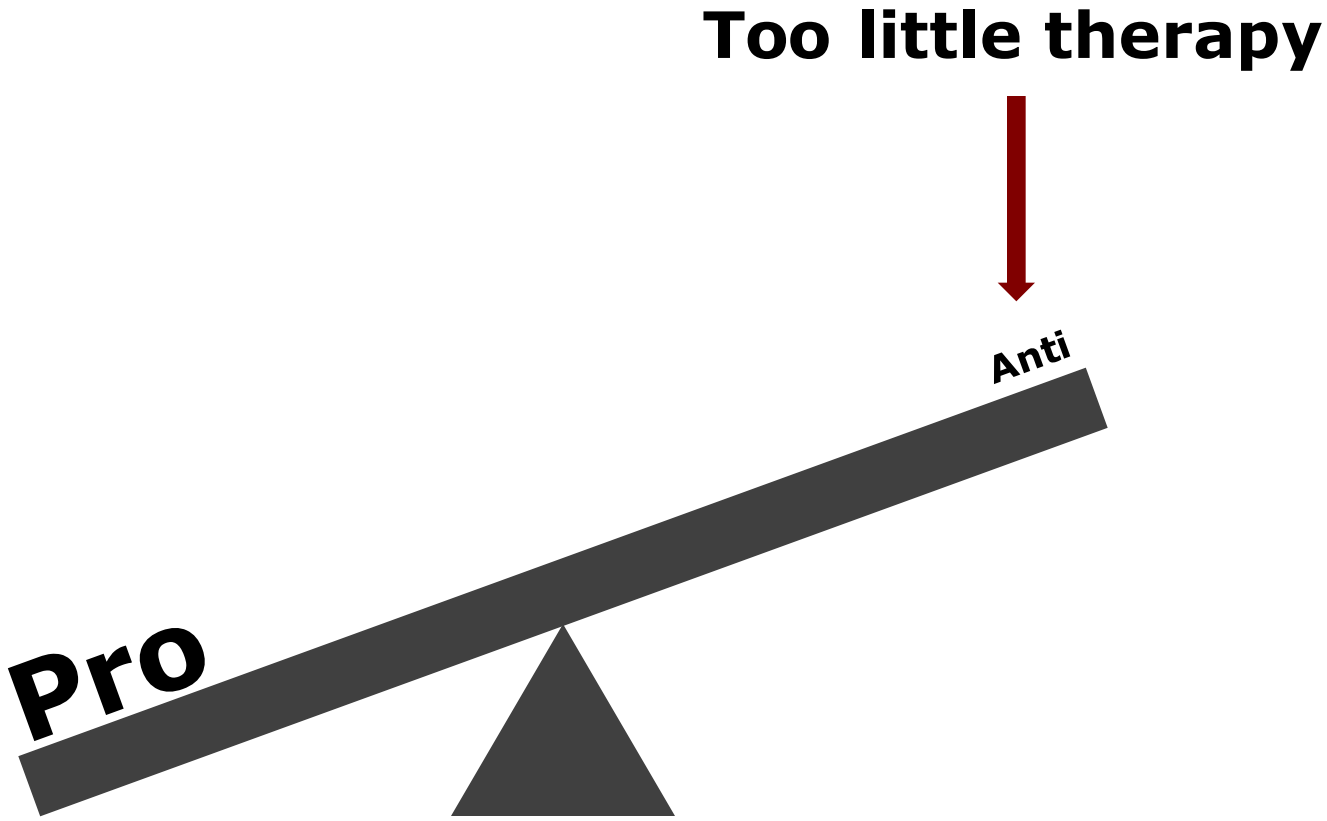
Homeostasis in Human Physiology



Loss of Homeostasis in Human Disease



Restoring Homeostasis Difficult with Non-Closed-Loop Therapies



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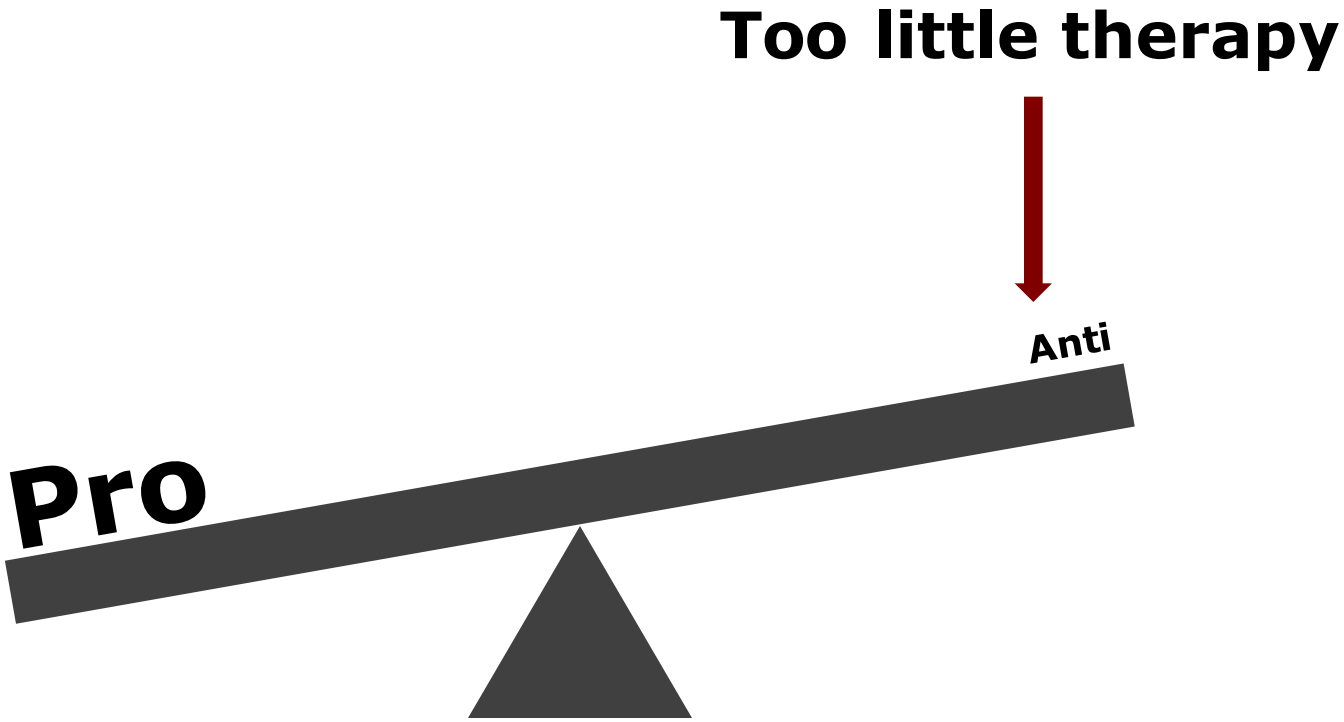

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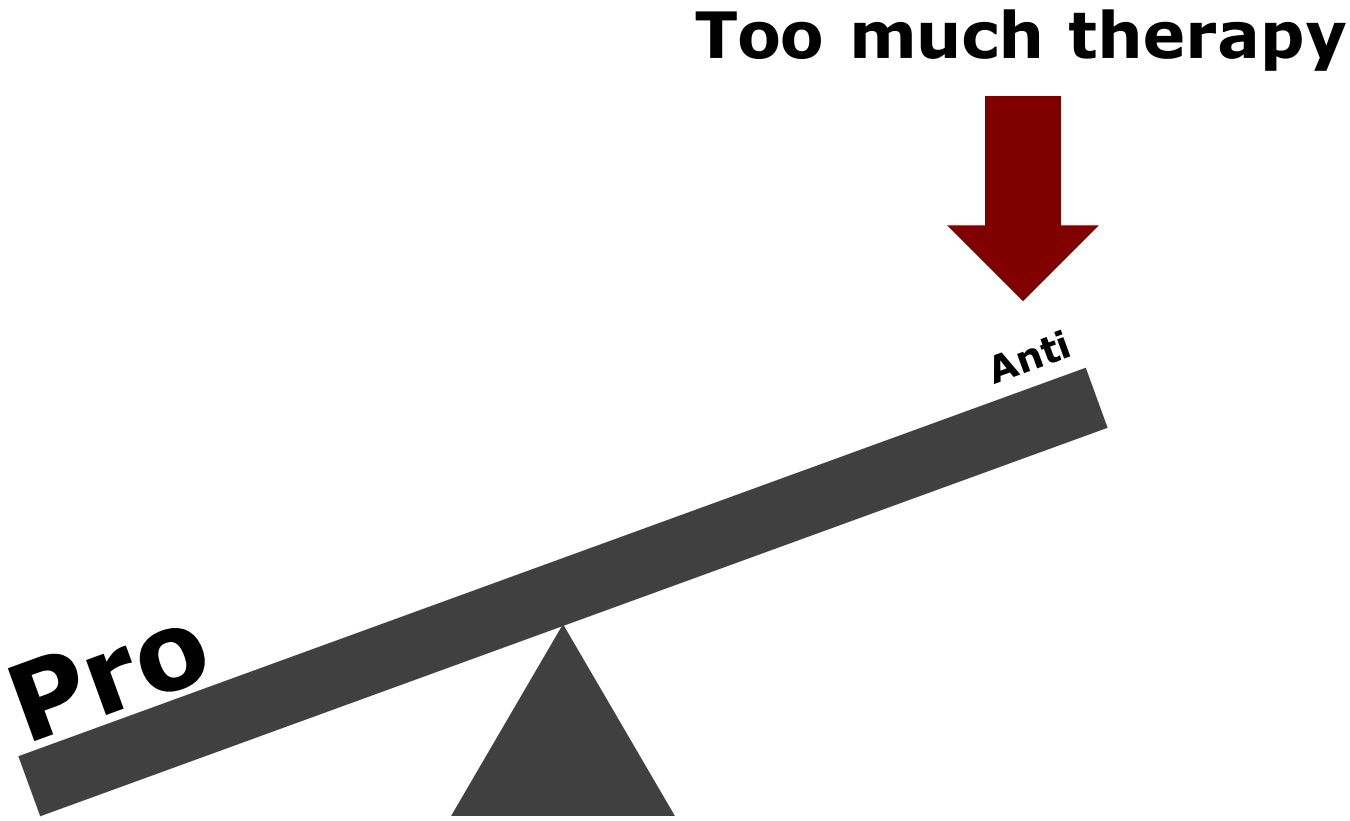

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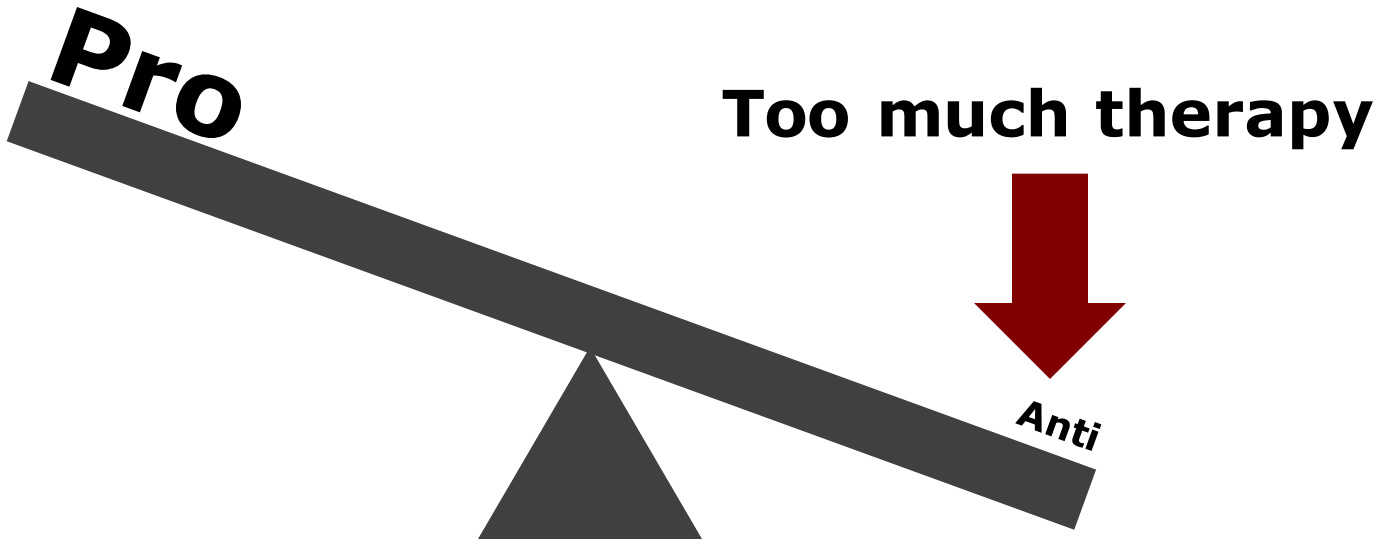

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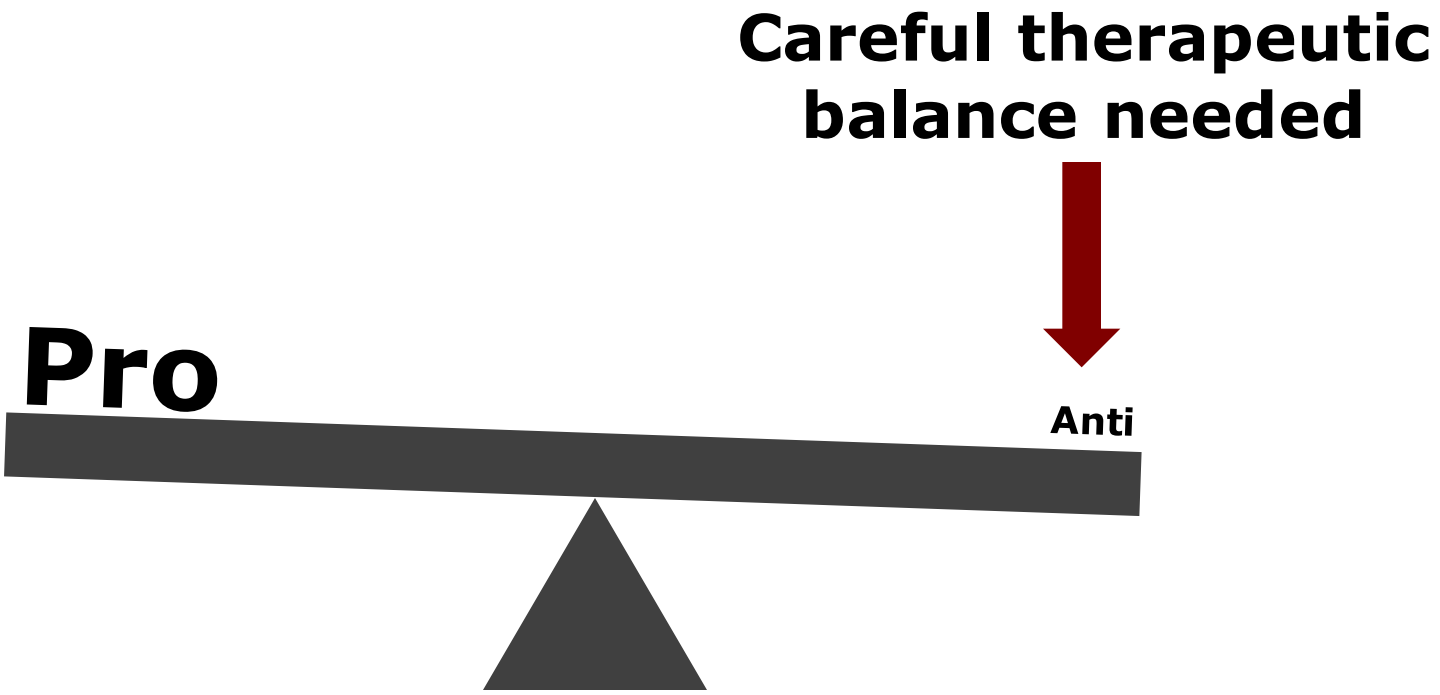
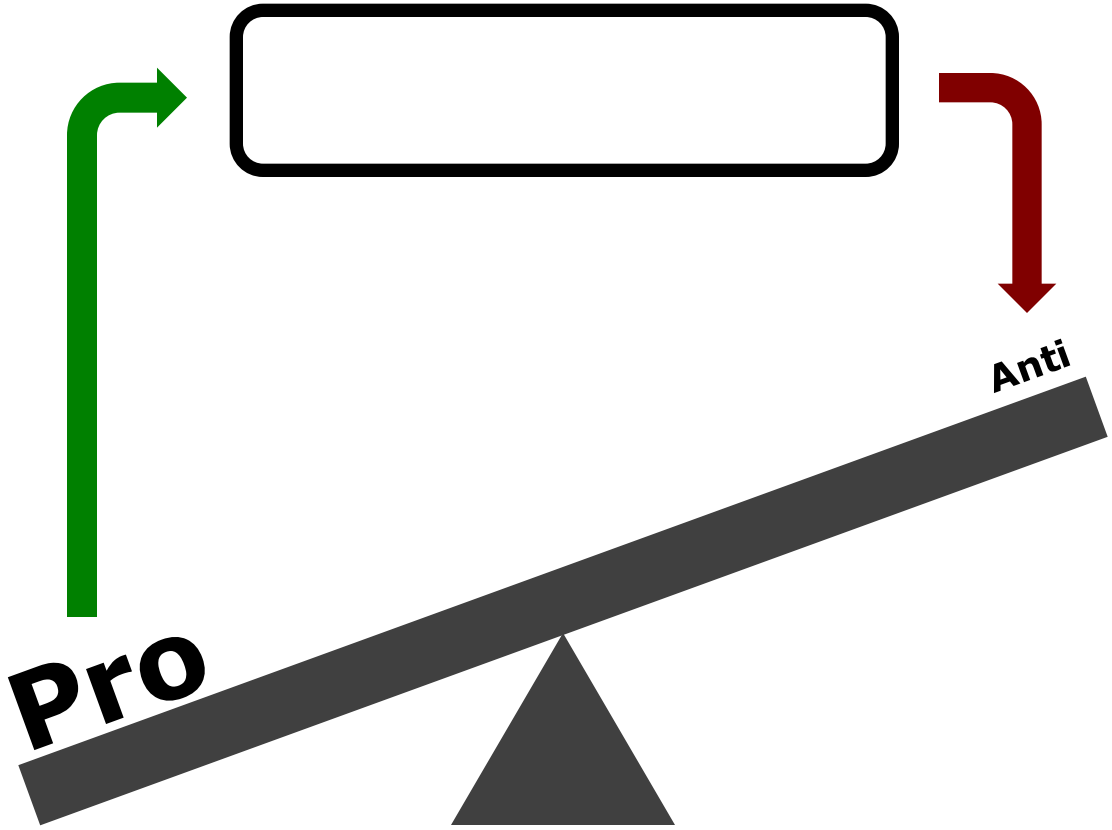
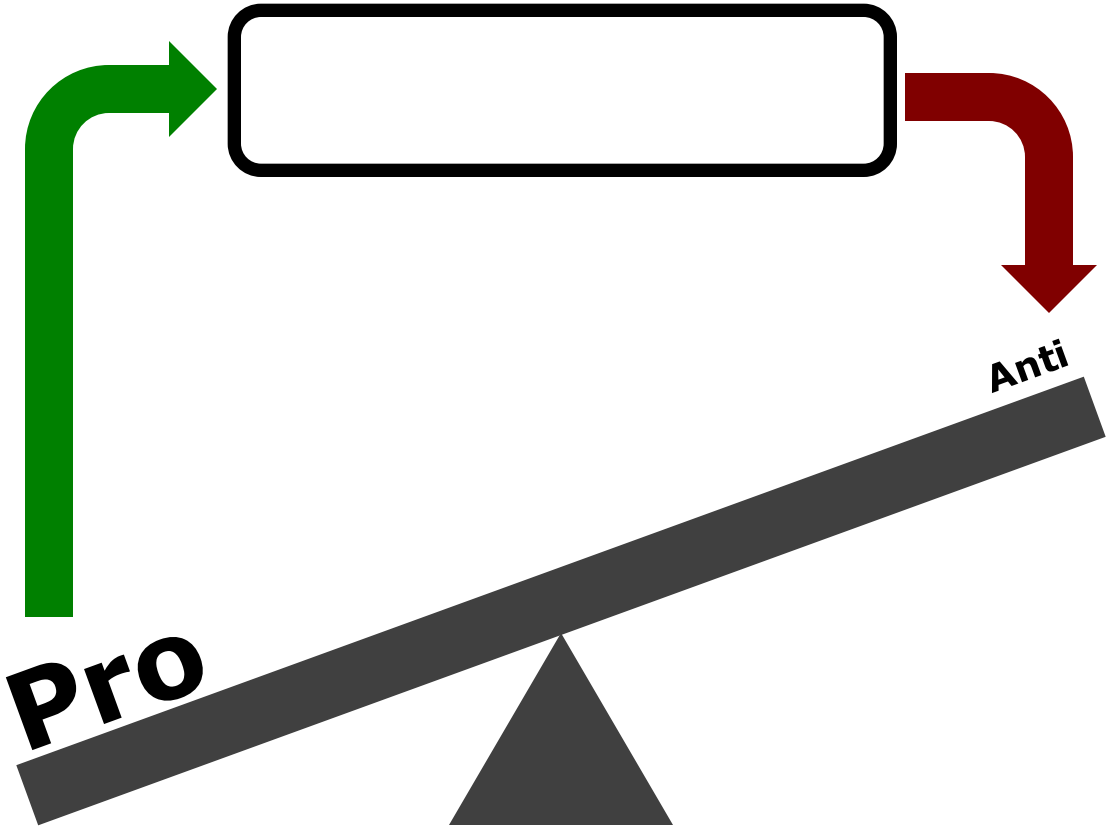


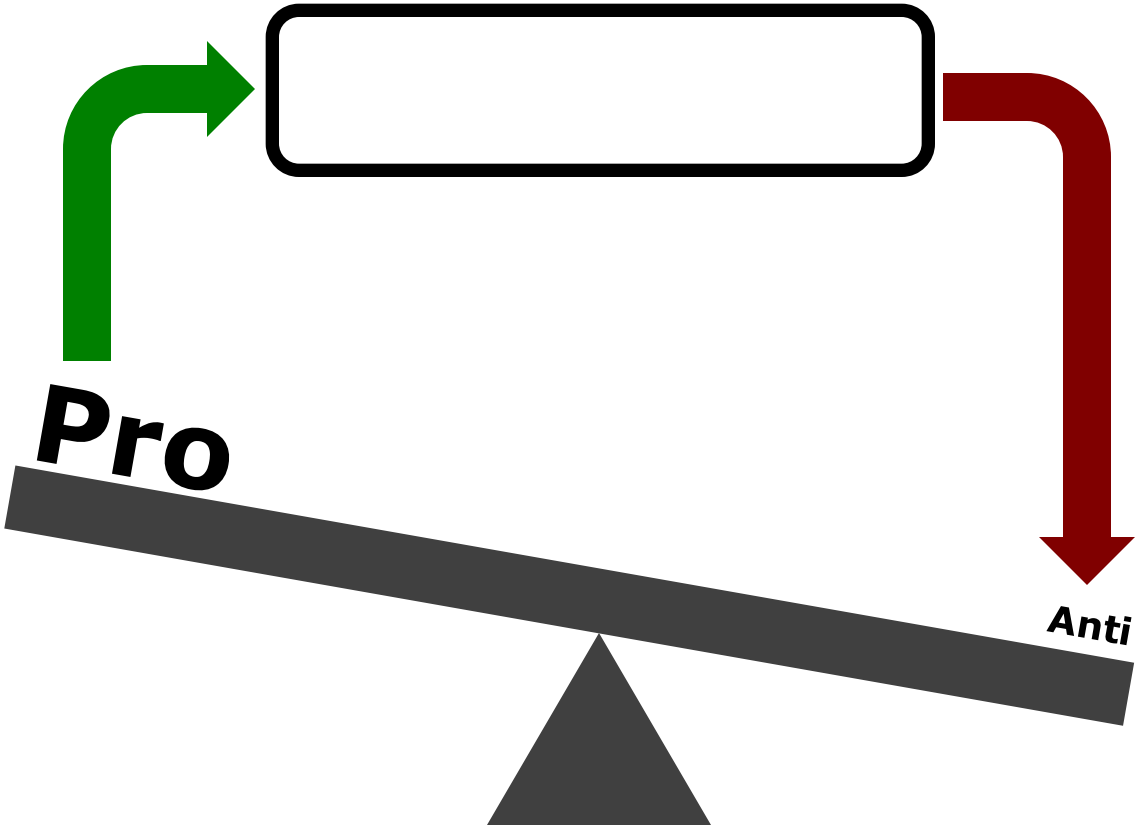
Closed-Loop Therapies Sense and Balance Therapeutic Effect



Closed-Loop Therapies Sense and Balance Therapeutic Effect

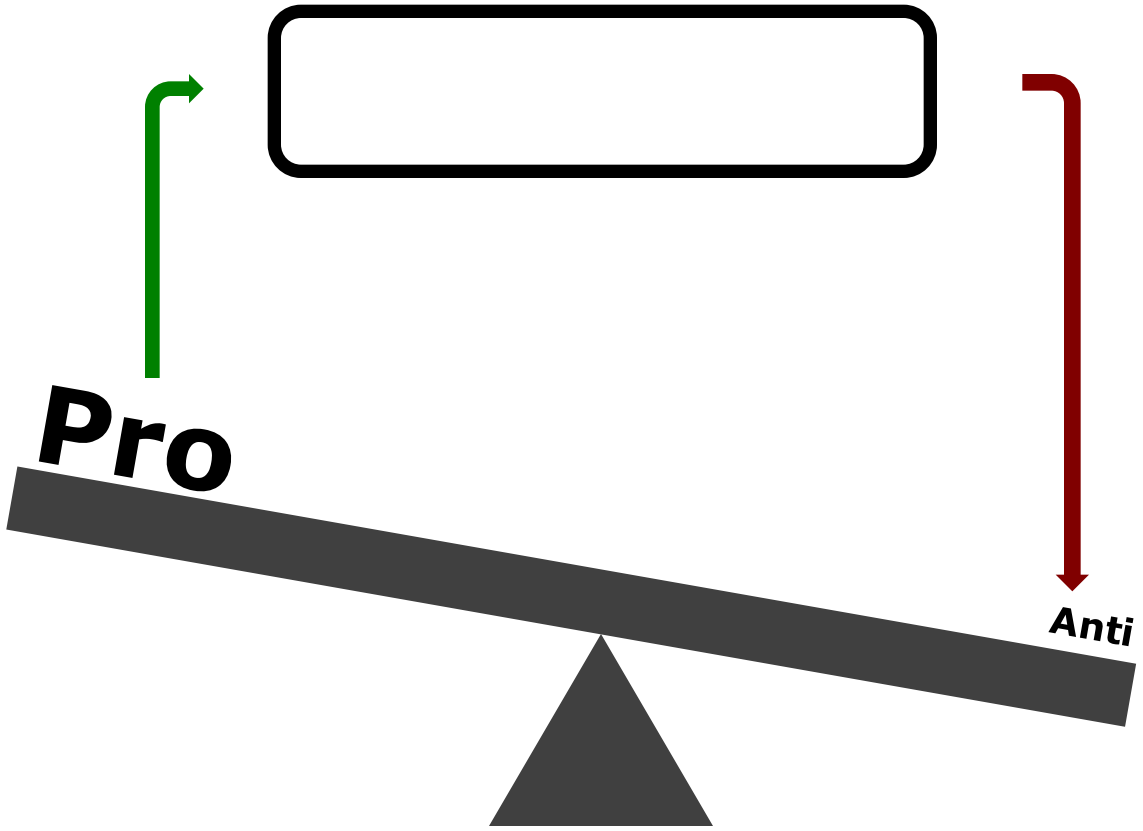


Closed-Loop Therapies Sense and Balance Therapeutic Effect



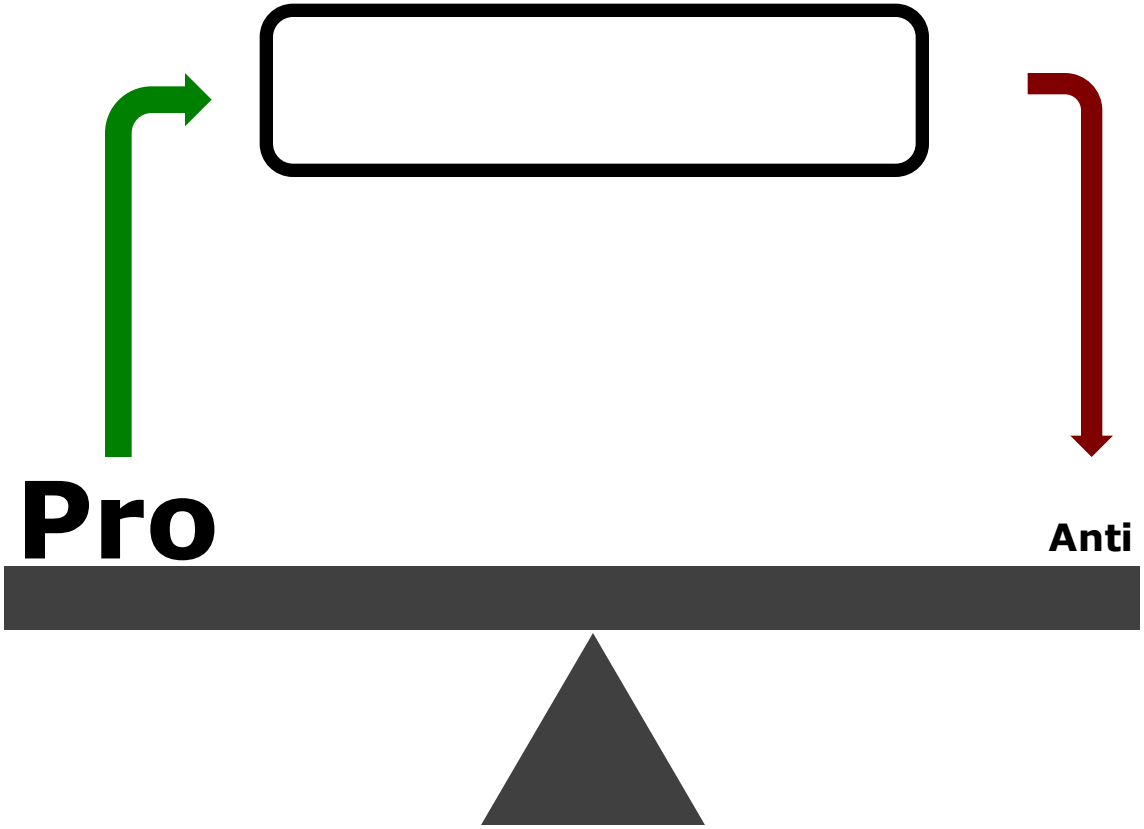
Too much therapy

Closed-Loop Therapies Sense and Balance Therapeutic Effect



Sense and reduce therapy

Closed-Loop Therapies Sense and Balance Therapeutic Effect



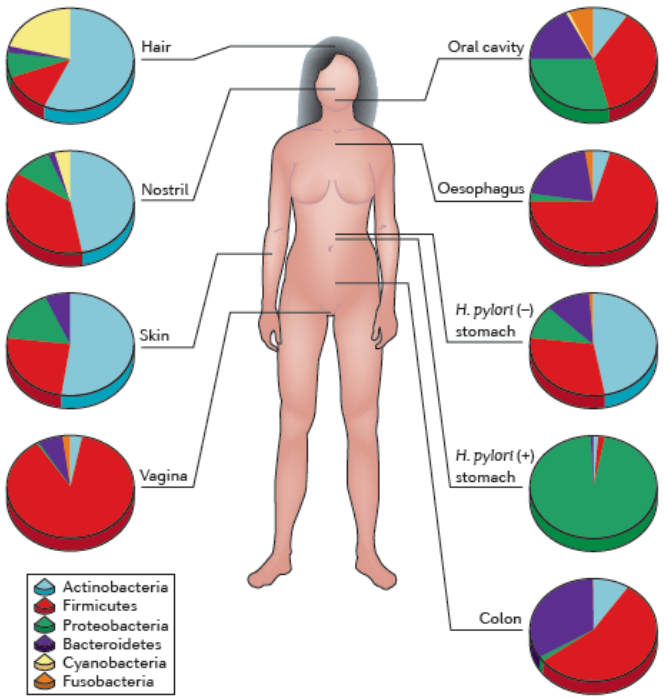
Sense and maintain homeostasis

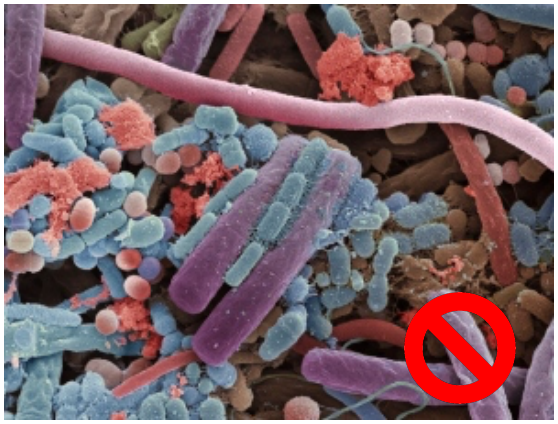
Need for New Technologies to Modulate the Human Microbiome

- Human body is shared with trillions of commensal microbes

- Involved in:
  - Development
  - Immunity
  - Digestion
  - Mood/Behavior

- Tools to manipulate microbiota crude and poorly understood
  - Antibiotics
  - Probiotics
  - Prebiotics



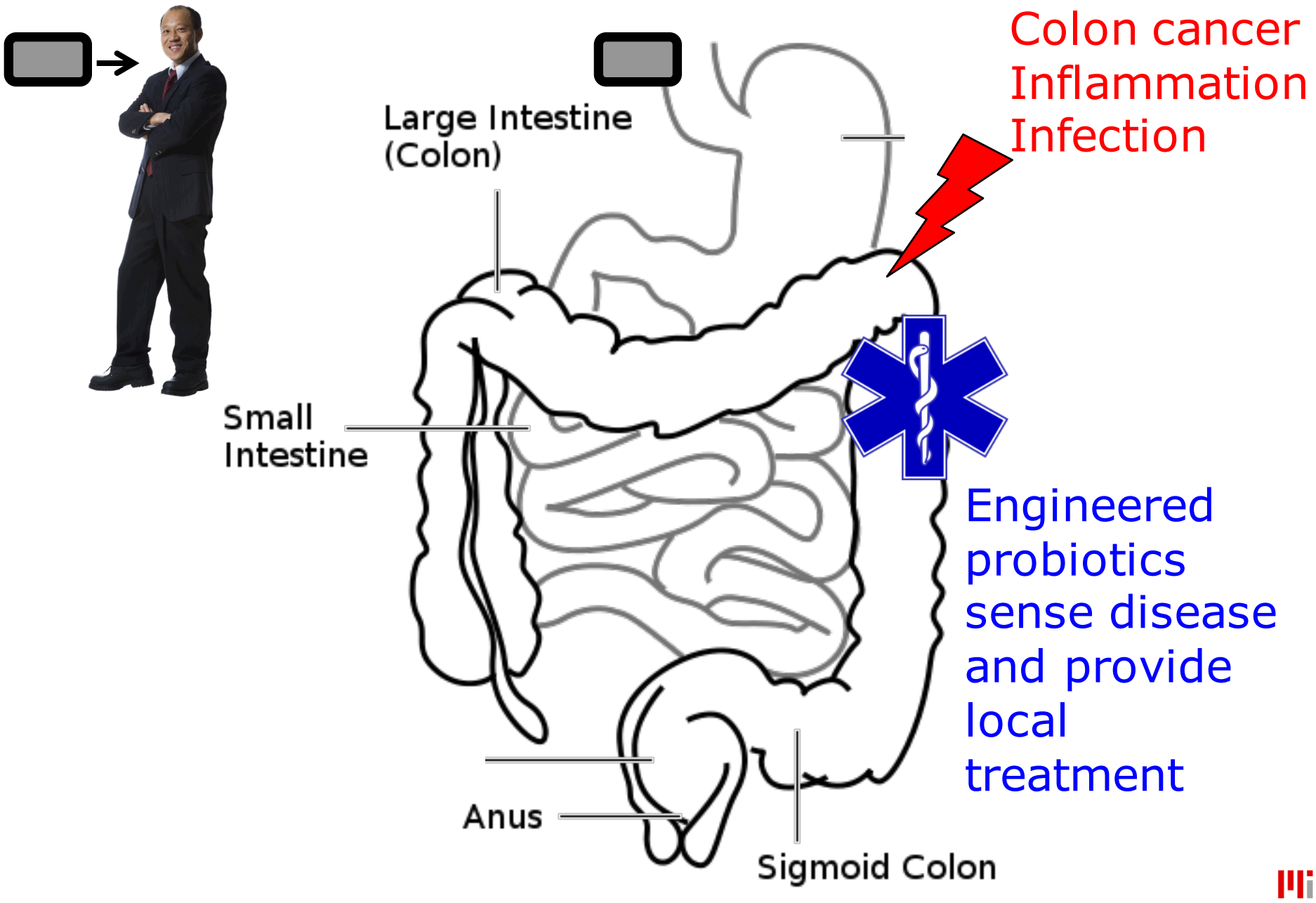


Additive

Subtractive

http://www.nature.com/news/microbiome-sequencing-offers-hope-for-diagnostics-1.10299; Cho and Blaser, *Nat Rev Genet,* 2012

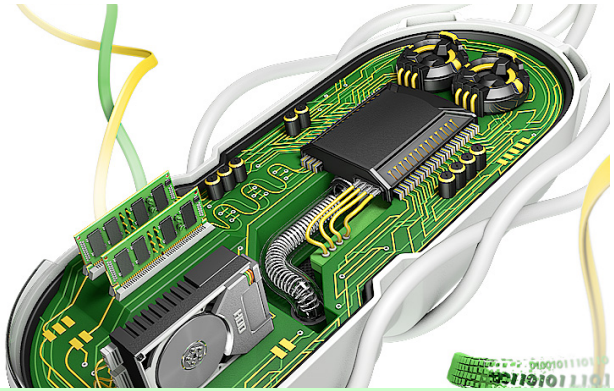
Applications of Synthetic Biology to Microbiome Engineering



Digital and Analog Paradigms for Computing and Memory

Computing **Memory**

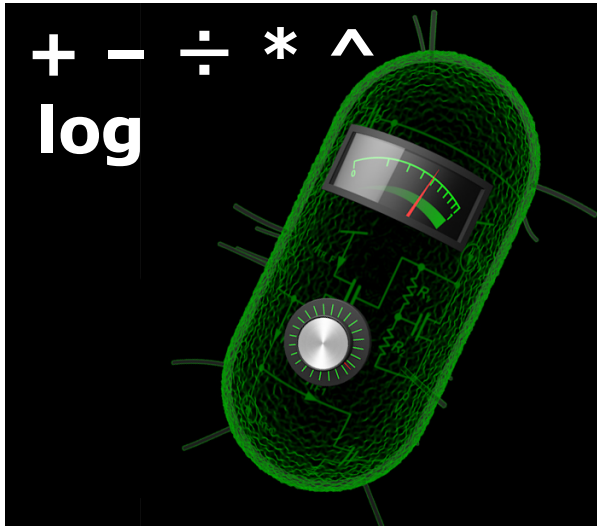
Digital
"0"s and "1s"



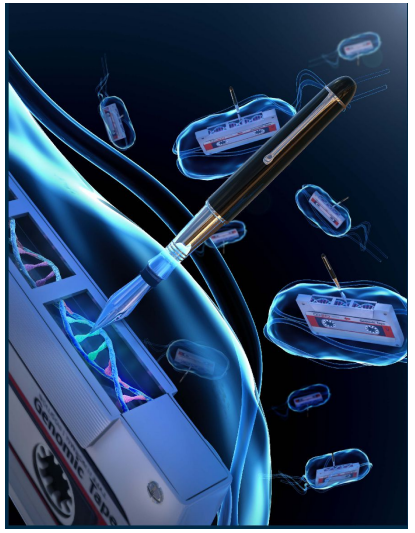
Towards Time, Order, and State-Dependent Cellular Programs

Biotech 2013

Analog
Continuous Info

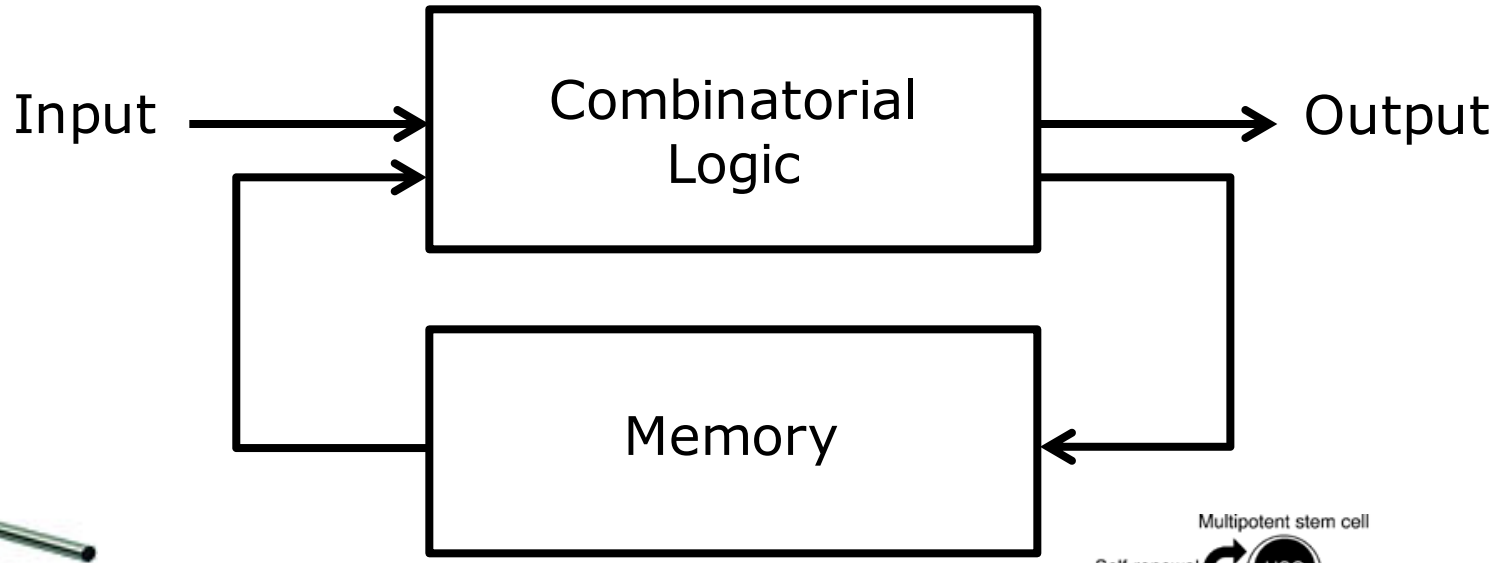


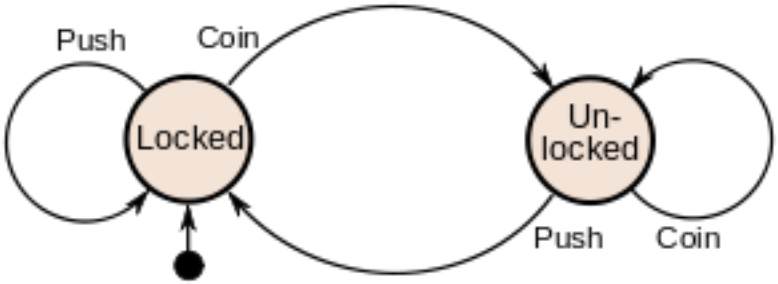
Daniel et al. Nature 2013

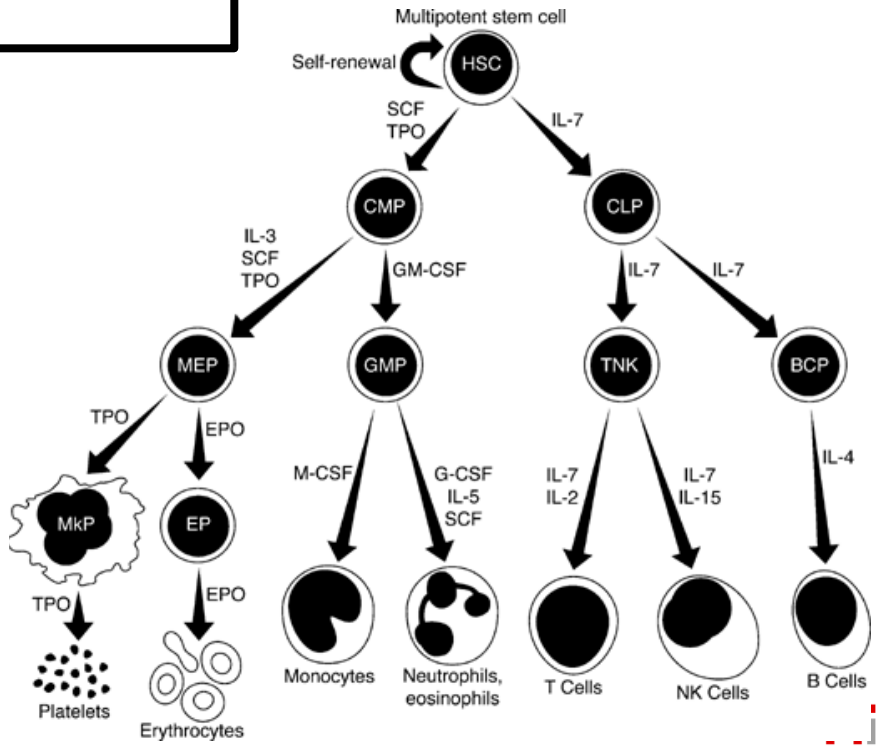


Farzadfard et al. Science 2014

Incorporating History into Sense-and-Respond Circuits



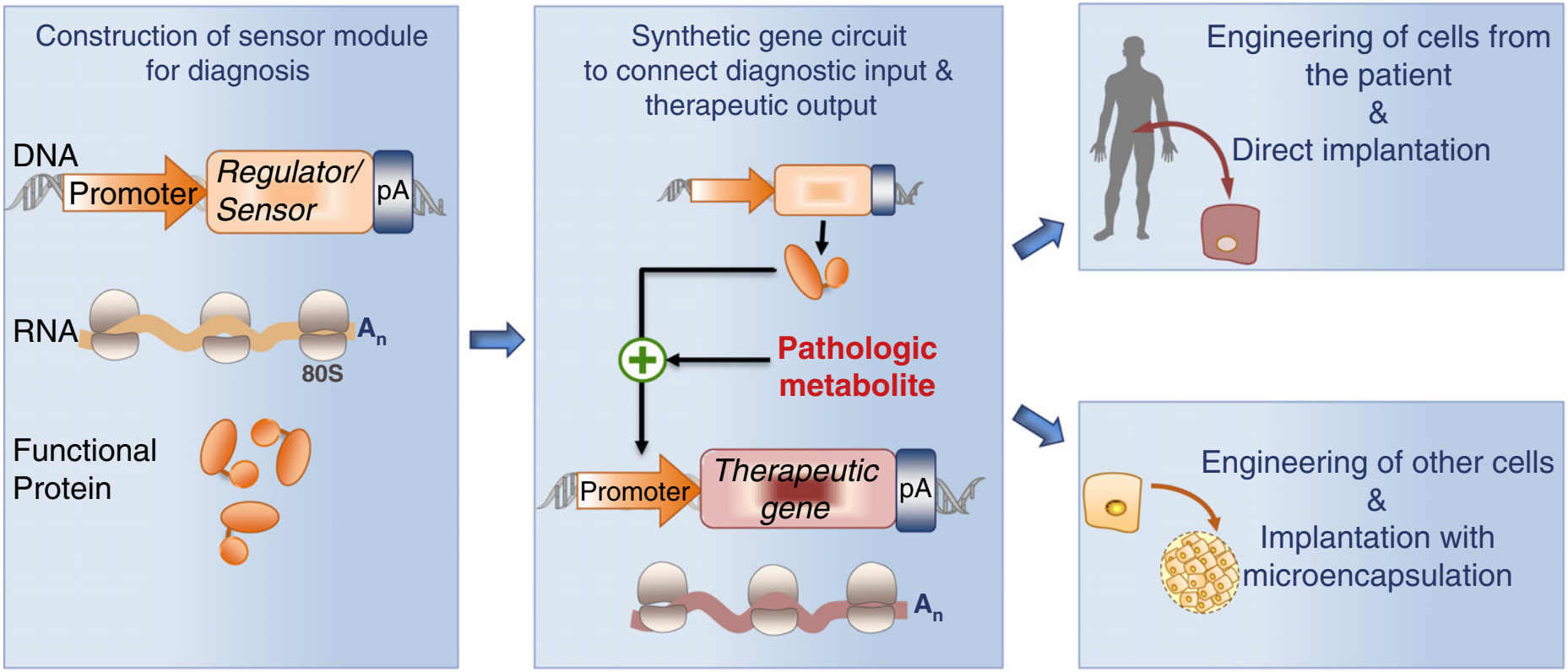




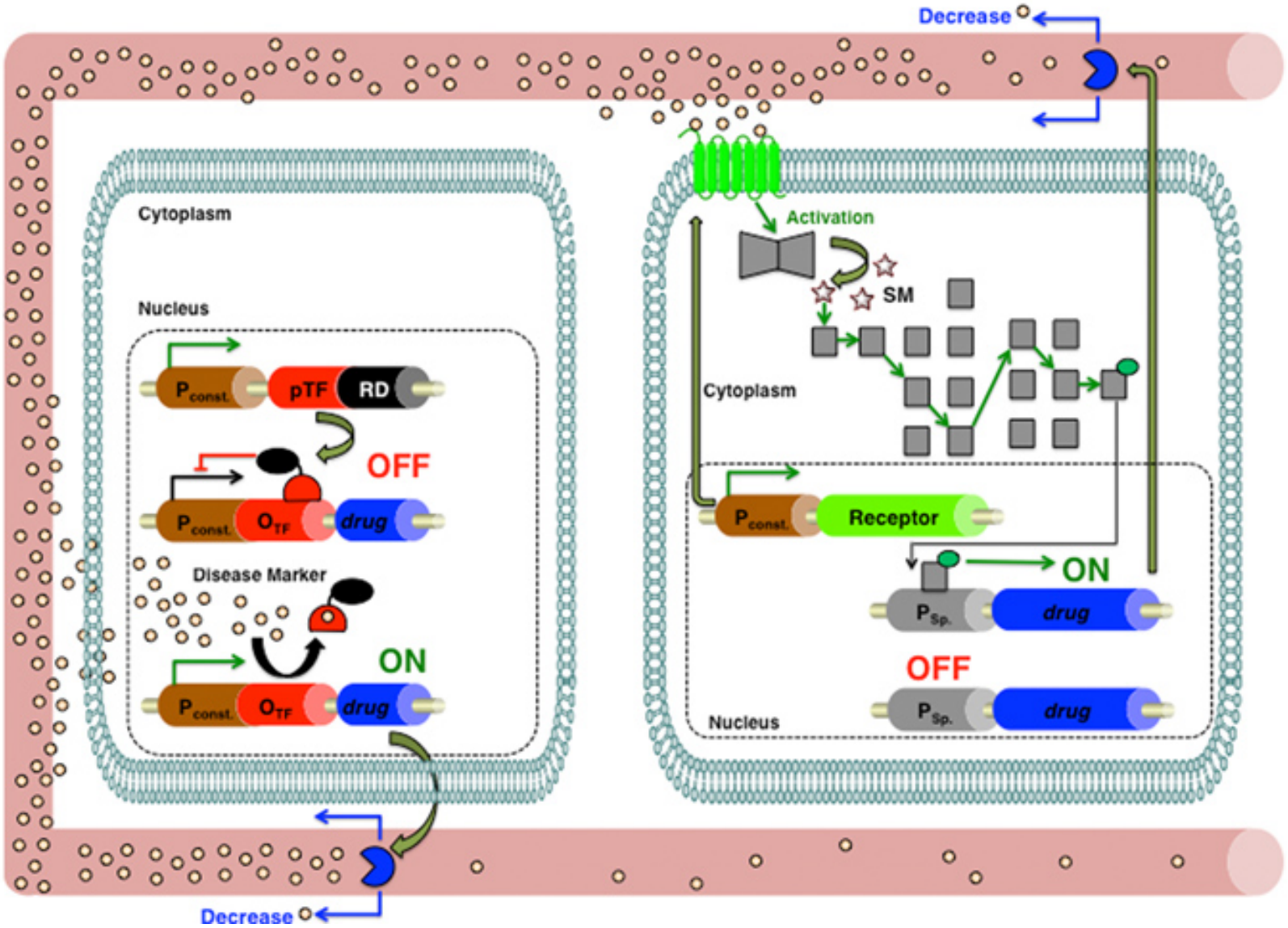
Wikipedia

Engineering Dynamic, Regulated Cell Implants

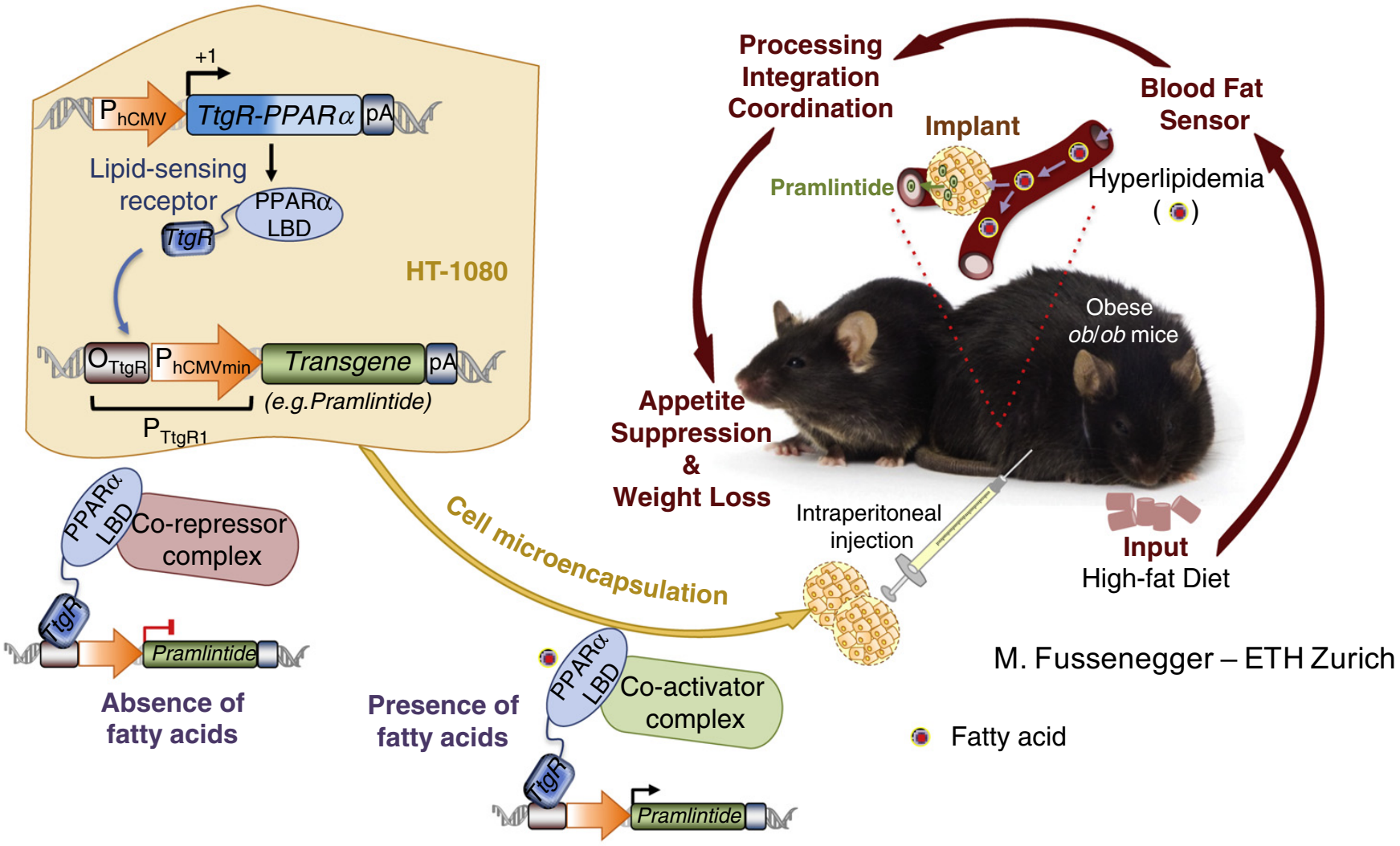
M. Fussenegger – ETH Zurich



Cell Therapies with Closed-Loop Feedback



Obesity Treating Cell Circuits



Obesity Treating Cell Circuits

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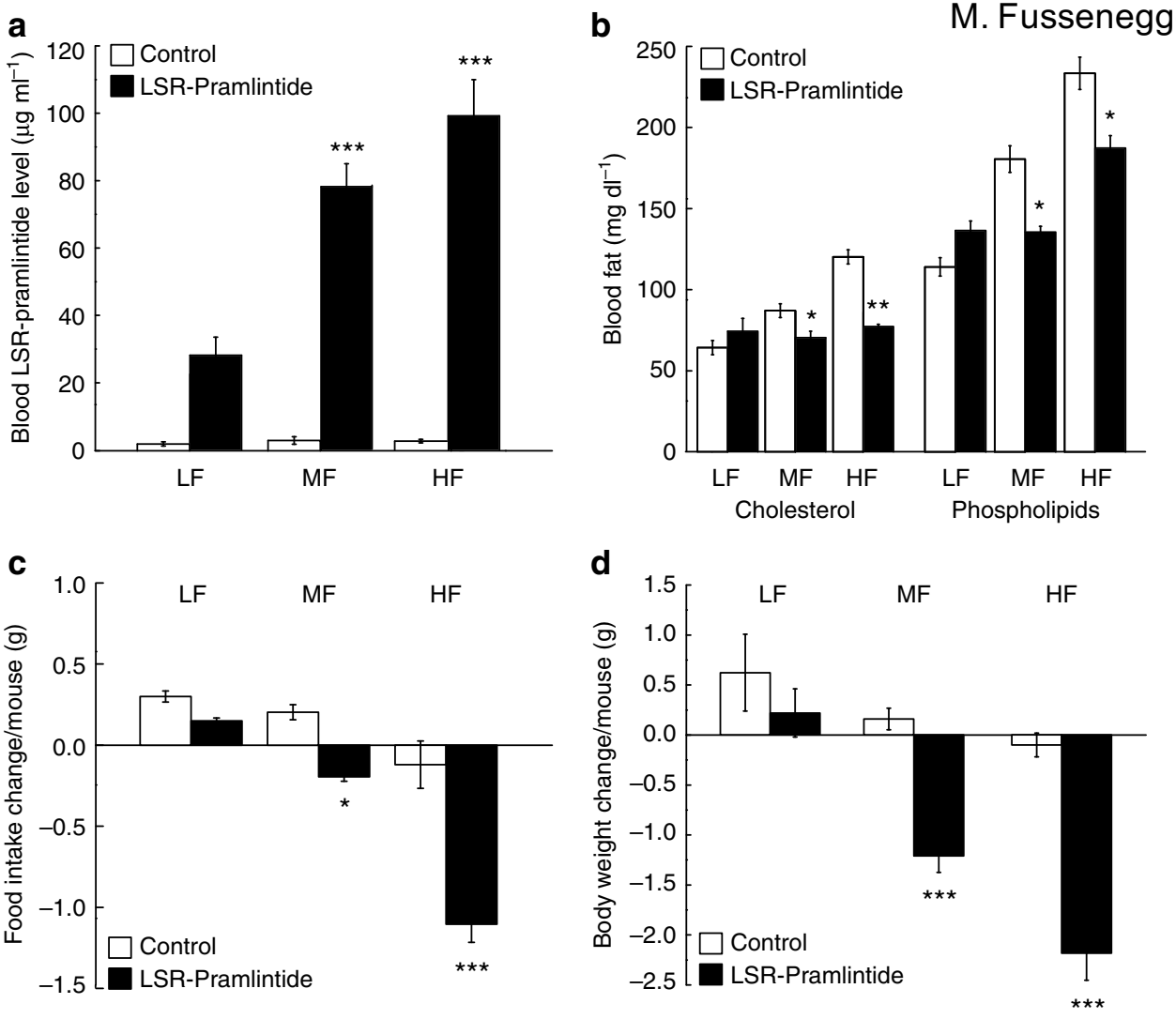
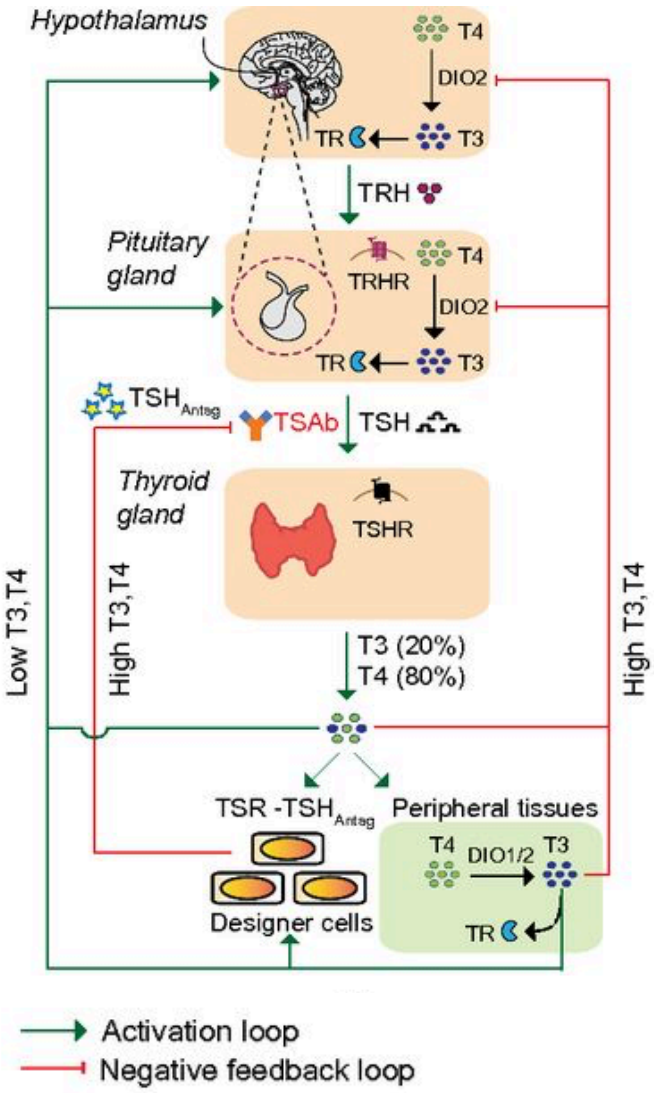
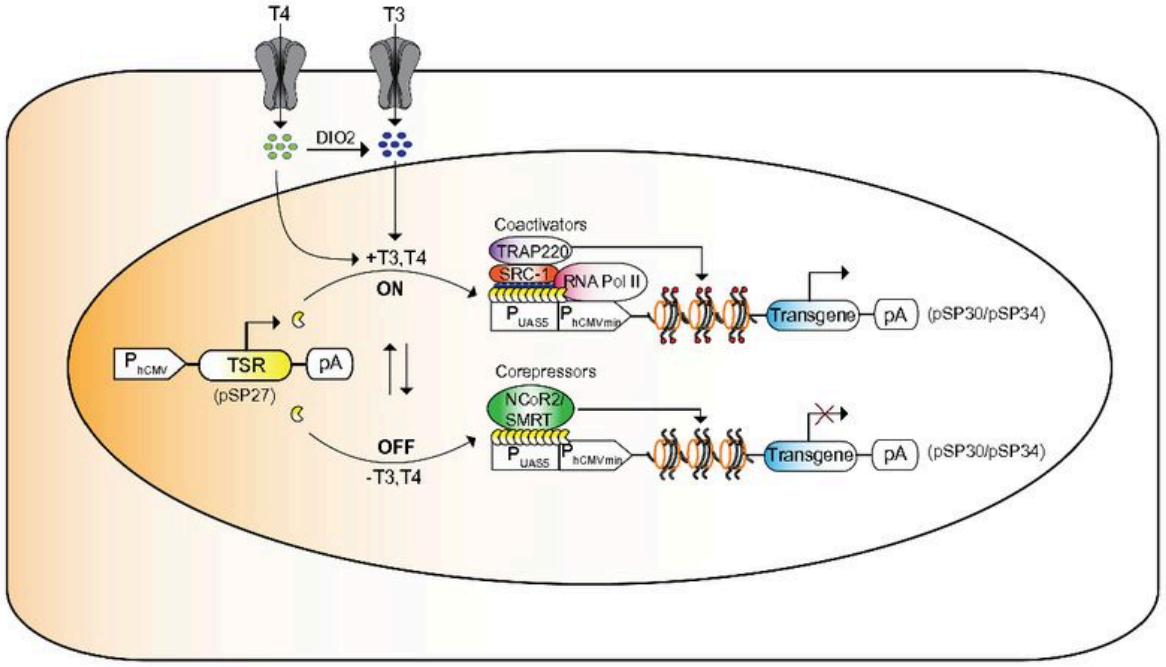
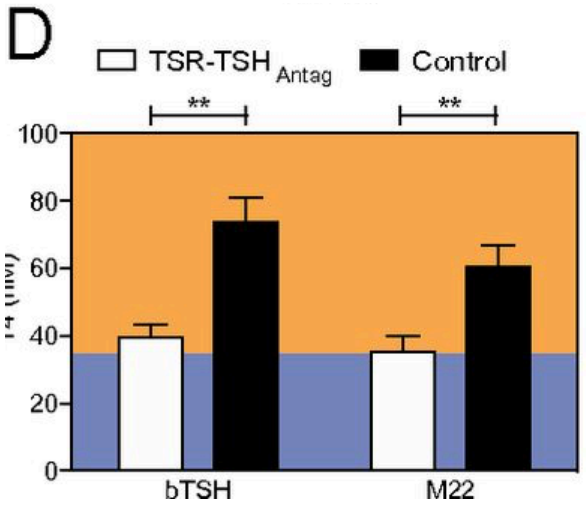
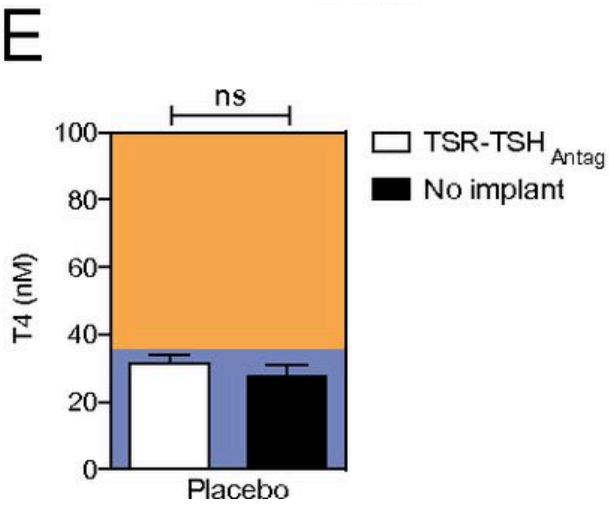


Cell Therapy for Graves' Disease

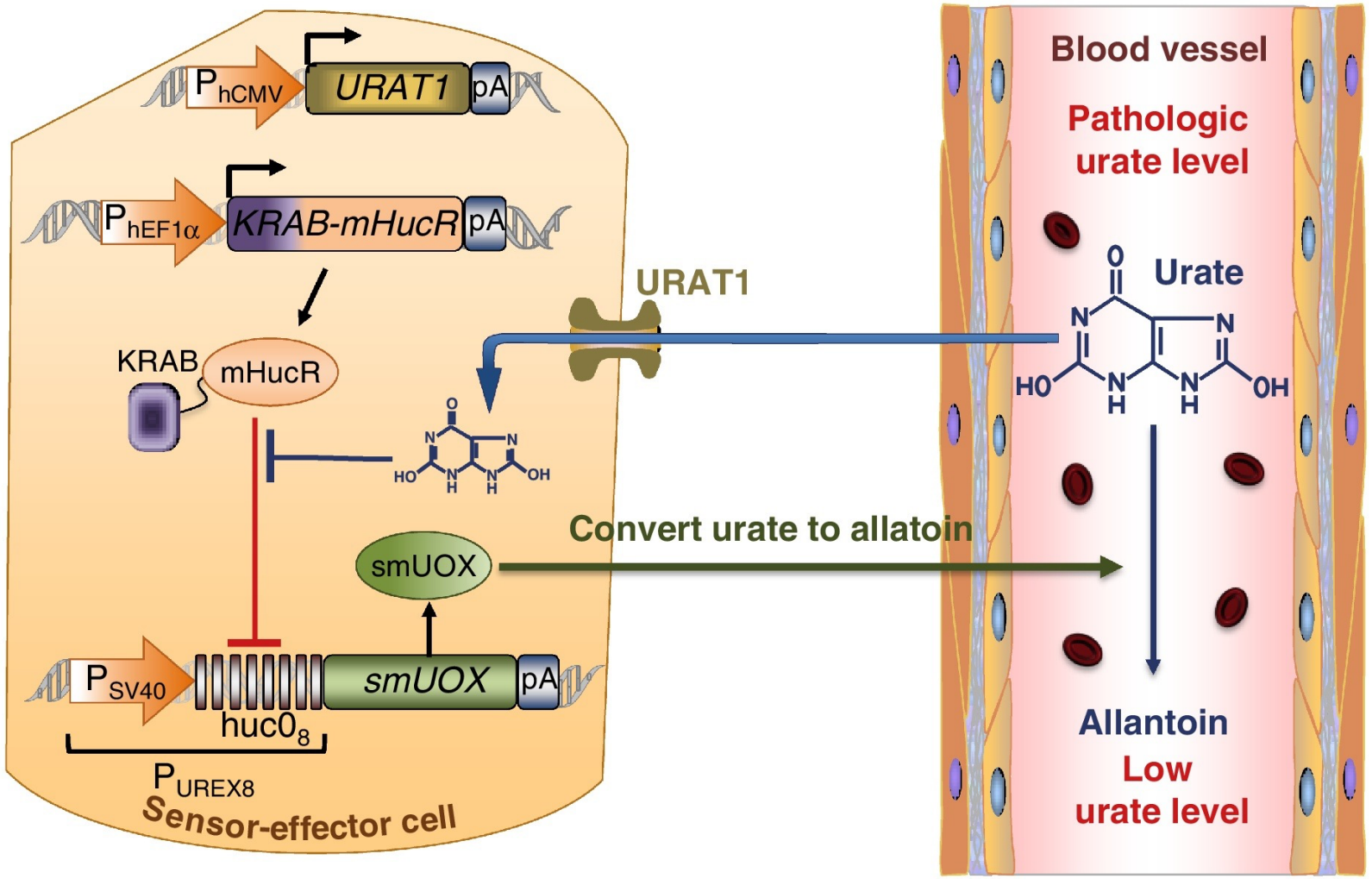




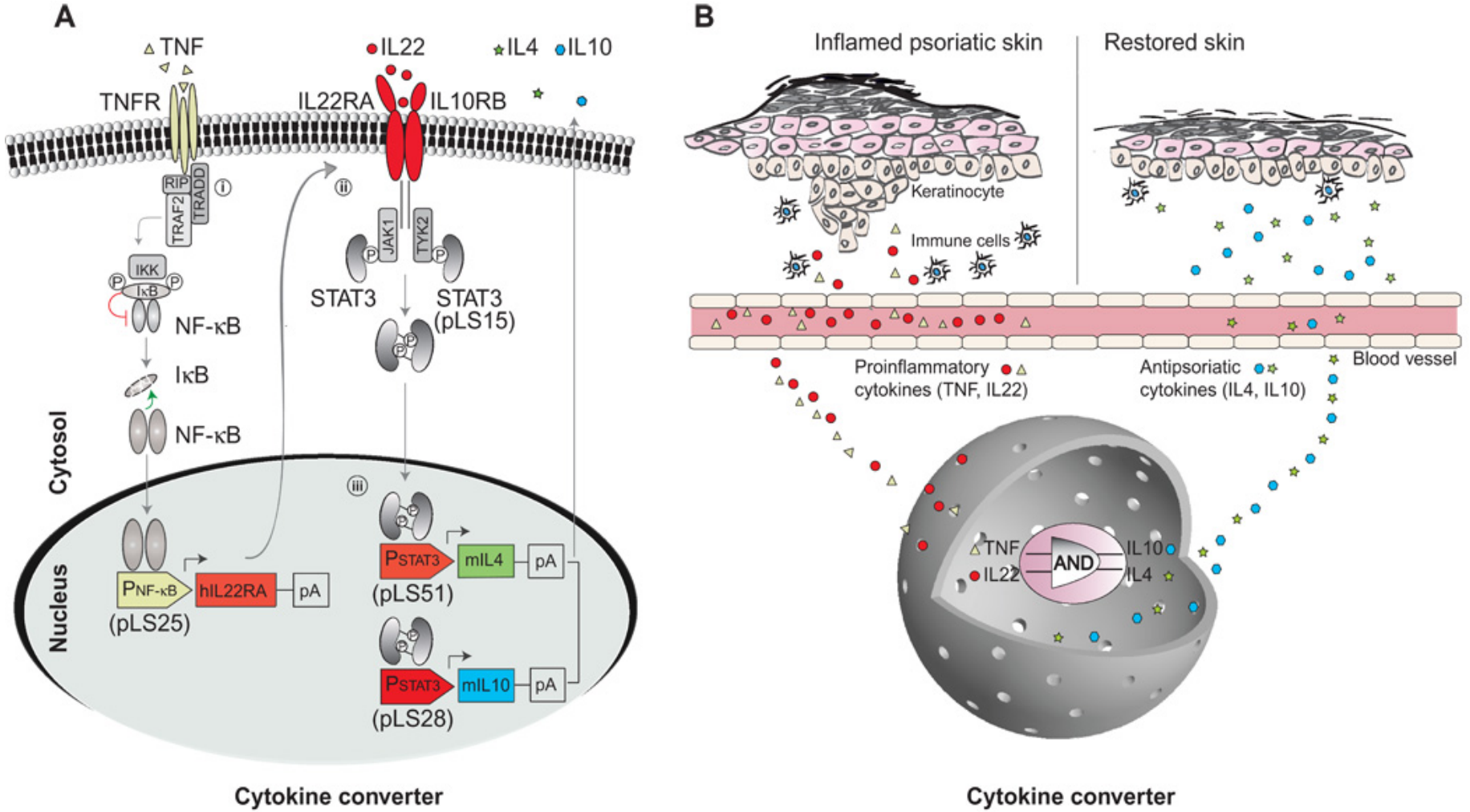




Cell Therapy to Maintain Uric Acid Homeostasis



Cell Therapy for Psoriasis



Schukur … Fussenegger *STM* 2015

Technical Challenges

- Designing state-dependent cell therapies
- Creating circuits that match the time-scale of desired responses
- Building robustness into closed-loop therapies
  - Redundancy? Multiple-feedback loops? Isolation strategies to minimize environmental effects?
- Designing cellular sensors for a wide range of analytes
- Ensuring specificity of cellular sensing circuits for desired disease states
- Maximizing the durability of closed-loop therapeutics despite evolving cellular background
- Choosing best delivery method or chassis introducing desired therapeutic effect into humans
  - Engineered bacteria or human cells? Gene therapies via non-viral or viral vectors?

Questions for Clinical Use

- What are the best indications for the first clinical applications, balancing risk / benefit?
- How to do preclinical modeling of closed-loop therapies *in vitro* and animals?
- How to characterize the pharmacodynamics / pharmacokinetics of closed-loop therapies?
- How to quality-control the manufacturing of closed-loop therapies?
- How to monitor the *in vivo* performance of closed-loop therapies when introduced into patients?
- How to measure the long-term durability of closed-loop therapies?
- How to incorporate safeguards or external control over closed-loop therapies?
- How does this fit into existing regulatory frameworks? Do these make sense?
  - When in the process does environmental risk assessment come into play?
  - How are fecal transplants regulated?

timlu@mit.edu

We are hiring for talented and motivated researchers!