

The UCI Institute for Genomics and Bioinformatics

P. Baldi, Director
www.igb.uci.edu

Institute for Genomics and Bioinformatics (IGB)

- Collection of about 100 laboratories across the Schools of Biological Sciences, Engineering, Information and Computer Sciences, Medicine, and Physical Sciences
- Physical building for the central administration and computational personnel and facilities

IGB Mission

1. **RESEARCH:** Foster and Conduct world-class basic and applied research and promote innovation at the intersection of the life and computational sciences

IGB Mission

2. EDUCATION: Train the next generation of scientists at the intersection of the life and computational sciences

Biomedical Informatics Training Program supported by largest NIH/NLM Training Grant over the past 10 years (over 70 alumni, ~1 M per year). Currently: 28 graduate students, 6 postdocs. Annual BIT Symposium.

IGB Mission

3. TECHNOLOGY TRANSFER AND

OUTREACH: Work with established companies, start-ups, government agencies, and other research centers and universities world-wide to develop and transition technologies to widespread and practical applications

Several successful startups including: Antigen Discover, Reaction Explorer, and Verdezyne

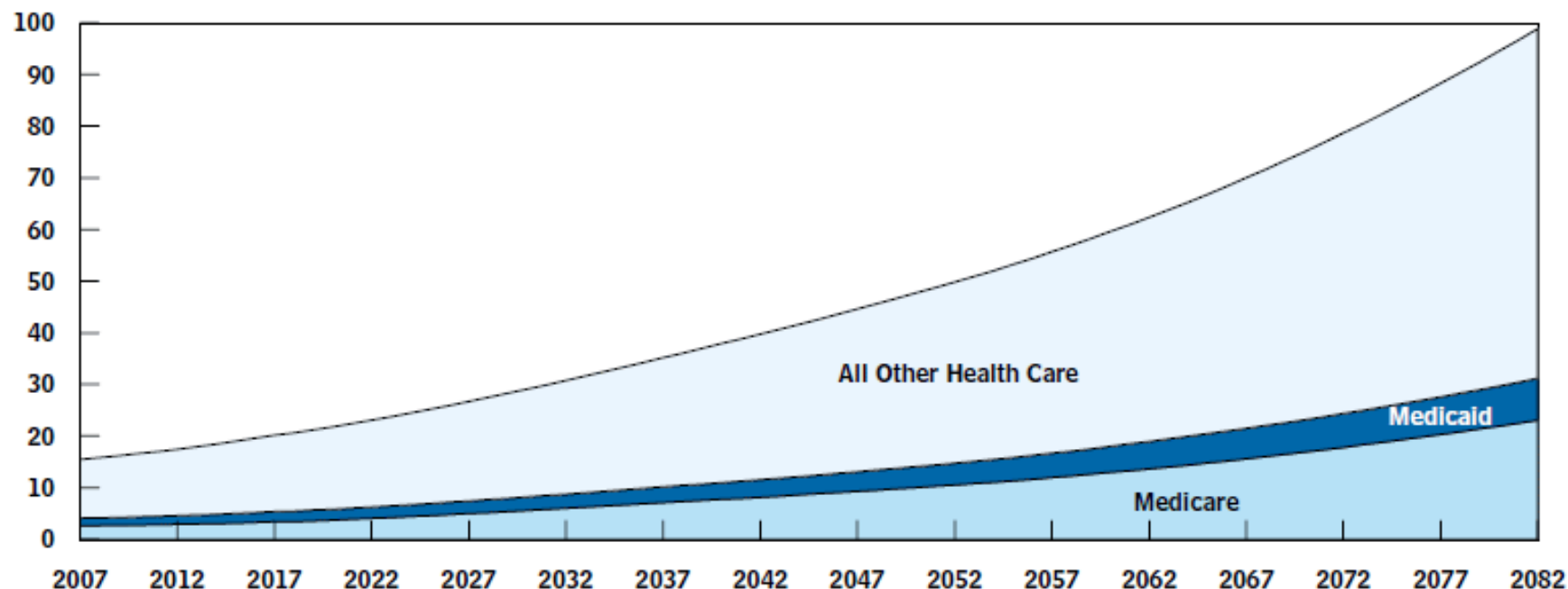
The Great Challenges

- Climate Change
- Energy
- Health Care

Figure D-1.

Projected Spending on Health Care Under an Assumption That Excess Cost Growth Continues at Historical Averages

(Percentage of gross domestic product)

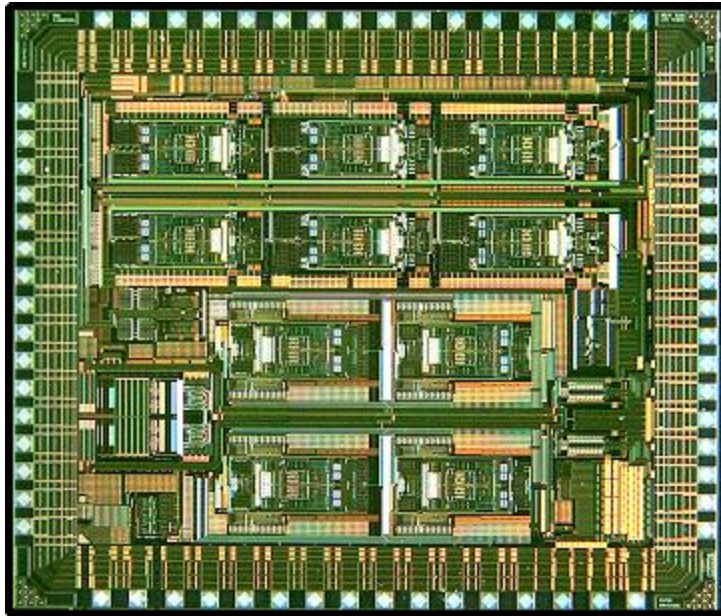


Source: Congressional Budget Office.

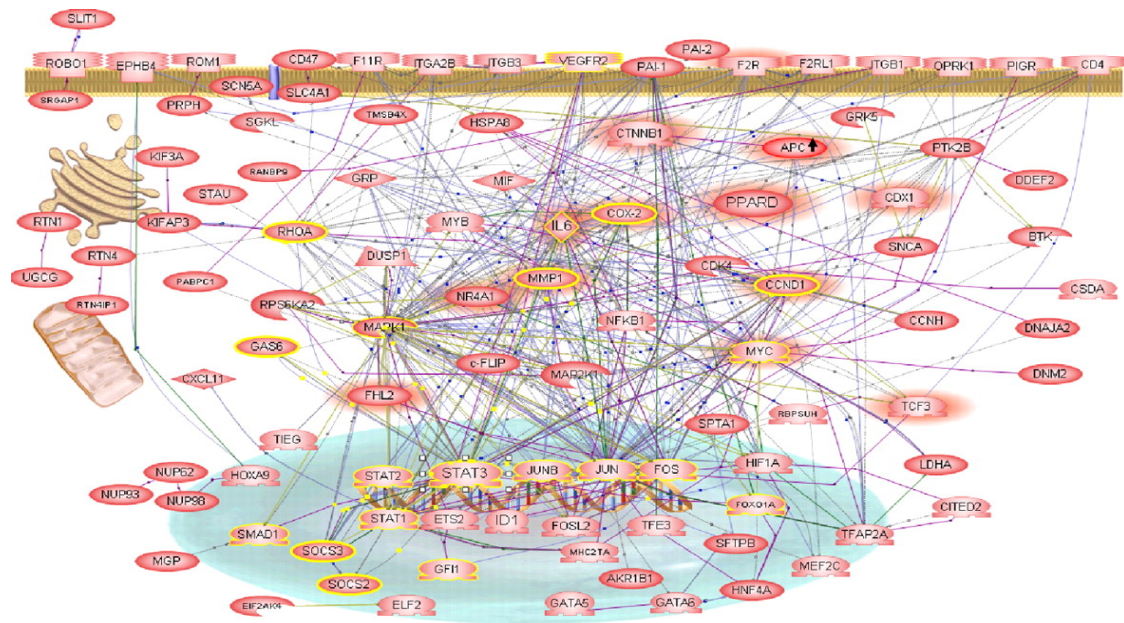
Notes: Excess cost growth refers to the number of percentage points by which the growth of spending on Medicare, Medicaid, or health care generally (per beneficiary or per capita) is assumed to exceed the growth of nominal gross domestic product (per capita).

Amounts for Medicare are net of beneficiaries' premiums. Amounts for Medicaid are federal spending only.

The Great Opportunities



Silicon-based computing



Carbon-based computing

TTCTCGATTATCCTTATAGTTTCATACG
GCATGCTTCAATTGTATGATAATGTTTTCAATGTAAGAGATTTTCGATTATCCTTATAGTTCATACATGCATGCTTCAACTACTTAAATAAATGATTGTATGATAATGTTT
CAATGTAAGAGATTTTCGATTATCCTTATAGTTCATACATGCATGCTTCAACTACTTAAATAAATGATTGTATGATAATGTTTTCTCCTTATCCTTATAGTTCATACATGC
TTCAACTACTTAATAAATGATTGTATGATAATTAATAAATGATTGTATGATAATGTTTTCAATGTAAGAGATTTTCGATTATCCTTATAGTTCATACATGCATGCTTCAAC
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Short History of Genomics

- Genomic Era:

1953: Watson-Crick	1989: Human Genome Project	2001: Human Genome Draft	2008: Venter/Watson Genomes //1,000 Genome Project	2012: \$,1000/ Genome	2016: \$ 100/ Genome	2025-2030: “brain- equivalent” computer power

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- Post Genomic Era:

Short History of Genomics

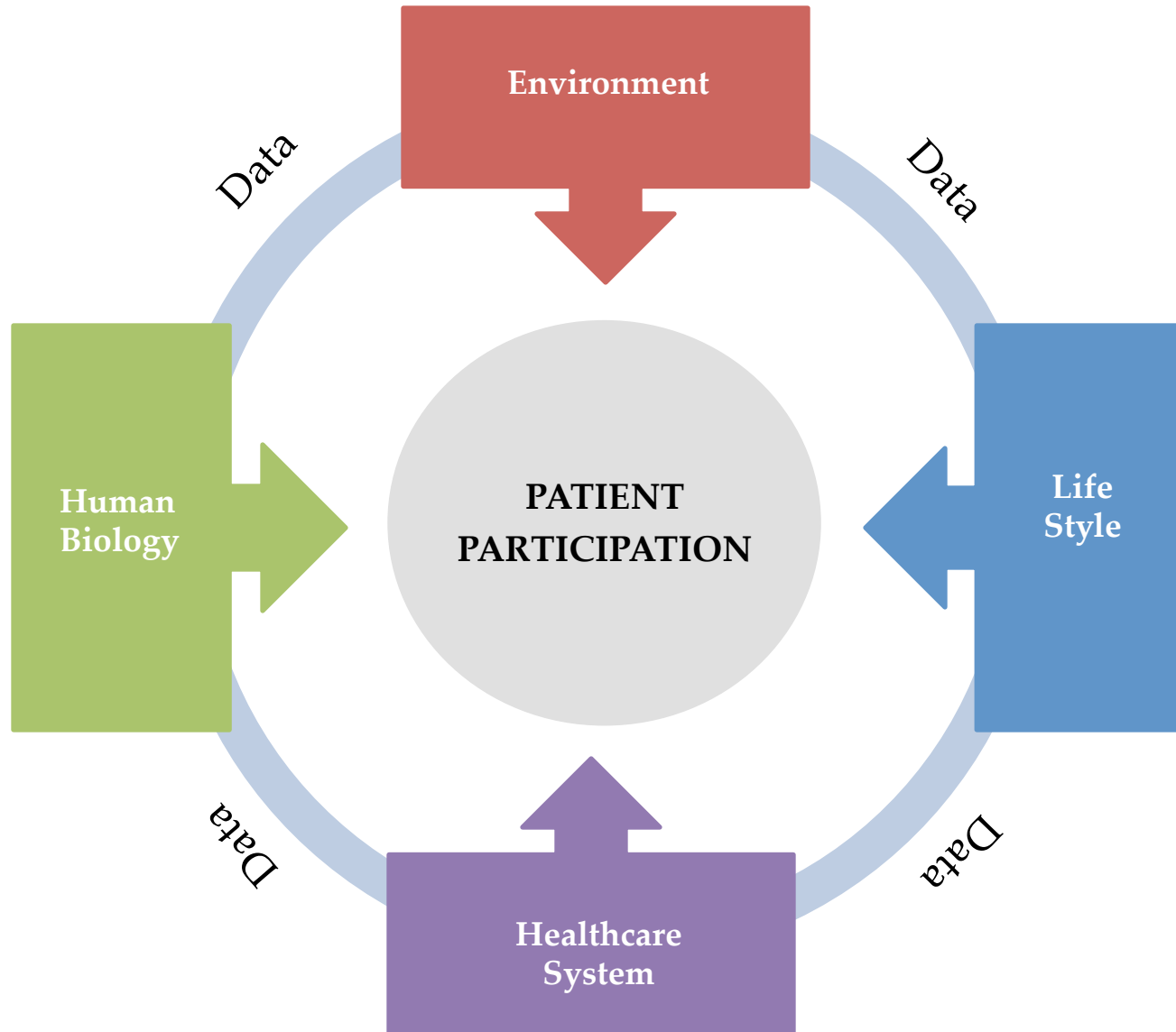
- Genomic Era:

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- Post Genomic Era:

- P4 Medicine (predictive, preventative, personal, participatory) Era:

Optimization of Health



[illegible]

[illegible]

Known motifs are preferentially conserved

human	CTCTTAATGGTACACGTTCTGCCT----	AAGTAGCCTAGACGCTCCCGTGCGCCC-GGGG
dog	CTCTTA-CGGGGCACATTCTGCTTTCAACAGTGGGGCAGACGGTCCCGCGCGCCCCAAGG	
mouse	GTCTTAGGAGGCT-CGATCGCC-----	GCCTGCATTATT-----
rat	GTCTTAGTTGGCCACGACCTGC-----	TCATGCATAATT-----

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Error

human	CGGGTAGGCCTGGCCGAAAATCTCTCCCGCGCGCC	TGACCTTG	GGTTGCCCCAGCCAGGC
dog	CAGGC---CCGGGCTGCAGACCTGCCCTGAGGGAA	TGACCTTG	GGCGGCCGCAGCGGGGC
mouse	-----CACAAGCCTGTGGCGCGC-CG	TGACCTTG	GGCTGCCCCAGGCGGGC
rat	-----CACAAGTTTCTC---TGC-CG	TGACCTTG	GGTTGCCCCAGGCGAG-

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human	TGCGGGCCCGAGACCCCCG-----	GGCCTCCCTGCCCCCGCGCCG
dog	CGCGGGCCCGAGCCCCCCTCCCTCCCTCCCTCCCTCCCTCCCTGCCCCCGGACCG	
mouse	TGCAGGCTCACCACCCCGTCTTTTCT-----	GCTTTTCGAGTCG
rat	-GCATACACCCCGCCTTTTTTTTTTTTTTTT-----	TTTTTTTTTGGCGTTCAAG-AG

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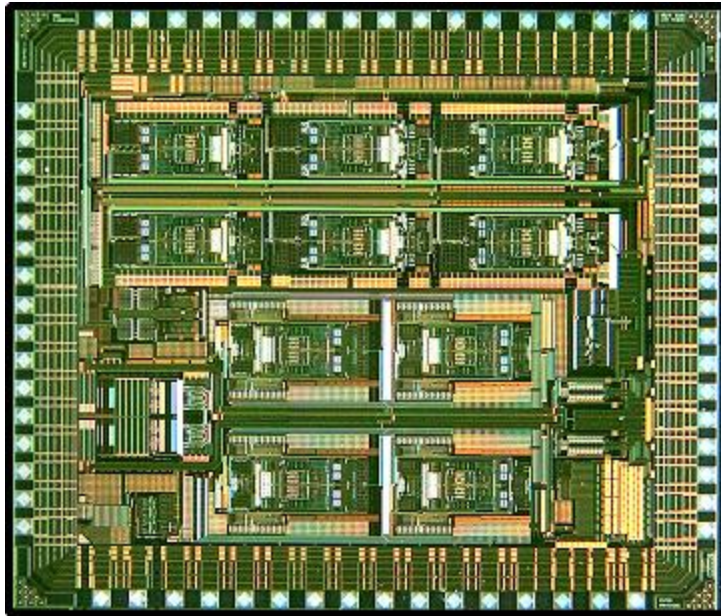
- Post Genomic Era:

- P4 Medicine (predictive, preventative, personal, participatory) Era:

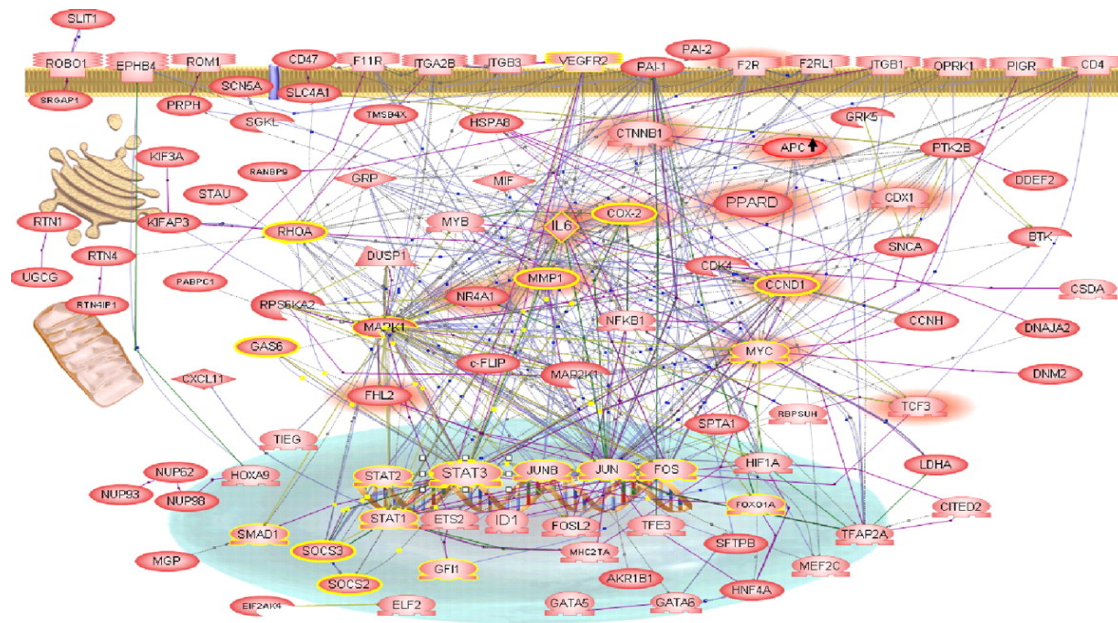
IT Infrastructure for Genomic Enabled Personalized Medicine

- \$100 Genome
- Genome Storage and Integration (EMR)
- Genome Compression
- Genome Privacy
- Genome Annotation/Interpretation
- Accelerate Drug Discovery

The Great Opportunities

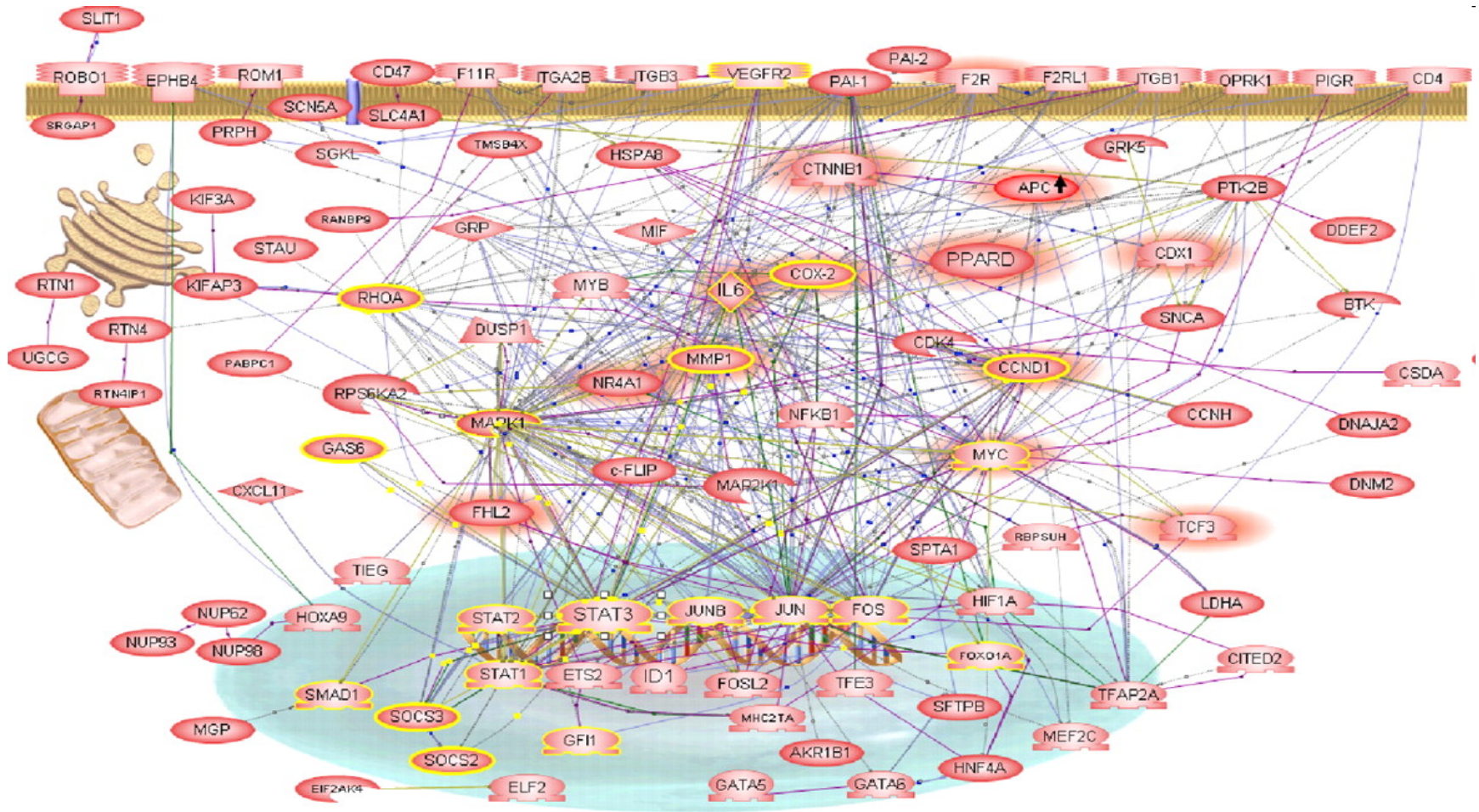


Silicon-based computing



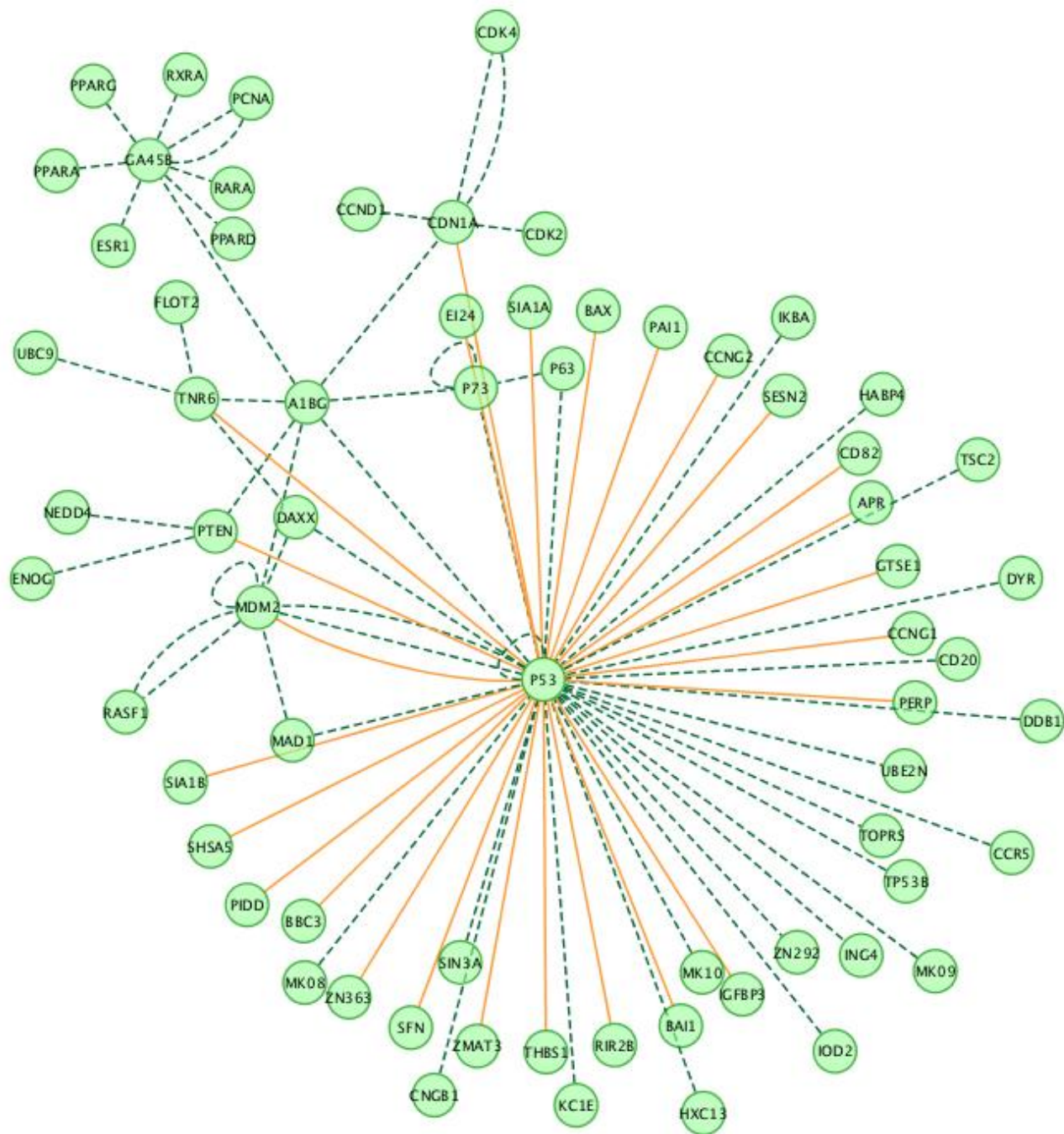
Carbon-based computing

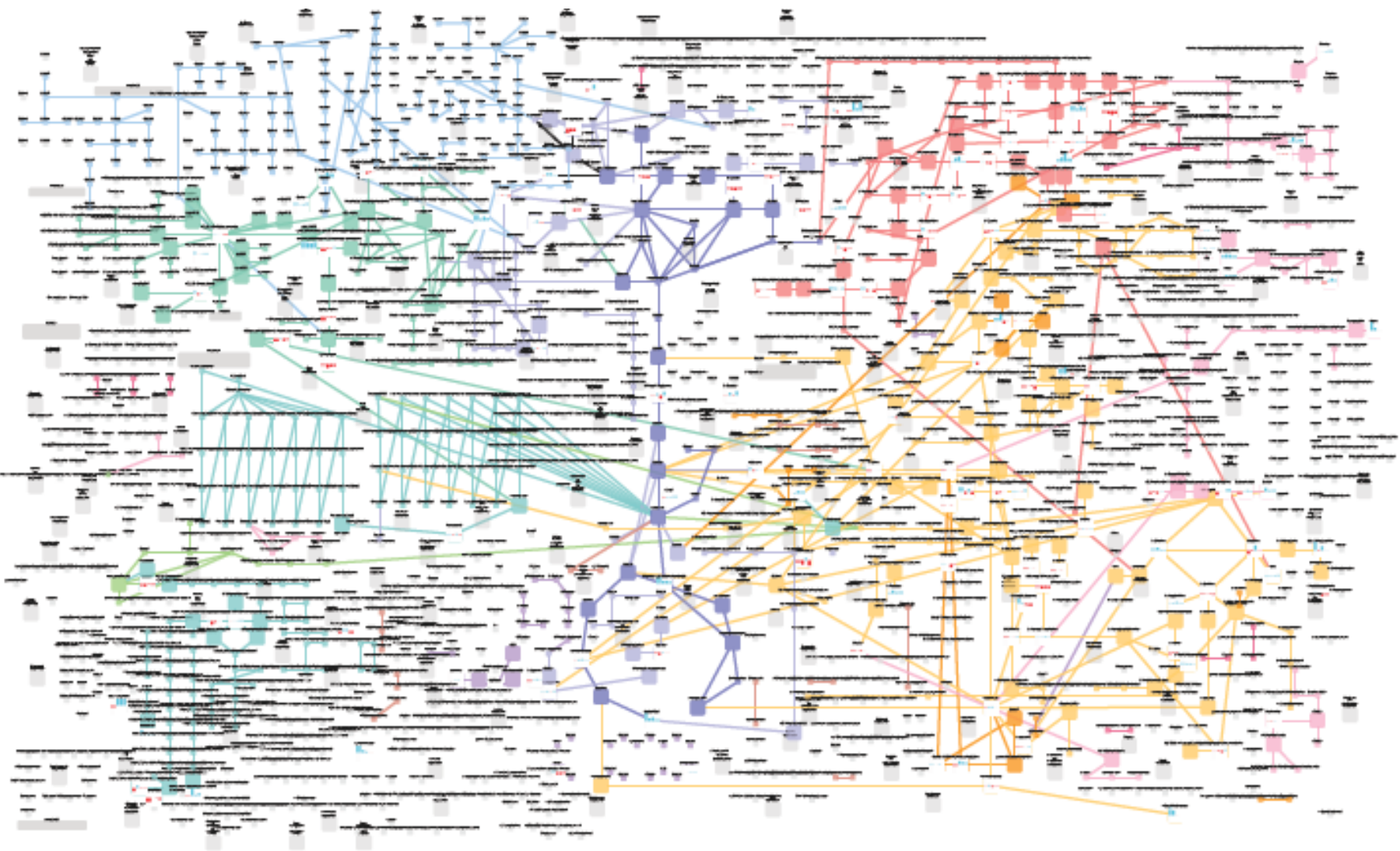
Genome Interpretation

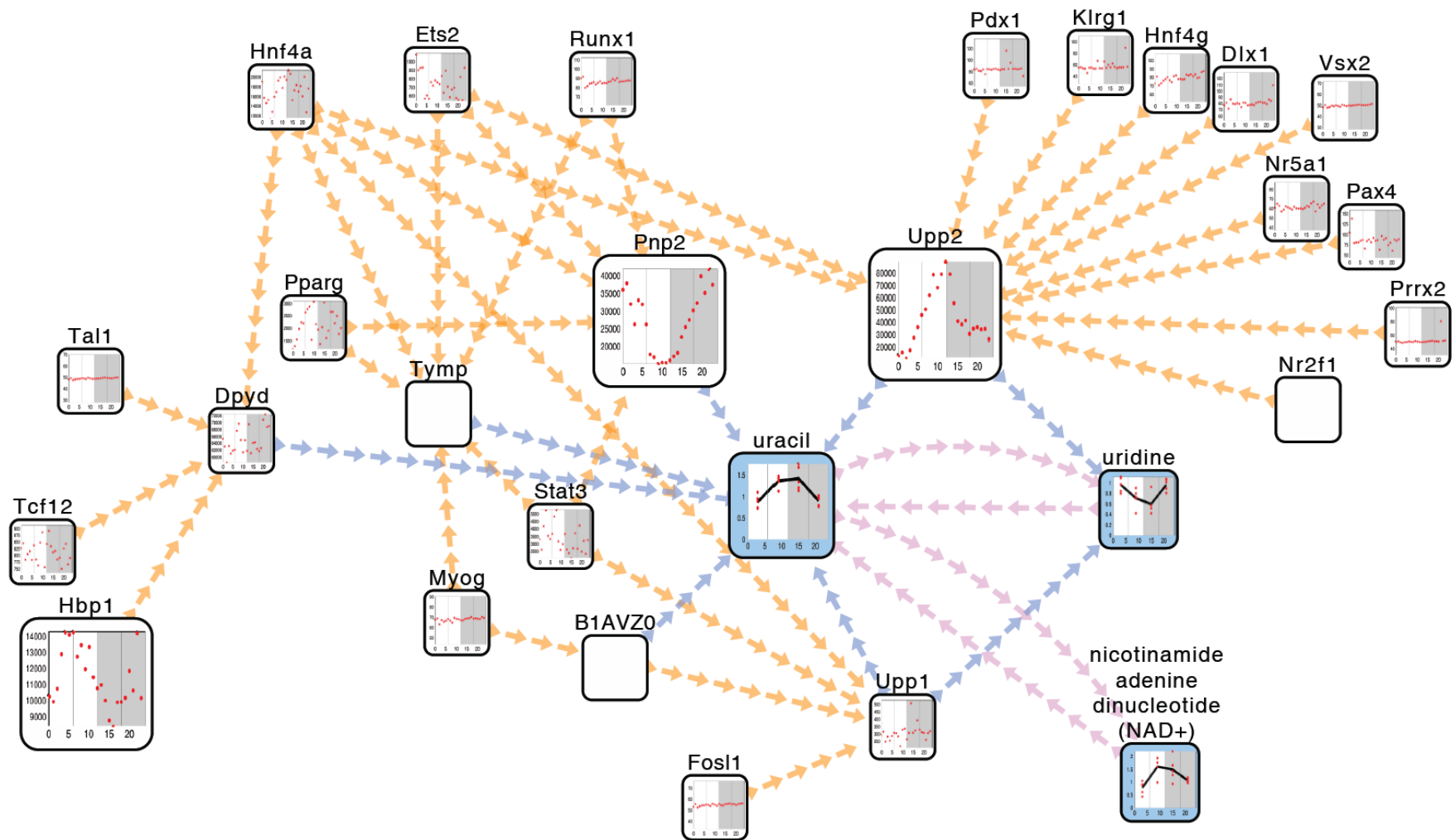


Can we begin to draw biological circuits automatically?

ctions(Orange)



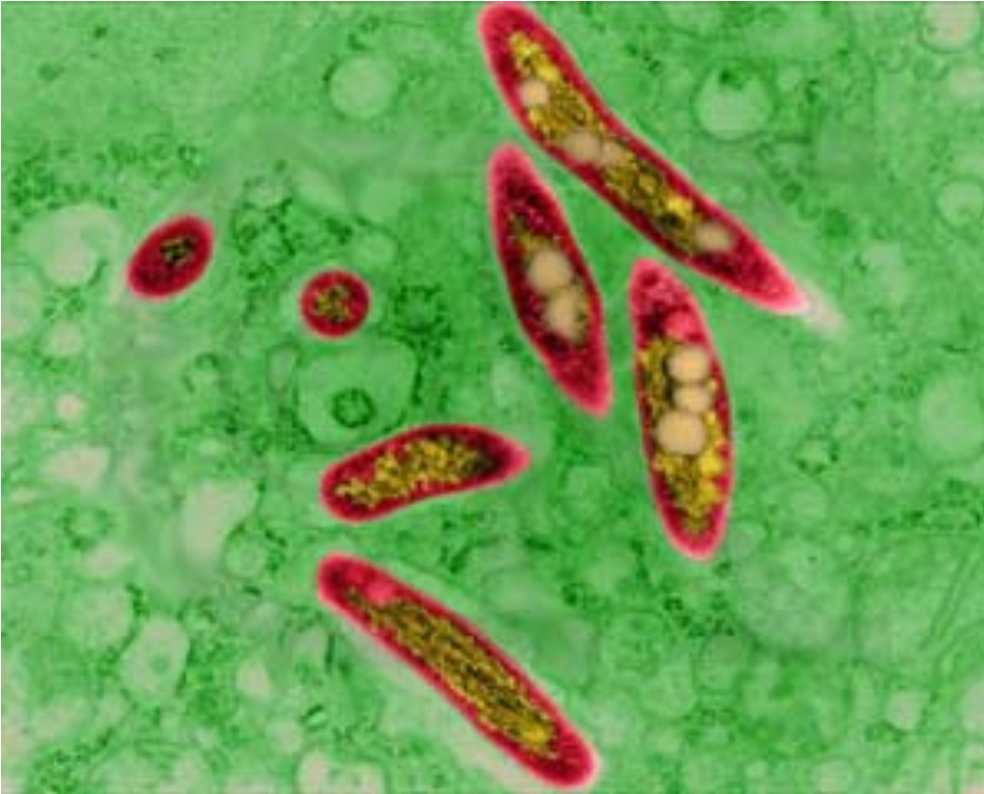




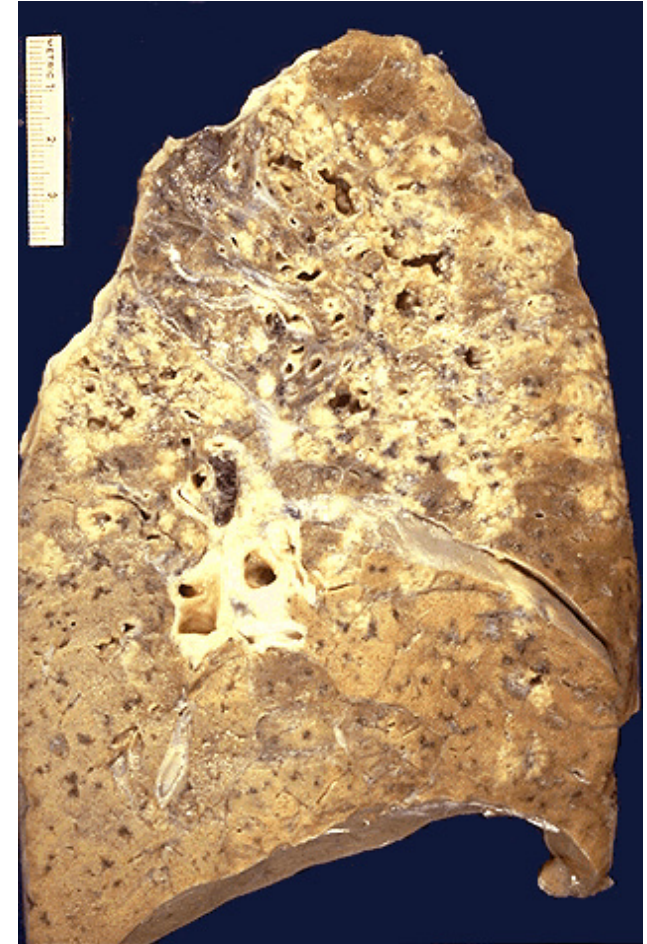


Drug Discovery

Example: Tuberculosis



Mycobacterium Tuberculosis
Very thick, waxy cell wall



TB: still a real threat, because.....

Urogenital Infection by *Mycobacterium bovis* Relapsing after 50 years

K. E. Lewis¹, M. G. Lucas², R. Smith³ and N. K. Harrison^{*1}



Its ability to stay alive

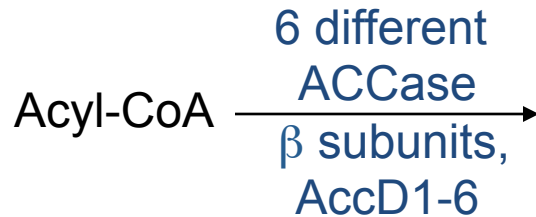


Multi-Drug Resistant
(Super TB strain)

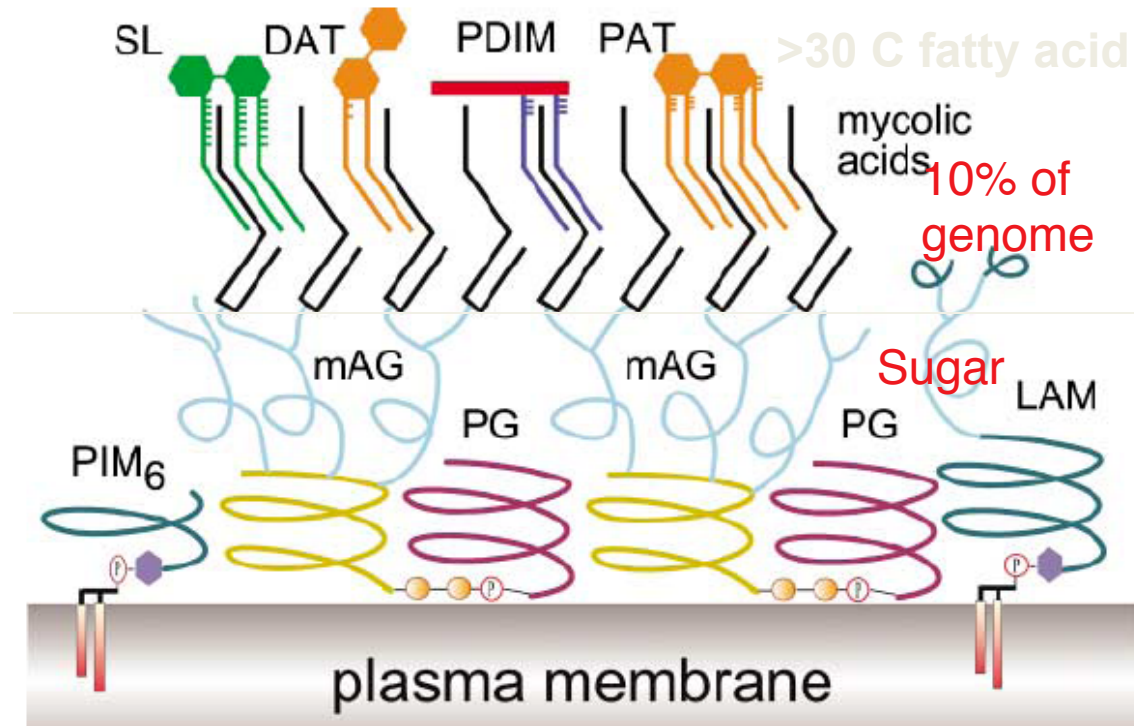
The Cell Wall: Key to Pathogen Survival

Tuberculosis

- 7th cause of death worldwide
- 1 in 3 people have TB
- Leading cause AIDS death
- Multi-drug resistant
- *Mycobacterium tuberculosis*



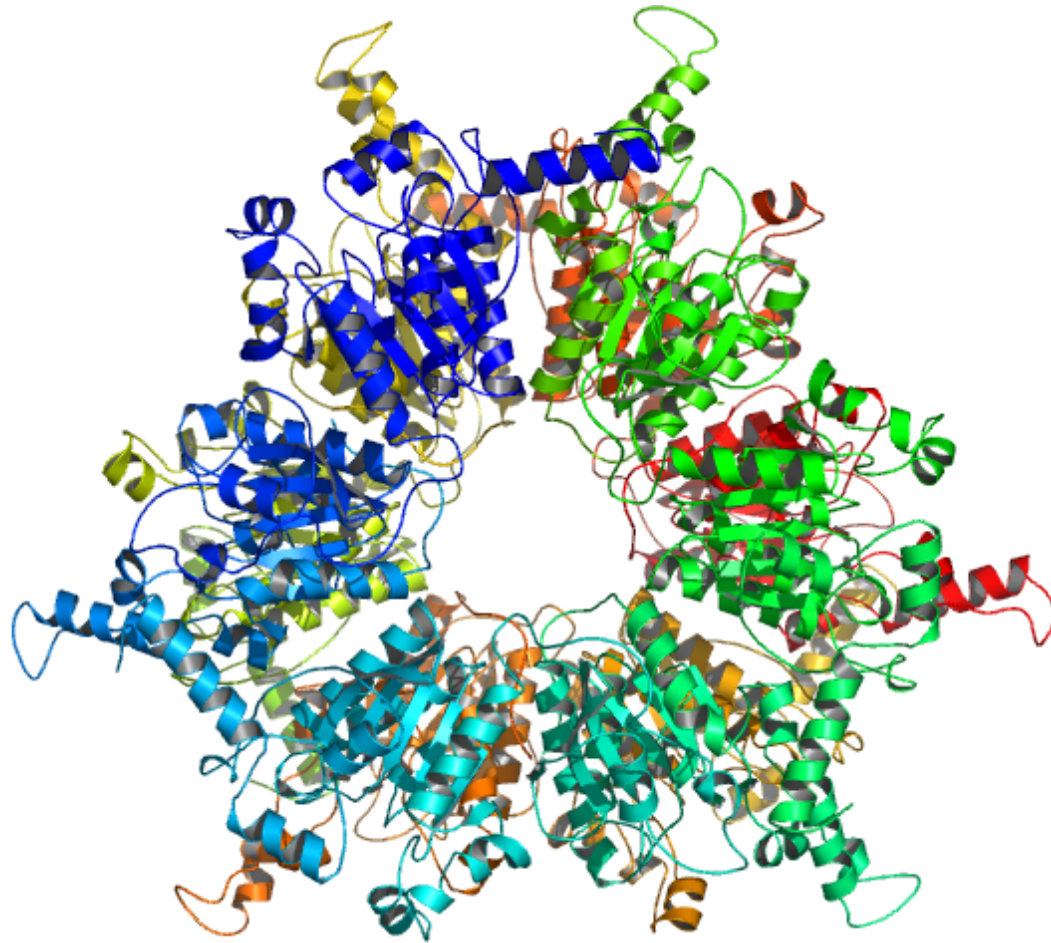
Homologs of PccB Focus on AccD4-6



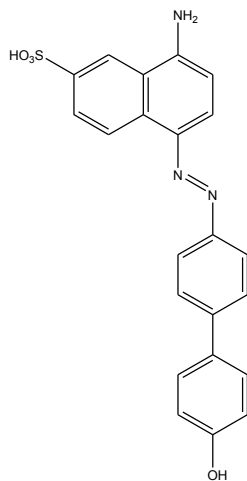
Cell wall lipids: Important for pathogen virulence, survival and latency

Substrate specificity for AccD4-6?

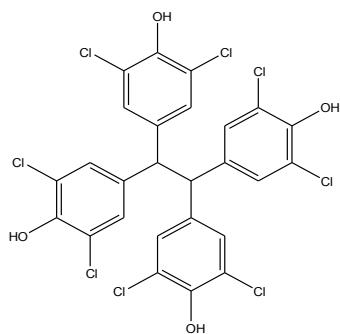
Structure of AccD5



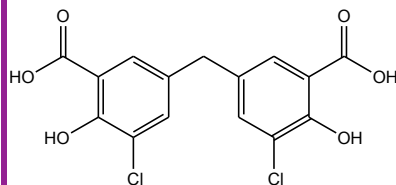
NCI 65828 (Lead 1)



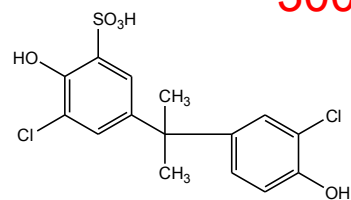
NCI 172033 (Lead 2)



NCI 622444 (IN1)

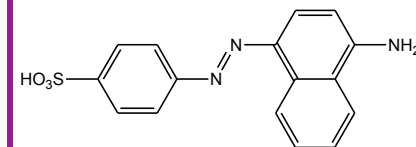


NCI 65079 (IN2)

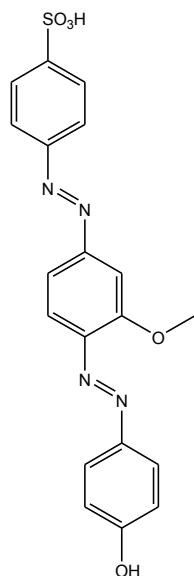


300uM

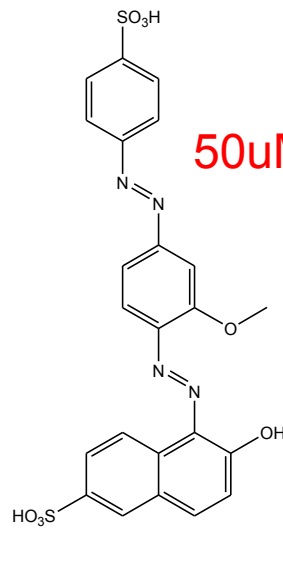
NCI 4901 (IN3)



NCI 65538 (IN4)

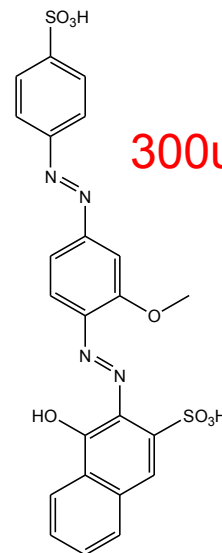


NCI 65553 (IN5)



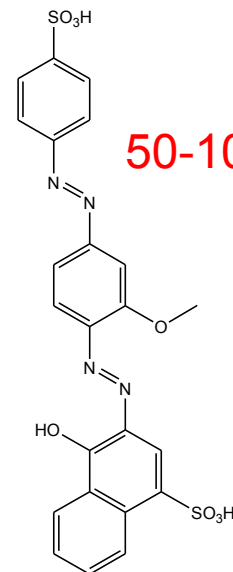
50uM

NCI 65554 (IN6)



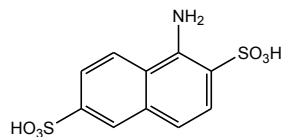
300uM

NCI 65555 (IN7)

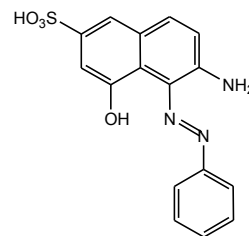


50-100uM

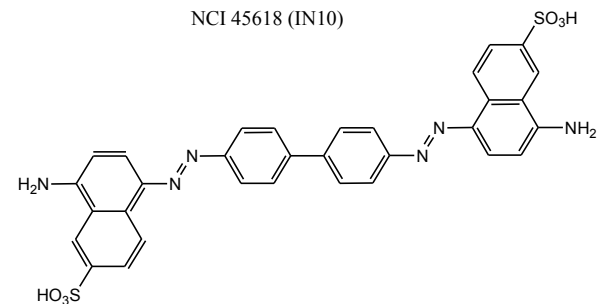
NCI 37050 (IN8)



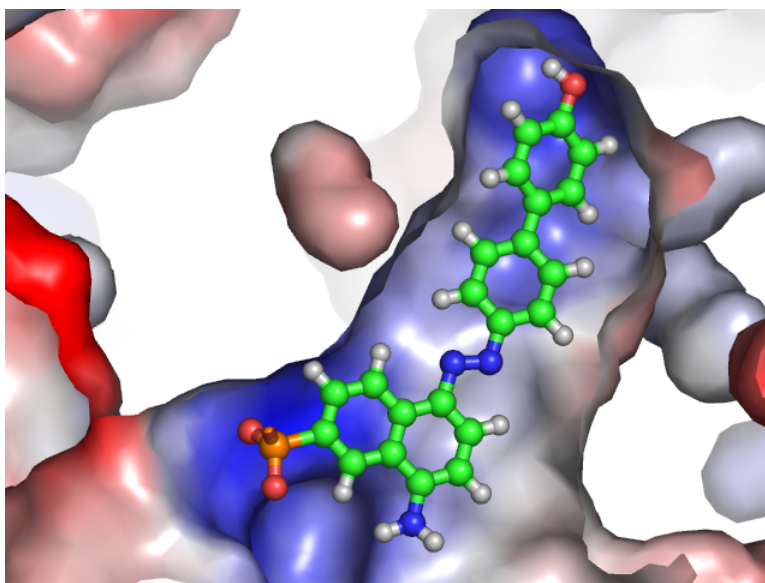
NCI 45188 (IN9)



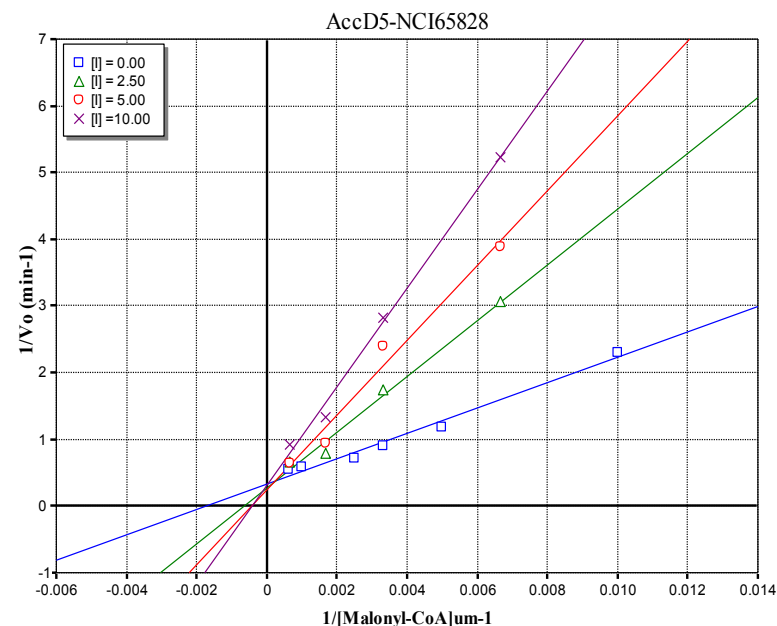
NCI 45618 (IN10)



Structure-Based Drug Design Identified AccD5 Inhibitors



$$K_i = 4.7 \mu\text{M}$$



➔ **New TB drug lead**

T. Lin, M. Melgar, S. J. Swamidass, J. Purdon, T. Tseng, G. Gago, D. Kurth, P. Baldi, H. Gramajo, and S. Tsai.
Structure-Based Inhibitor Design of AccD5, an Essential acyl-CoA Carboxylase Carboxyltransferase Domain of *Mycobacterium tuberculosis*.
Proceedings of the National Academy of Sciences USA, 103, 9, 3072-3077, .US Patent pending

Genome-Enabled Personalized Medicine: Whole Proteome Microarray Chip Fabrication

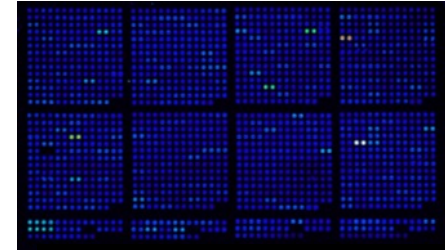
From genomic DNA to Proteome Array in 3 days

Day 1:

PCR

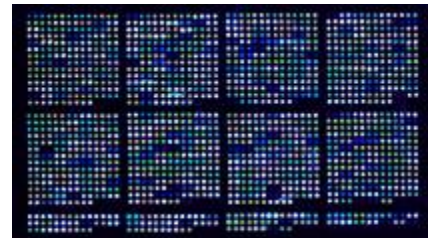
Genomic DNA +
Gene Specific
Primers

Transformation

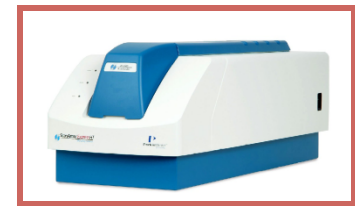


Day 2:

Plasmid DNA Miniprep
& Protein Expression



Scanning



Probing



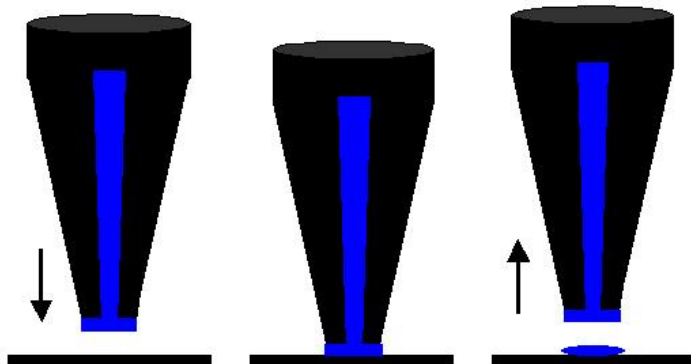
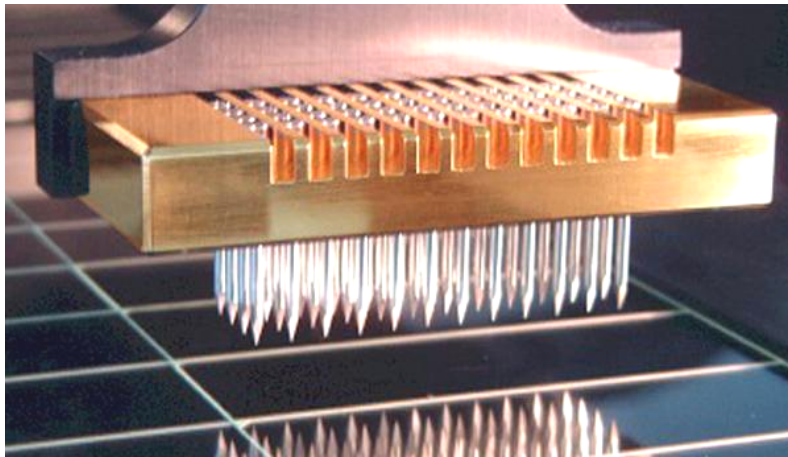
Day 3: Chip Printing



Proteome Microarray Chips

Fabrication

Contact Printing



Proteome Microarray Chips

Serology

**Serum from Infected
Animals or Humans (1
mu l)**

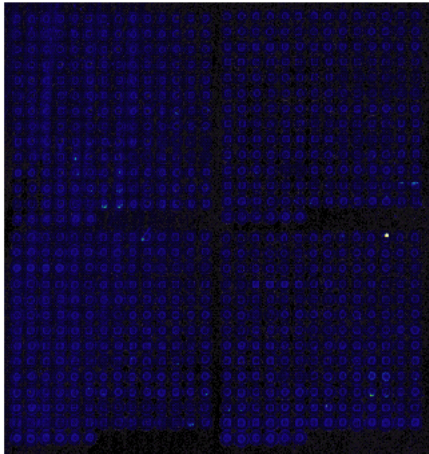


**Probe a
Microarray Chip**

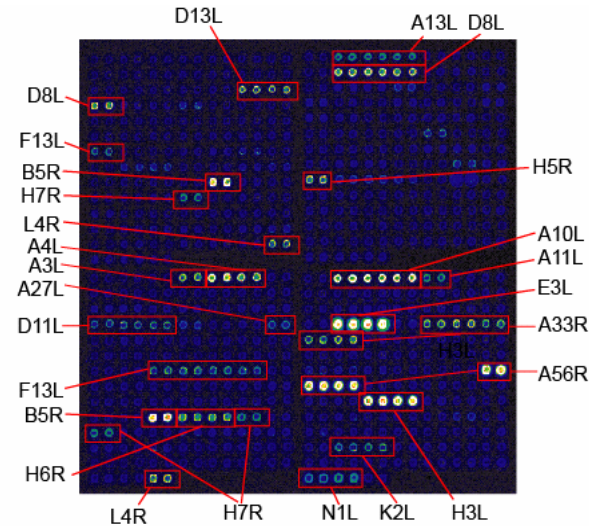


Smallpox Microarrays Probed with Mouse or Human VV Serum

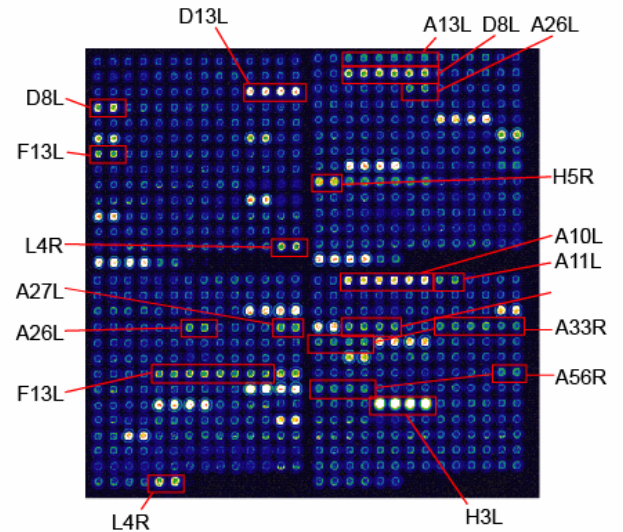
Naive Mouse



Vaccinia WR Immunized Mouse



Human Vaccinia Immune Globulin



Inventory of Cloned Genes

BLUE – New Targets
Homo Sapiens.....

BLACK – Previously
Supported Targets

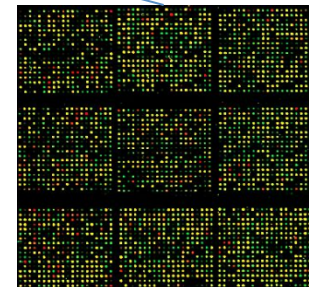
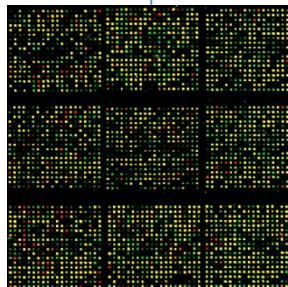
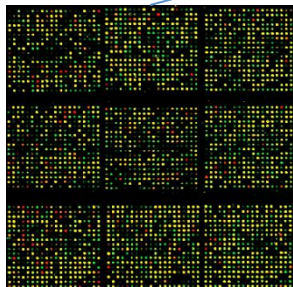
	Genomic gene #	Genes cloned	Percent Cloned
<i>F. tularensis</i>	1933	1874	97%
<i>C. burnetii</i> (TAP)	2065	2065	100%
<i>B. burdorferi</i>	1600	1269	84%
<i>M. tuberculosis</i>	3990	3899	98%
<i>B. pseudomallei</i>	5728	1333	23%
<i>C. Trachomatis</i> serovar D	894	884	99%
<i>P. falciparum</i>	5268	1899	36%
<i>B. melitensis</i>	3198	1371	43%
<i>L. interrogans</i>	3658	98	3%
<i>P. vivax</i>	5300	200 (2000 planned)	4%
<i>Rickettsia</i>	1500	Planned	
<i>Bartonella</i>	1500	Planned	
Orthopoxviruses	244	242	99%
HPV (11 types)	88	88	100%
HIV-1 (4 sub-types)	83 attempted	74	89%
Herpes 1 & 2	172	140	81%
West Nile	10	10	100%
Dengue (3 types)	55 attempted	42	76%
Arboviruses (12 types)	120	Planned	
Total	37,240	13,064	35%

Arrays and Immunostrips

- Being tested on the field:
- *F. Tularensis* (Spain)
- Dengue (Brazil, Thailand, India)
- *Burkholderia* (Thailand)
- TB (Africa, India)
- Malaria (Africa)

Research Directions in ICS

- Data structures and compression algorithms for genomic data



Short History of Genomics

- Genomic Era:

1953: Watson-Crick	1989: Human Genome Project	2001: Human Genome Draft	2008: Venter/Watson Genomes //1,000 Genome Project	2012: \$,1000/ Genome	2016: \$ 100/ Genome	2025-2030: “brain- equivalent” computer power

- Post Genomic Era:

- P4 Medicine (predictive, preventative, personal, participatory) Era:

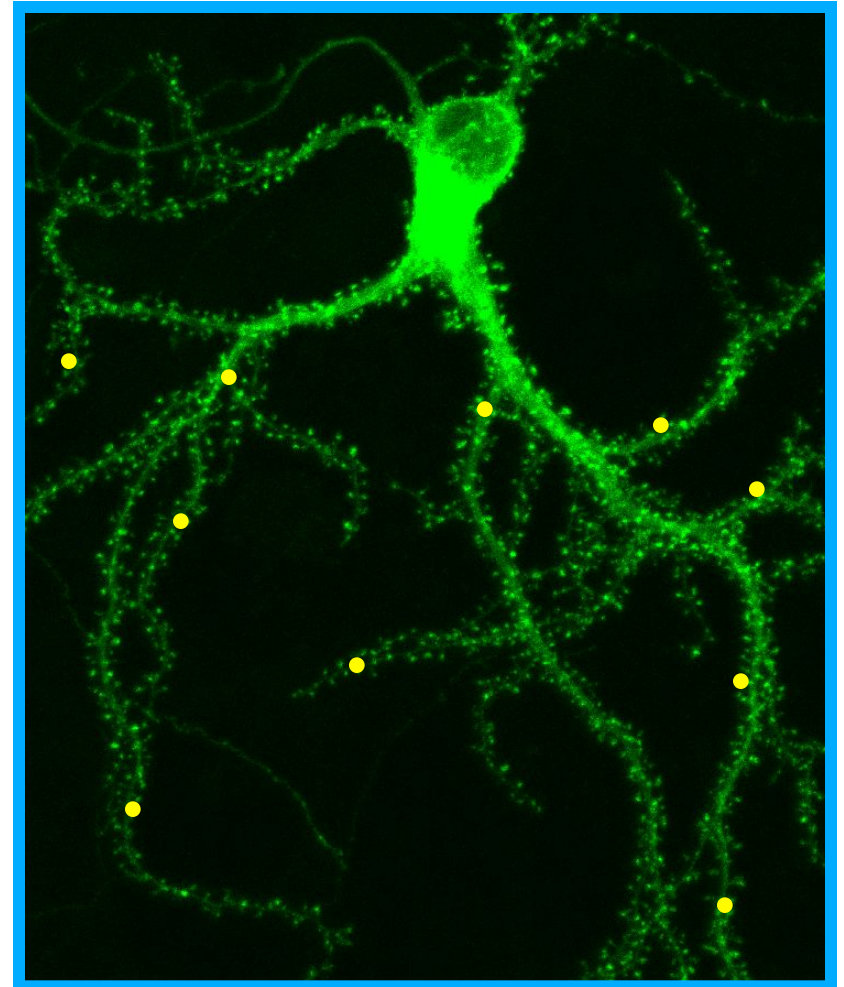


Where do you store your telephone number?

THE SYNAPTIC BASIS OF MEMORY CONSOLIDATION



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Many Other Activities

- Education
- Symposia, Speaker Series
- Incubator
 - Verdezyne
 - IMMport Therapeutics//Antigen Discovery Inc.
 - Reaction Explorer
- Virtual Campus