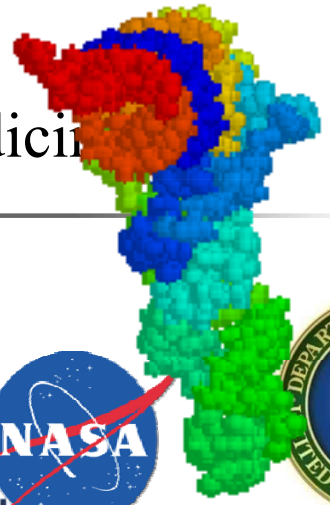
PGP- open access to genome sequences + trait data

2-2:45 PM 14-Sep-2011 Personalized Genomics/Medici



Edge Edge Edge

Thanks to:

.gov

NIGMS

.edu

.org

.com

National Cancer Institute

NLM

National Heart Lung and Blood Institute

NSF

NASA

Department of Energy United States of America

NHGRI

Bridging the Gap DARPA 50 Years Powered by Ideas 1958 2008

HSCI Harvard Stem Cell Institute

Wyss Institute

华大基因 BGI

Harvard

MIT

Broad Institute

Boston University

LSRF

ArmRev.org

PERSONALGENOMES.ORG

Oppenheimer Foundation

Bill & Melinda Gates foundation

PBS

The Ellison Medical Foundation

molecular systems biology

A new type of online journal from EMBO and Nature Publishing Group

Google

Isilon Systems

Autodesk

BBC

Ab Vitro

Merck

Knome

LS9, Inc.

Robinson Bradshaw

23andMe

Helicos BioSciences Corporation

Coriell Institute for Medical Research

P&G

Chevron

Azco

Affymetrix

Roche

GoodStart Genetics

illumina

enzymatics

Agilent Technologies

Joule

Gen9

life technologies

Complete genomics

Applied Biosystems

Danaher Motion

QTEROS Biofuels from advanced microbiology

OrbiMed Healthcare Fund Management

Cellular Dynamics International

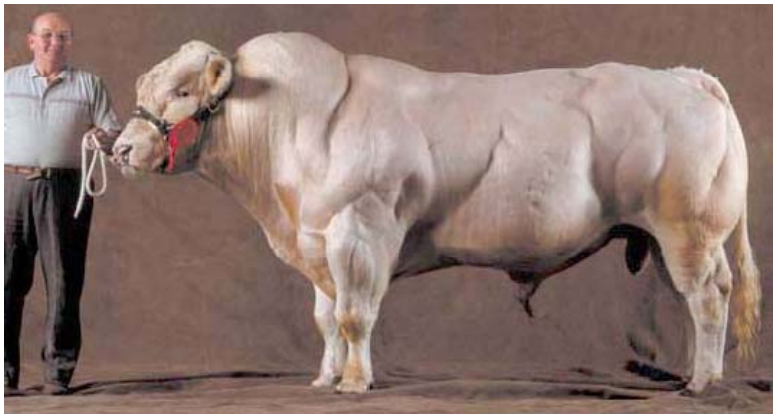
Read = = = = = = = = = I/O = = = = = = = = Write

2011: What's next

1. Handheld, no prep/library/amplification
2. In situ : 3D/4D tissues
   (cancer, inflammation, infection)
3. Interpretation & integration software
4. Great cohorts to test drive tech & personalized medicine

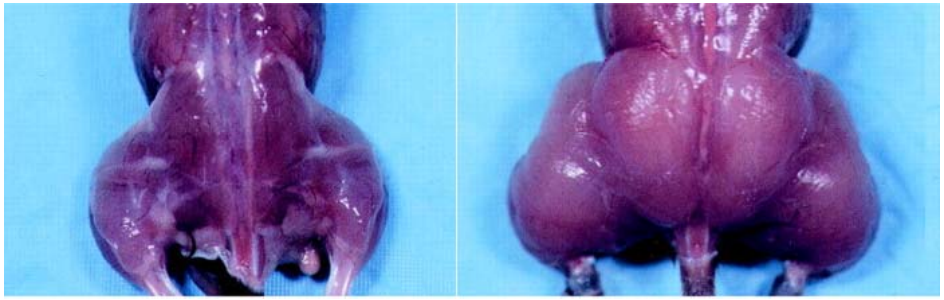
Myostatin extremes

Enhanced muscle growth, decreased body fat & decreased atherosclerosis (2009 Endocrine Society, Bhasin, et al BU)



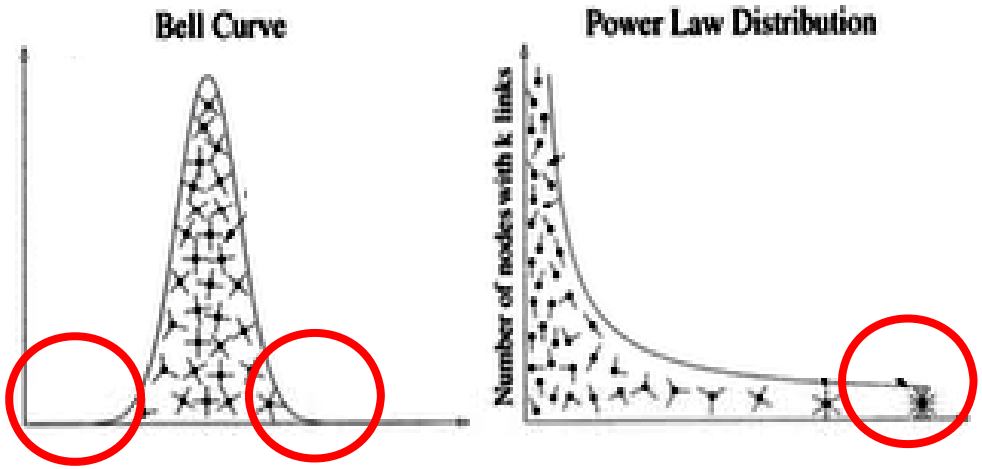
Flex Wheeler

MSTN -/-



Prevention/Cure can be creatively far from the initially discovered Cause.

- A minor allele can be a cure: e.g. CCR5
- Gene therapy T/B cells – e.g. CML
- Embrace the extremes: more informative & easier
- Next extremes: old age with youthful health



Genomes = Traits

Evidence.personalgenomes.org

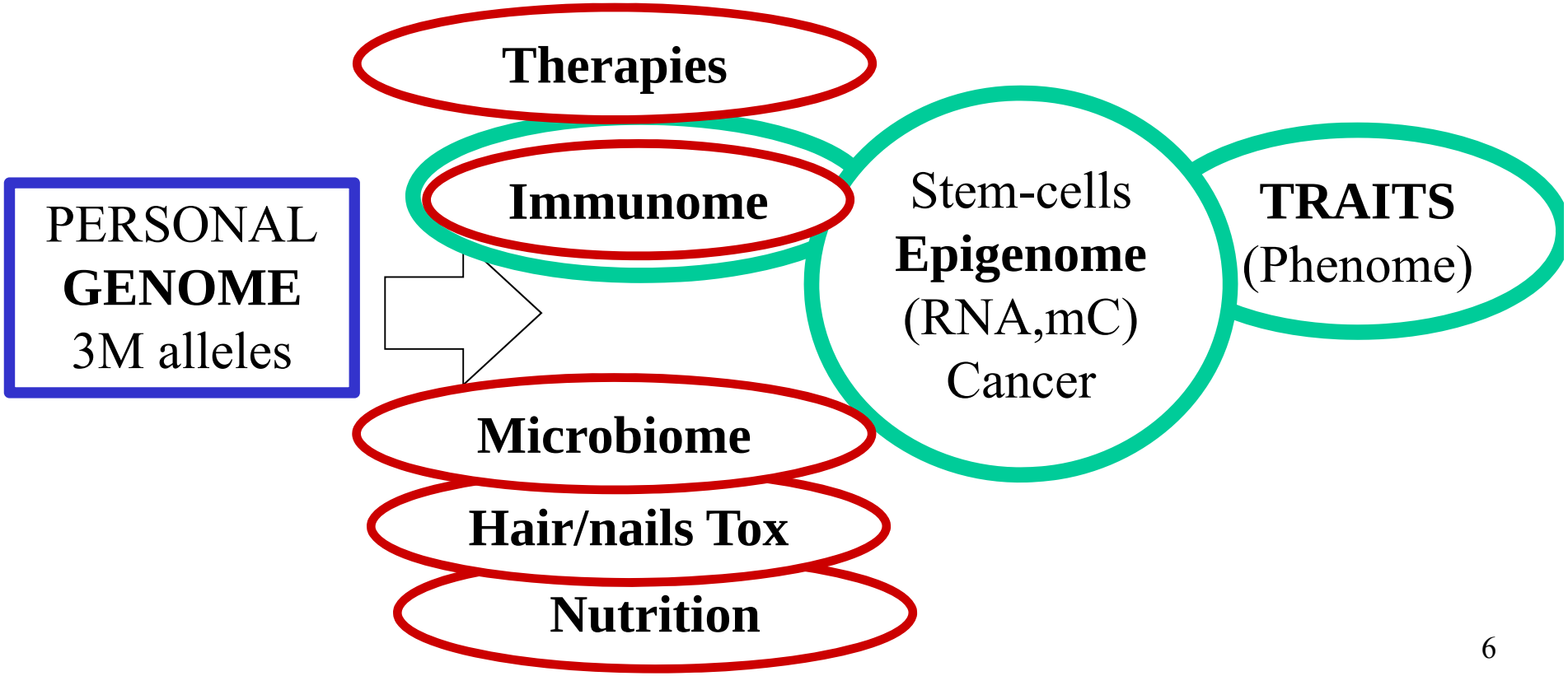
PERSONAL
GENOME
3M alleles

TRAITS
(Phenome)

Genomes + Environments = Traits

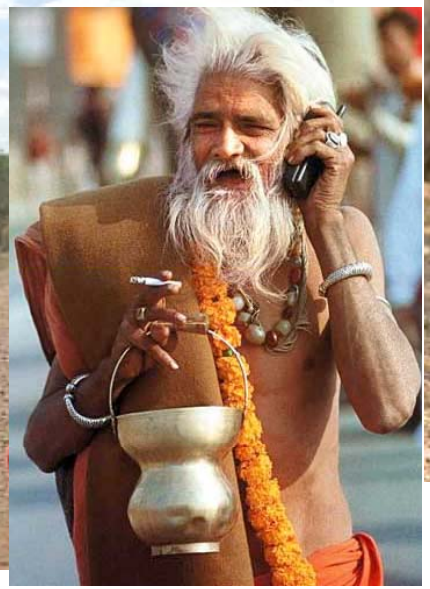
PersonalGenomes.org

Evidence.personalgenomes.org

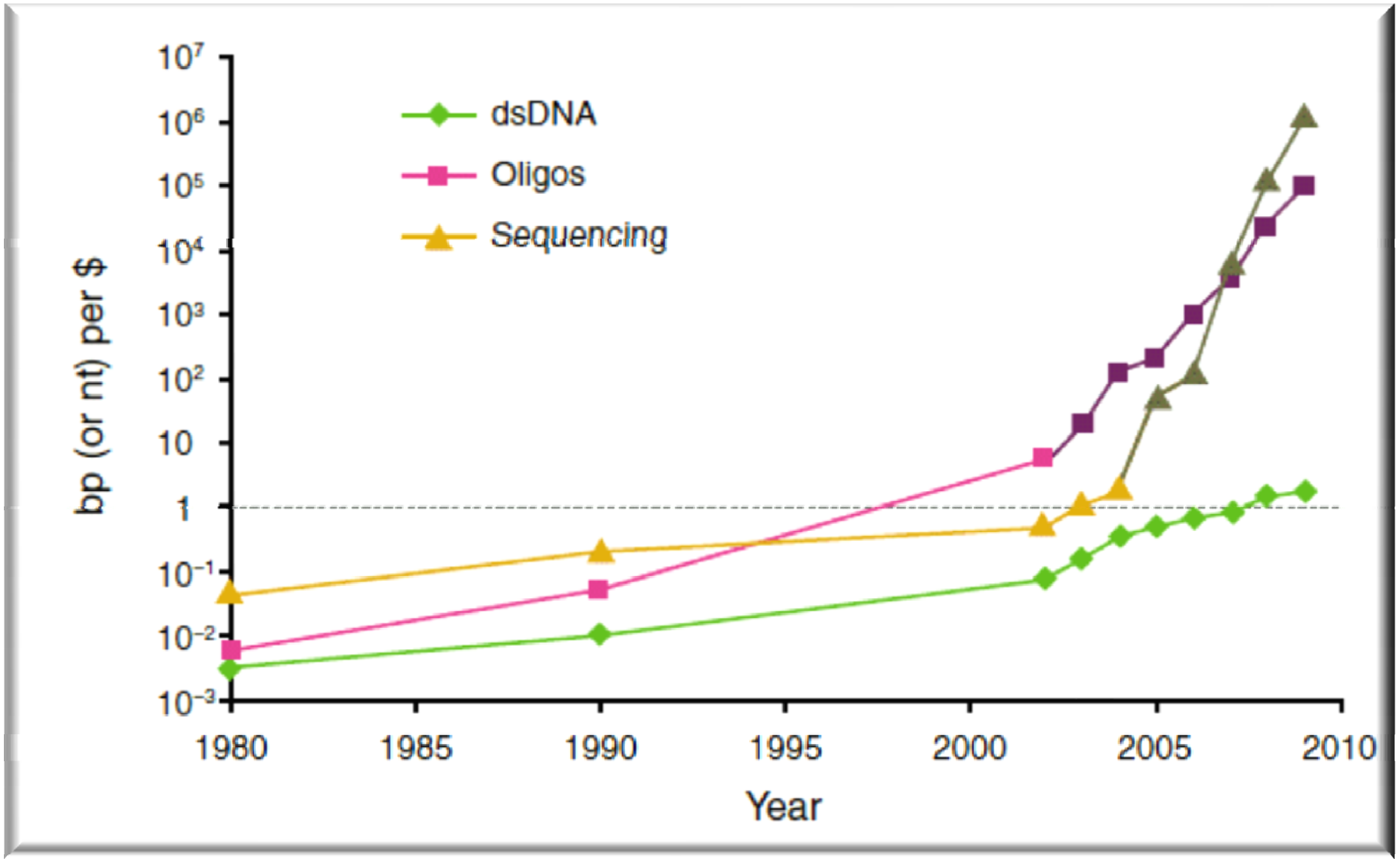


Cost reduction for developing nations: Diagnostics, preventions, therapies

"$20 per [outpatient cataract] surgery… intraocular lens replacement which costs $3,500 in the US"



2011: What's next



Carr & Church, Nature Biotech

37 Next-generation sequencing technologies

1. Polonator MA
2. Roche-454 CT
3. AB-SOLiD MA
4. Illumina CA
5. CGI CA
6. Helicos MA
7. Pacific Bio CA
8. Intelligent Bio MA
9. Ion Torrent CT
10. Genapsys CA
11. Electronic Biosci CA
12. **Nabsys RI**
13. **OxfordNanopore UK**
14. **IBM-Roche NY**
15. **NobleGen MA**
16. **Genia CA**
17. LightSpeed CA
18. GnuBio MA
19. Bionanomatrix PA
20. Halcyon CA
21. ZS Genetics NH
22. Genizon BioSci QC
23. LaserGen TX
24. Visigen/Starlight TX
25. GE Global NY
26. Stratos Genomics WA
27. Reveo NY
28. AQI Sciences AZ
29. Base4innovation UK
30. Li-Cor NE
31. U.S. Genomics MA
32. Mobious Genomics UK
33. Nanophotonics Biosci CA
34. Network Biosystems MA
35. SeiraD NM
36. Affymetrix CA
37. Population Gen Tech UK

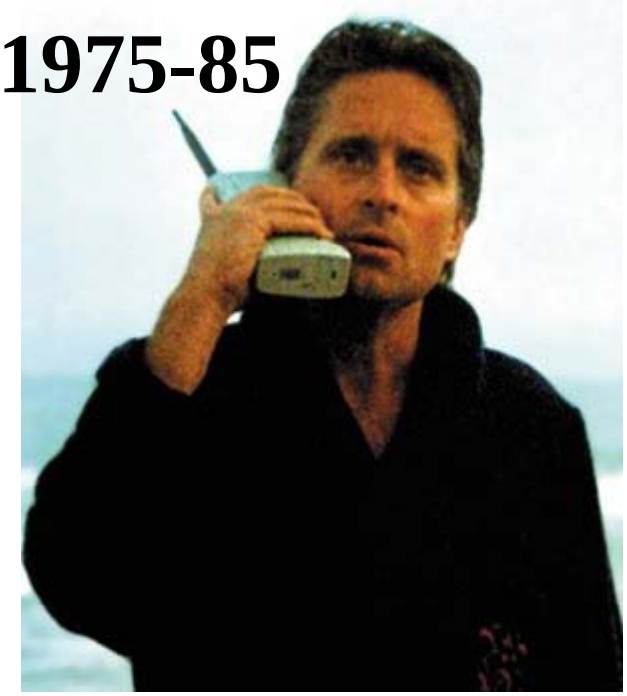
http://arep.med.harvard.edu/gmc/nexgen.html

8 Niches:

- $/bp
- $/run
- $/device
- Read length
- Repeats
- Speed
- In situ
- Portability

Technologies (phone, apps, web, wiki) only as good as their shared communities

1975-85



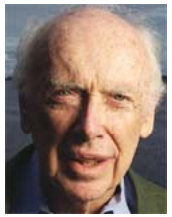
1990

2001

Open access cohorts to test-drive personalized medicine

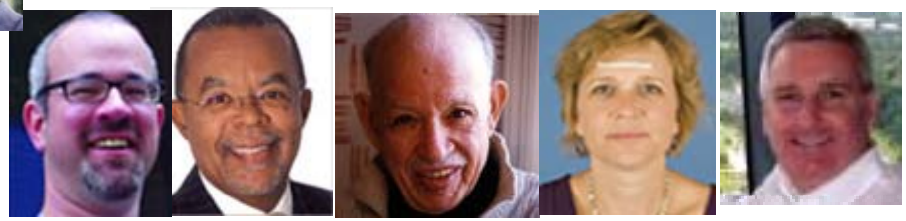
ABI Venter

454 Watson



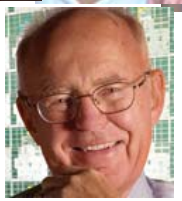
Helicos Quake

Illumina PGP#4,9,11,12,14



CGI PGP#1-10,13

IonTorr Moore



…

Genomes + Environments = Traits

PersonalGenomes.org

Individuals willing to have their genomes, cells (saliva, blood, skin, iPS), extensive trait data
Open-access : CC0

16K volunteers registered in 74 countries
2,418 achieved 100% on entrance exam
1,056 have medical records online
500 complete genomes in the pipeline

US clinics quietly embrace whole-genome sequencing

Nature 14-Sep-2010

Nic Volker

"**If one hospital is doing it, you can be sure others will start, because patients will vote with their feet**"
-- Elizabeth Worthey
HMGC & Children's Hospital of Wisconsin

"**At the age of 3, … more than 100 separate surgeries** …On the basis of [sequencing], the physician recommended a bone-marrow transplant in June 2010. By mid-July, the child was eating his first meal."
(XIAP gene C203Y; TGT>TAT)

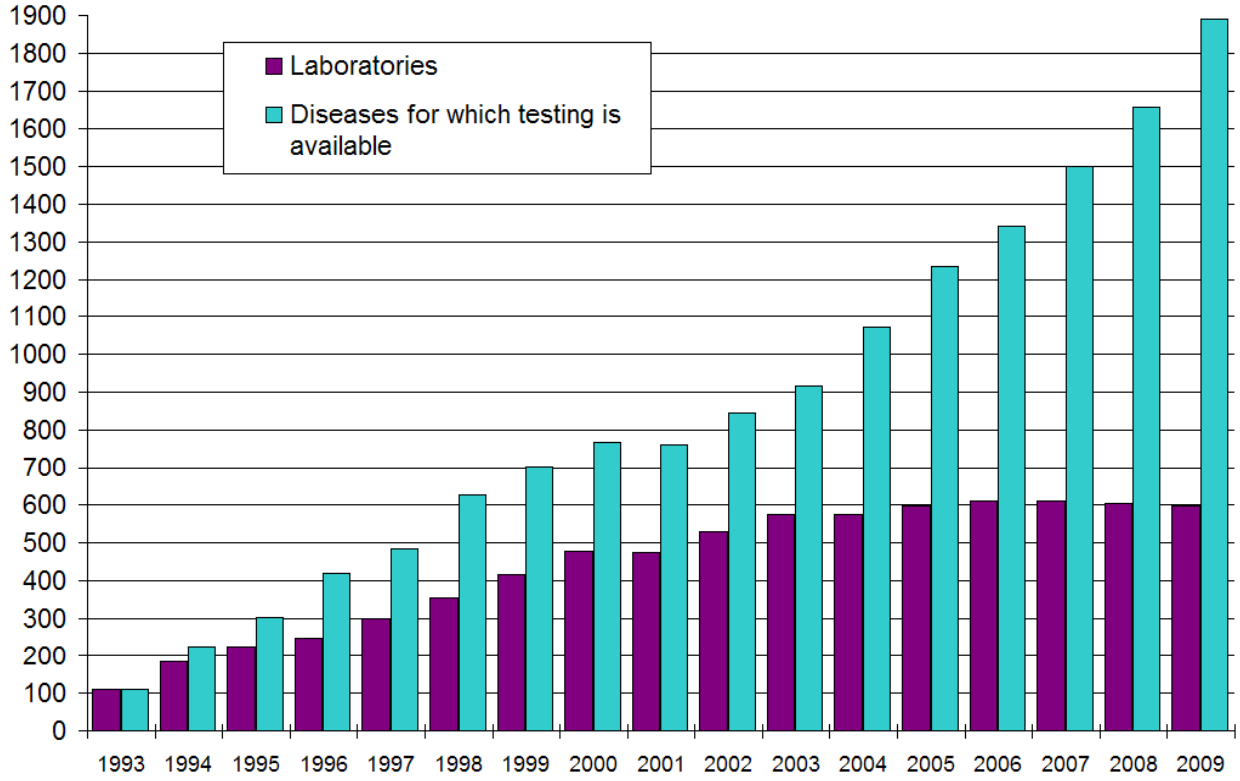
Individually Rare -- Collectively Common (10%)

2443 diseases (~6000 genes) are highly predictive & medically actionable

1963 PKU

1991 BRCA

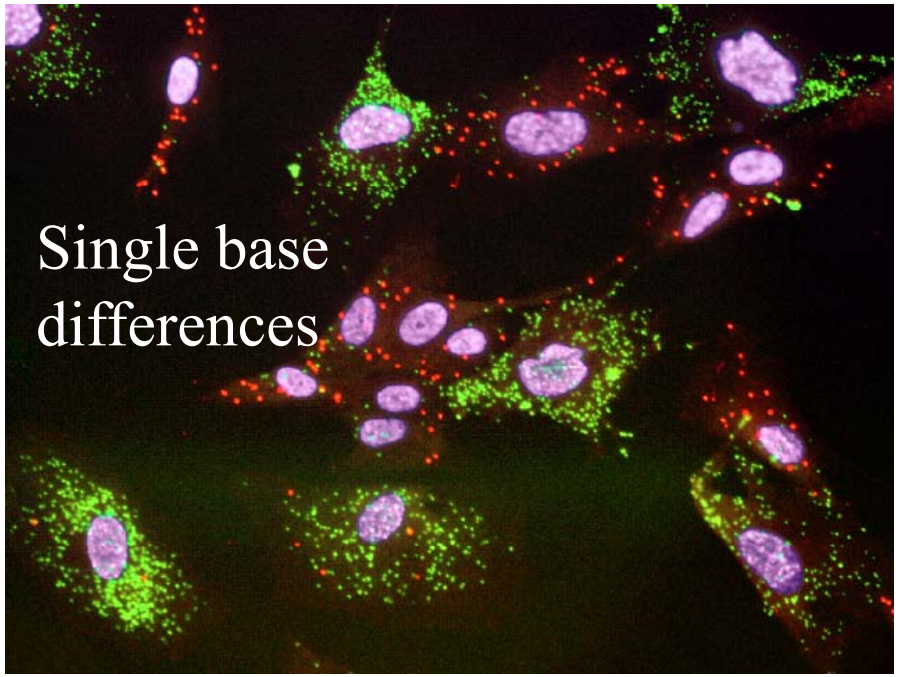
2010 HCM

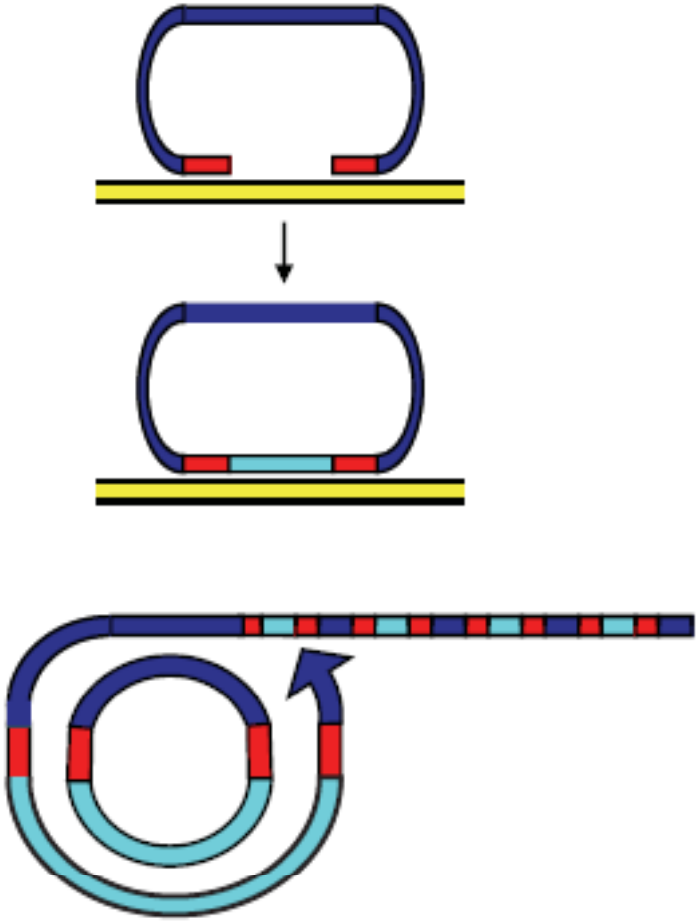


Genetests.org

Multiplex RNA Fluorescent in situ Sequencing (FISSEQ)

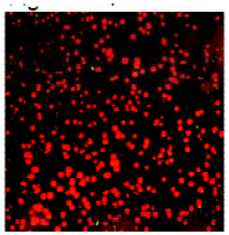
J. Lee, J.Yang, M. Nilsson et al.



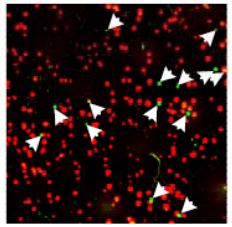


Rare cells: Resistance in Leukemia therapy

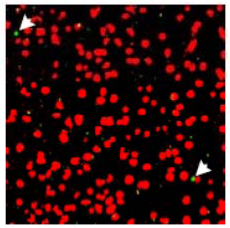
Nardi, Raz, Chao, Wu, Stone, Cortes, Deininger, Church, Zhu, Daley. Oncogene 27:775-82



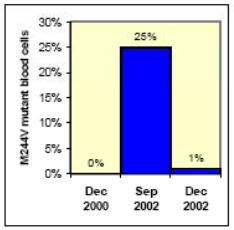
December 2000
CML diagnosis – November 2000
Pre-Gleevec treatment.



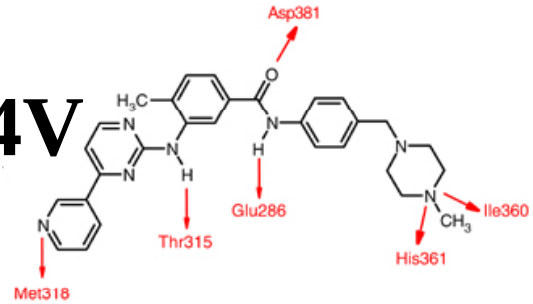
September 2002
Gleevec 400mg
Cytogenetic relapse – August 2002

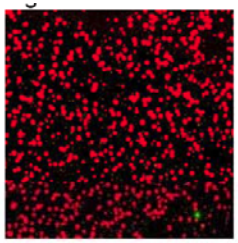


December 2002
Gleevec dose increase 800mg

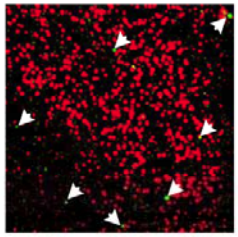


M244V

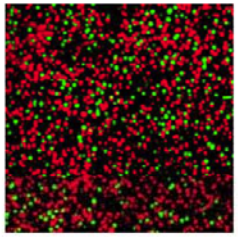




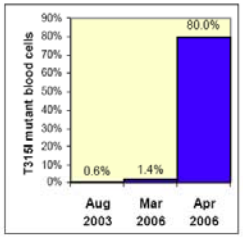
August 2003
Post transplant PCR negative



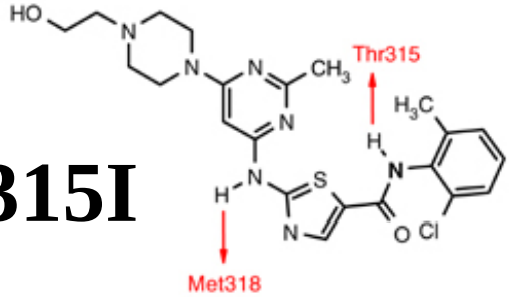
March 2006
(Started dasatinib in March)

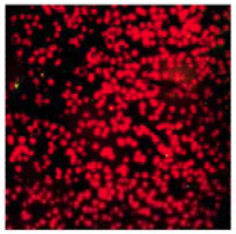


April 2006
Dasatinib for 1 month

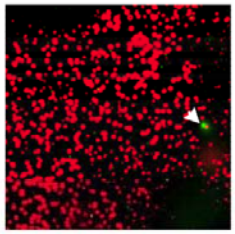


T315I

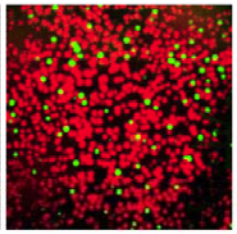




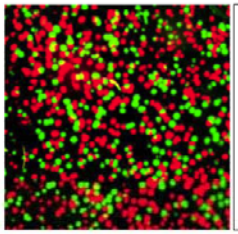
April 2001
on Gleevec
HR



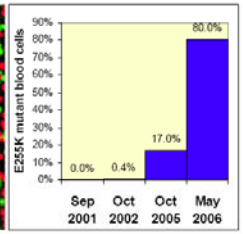
October 2002
Gleevec increased (Sep 2001) to achieve CR



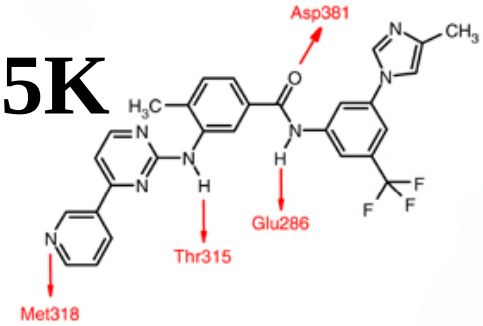
October 2005
Loss of HR response (??)



May 2006
nilotinib since March 2006



E255K



Simultaneously Cure AML & HIV1

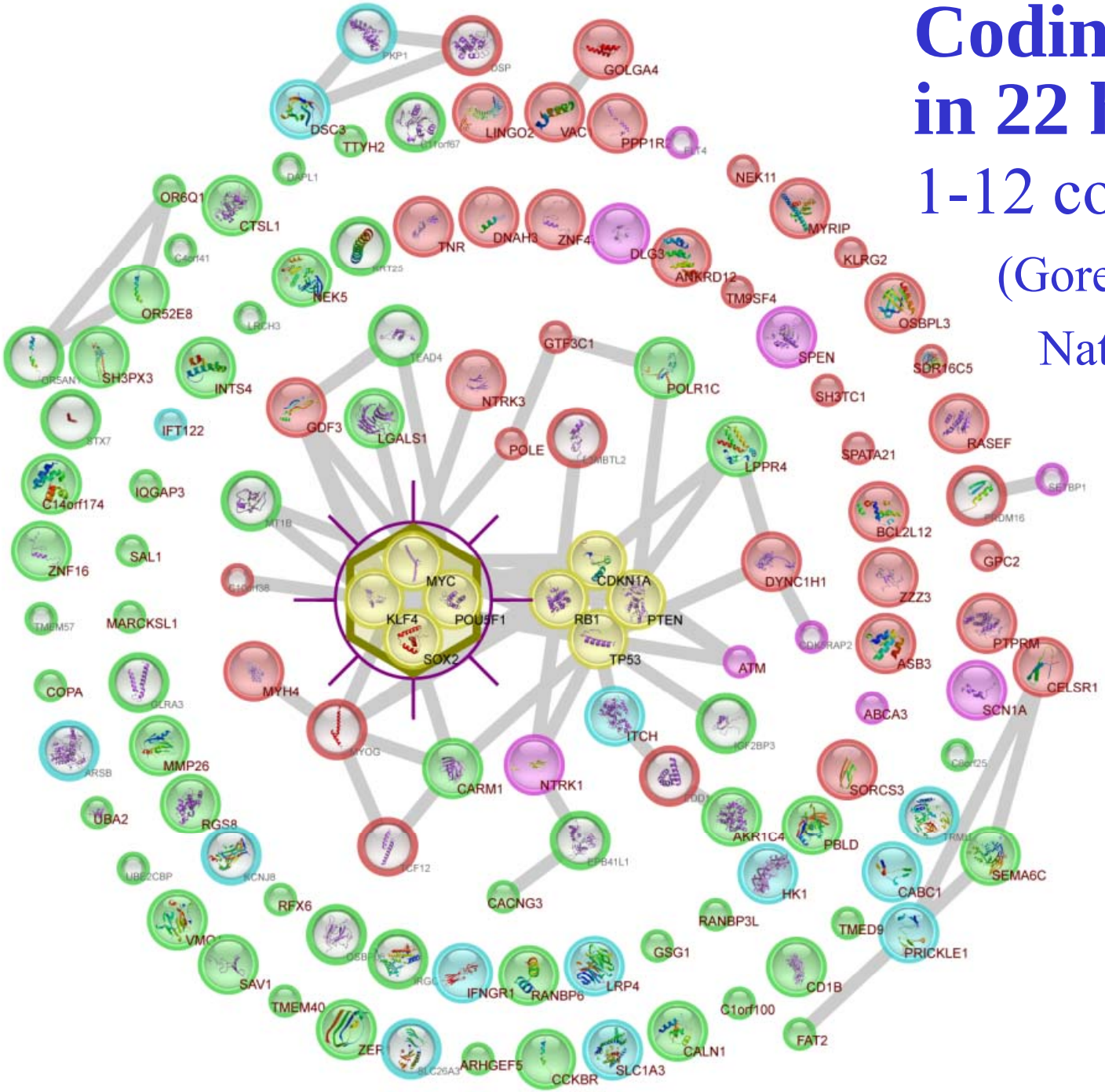
Hütter G, et al.
"Long-Term Control of HIV by CCR5 Δ32/Δ32 Stem-Cell Transplantation"
N Engl J Med 2009

Timothy Ray Brown
A*0201;
B*0702,3501;
Cw*0401,0702;
DRB1*0101,1501;
DQB1*0501,0602.

Coding variants in 22 hiPS lines

1-12 coding changes

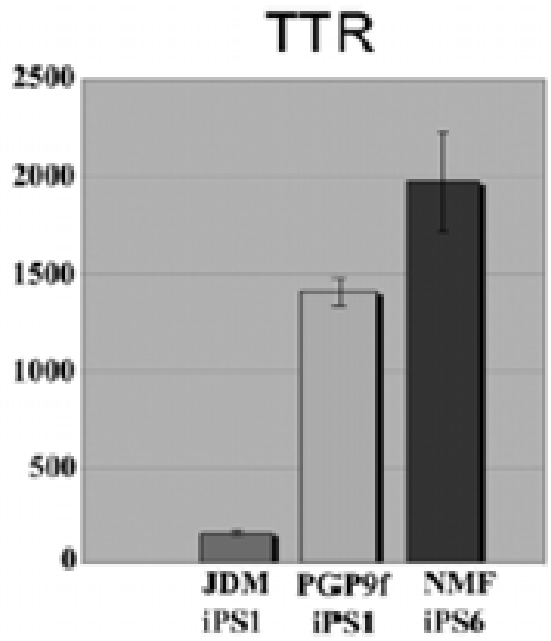
(Gore, Zhang et al. Nature 2011)

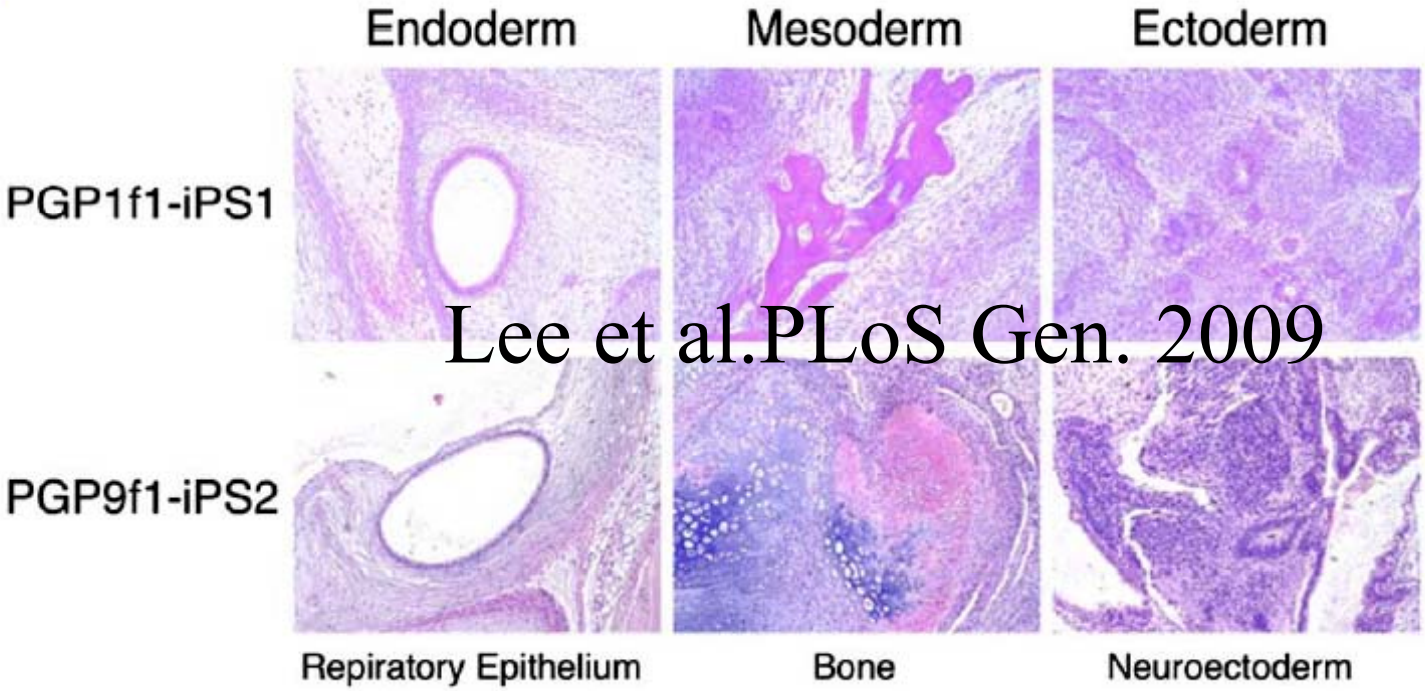


Red= COSMIC
Blue= OMIM
Purple= both.
Grey= interactions with 4 tumor suppressors & 4 reprogramming factors.
Solid= non-synonymous
BIG= known 3D

PGP stem cells biobank

Hepatic endoderm from hIPS cells
(Daley, Church, Wilmut labs)





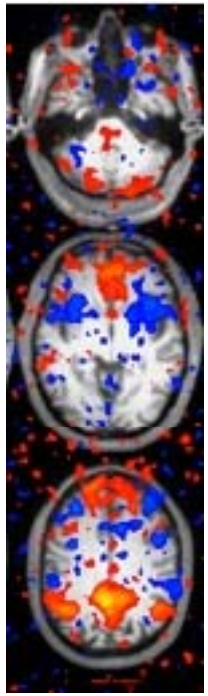
Lee et al.PLoS Gen. 2009

Tissue-specific Gene Expression Regulatory Variants Using Personalized hIPSC

PersonalGenomes.org

Testmybrain.org Cognitive & Prosopagnosia Ken Nakayama

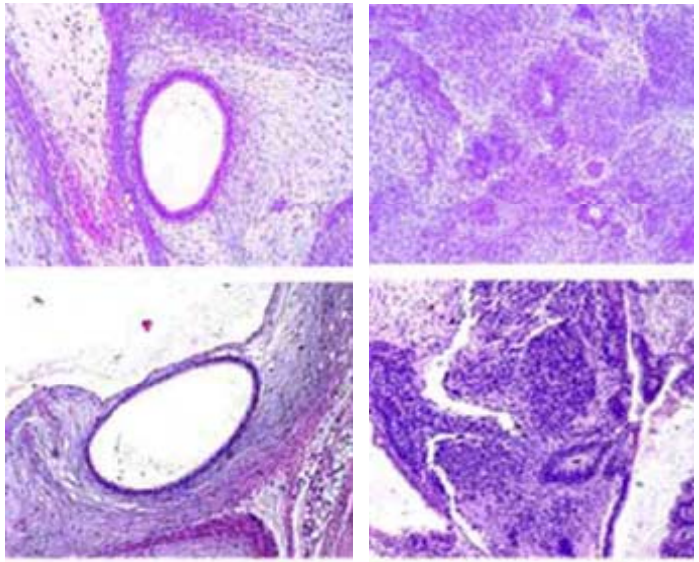
fMRI Variation Randy Buckner



#1

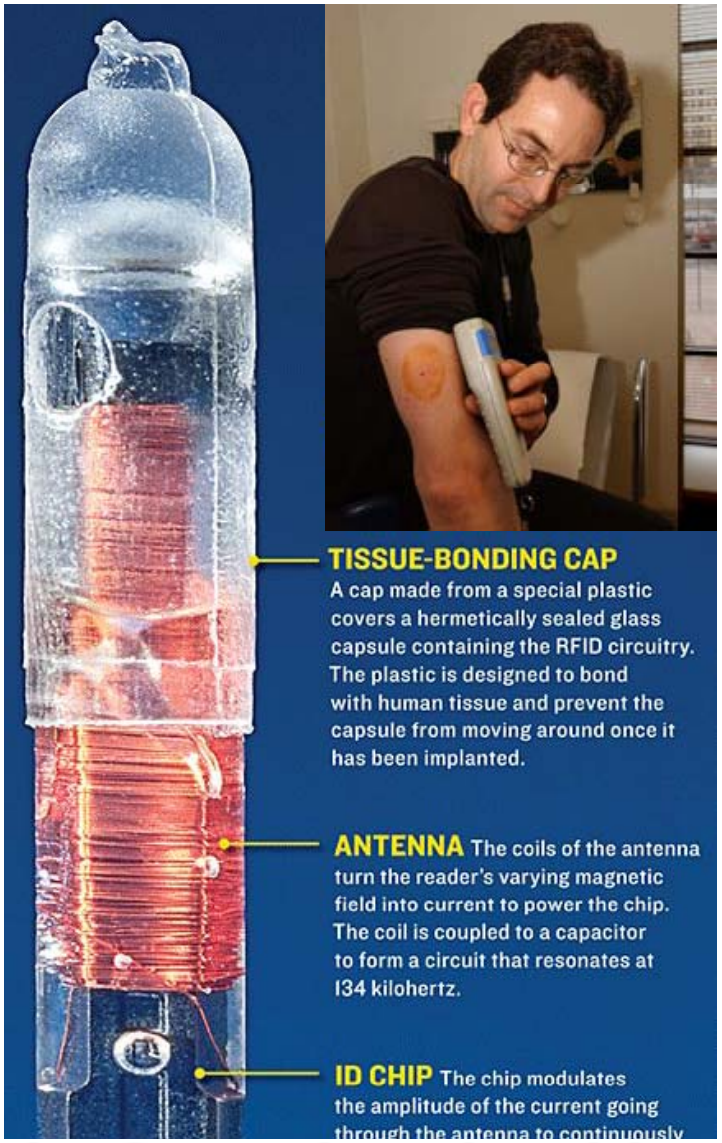
#1

#9



Repiratory Epithelium Neuroectoderm

Lee et al. 2009
PLoS Genet.



Straight from the Shoulder

John Halamka, M.D. #2

N ENGL J MED 353;4 WWW.NEJM.ORG JULY 28, 2005

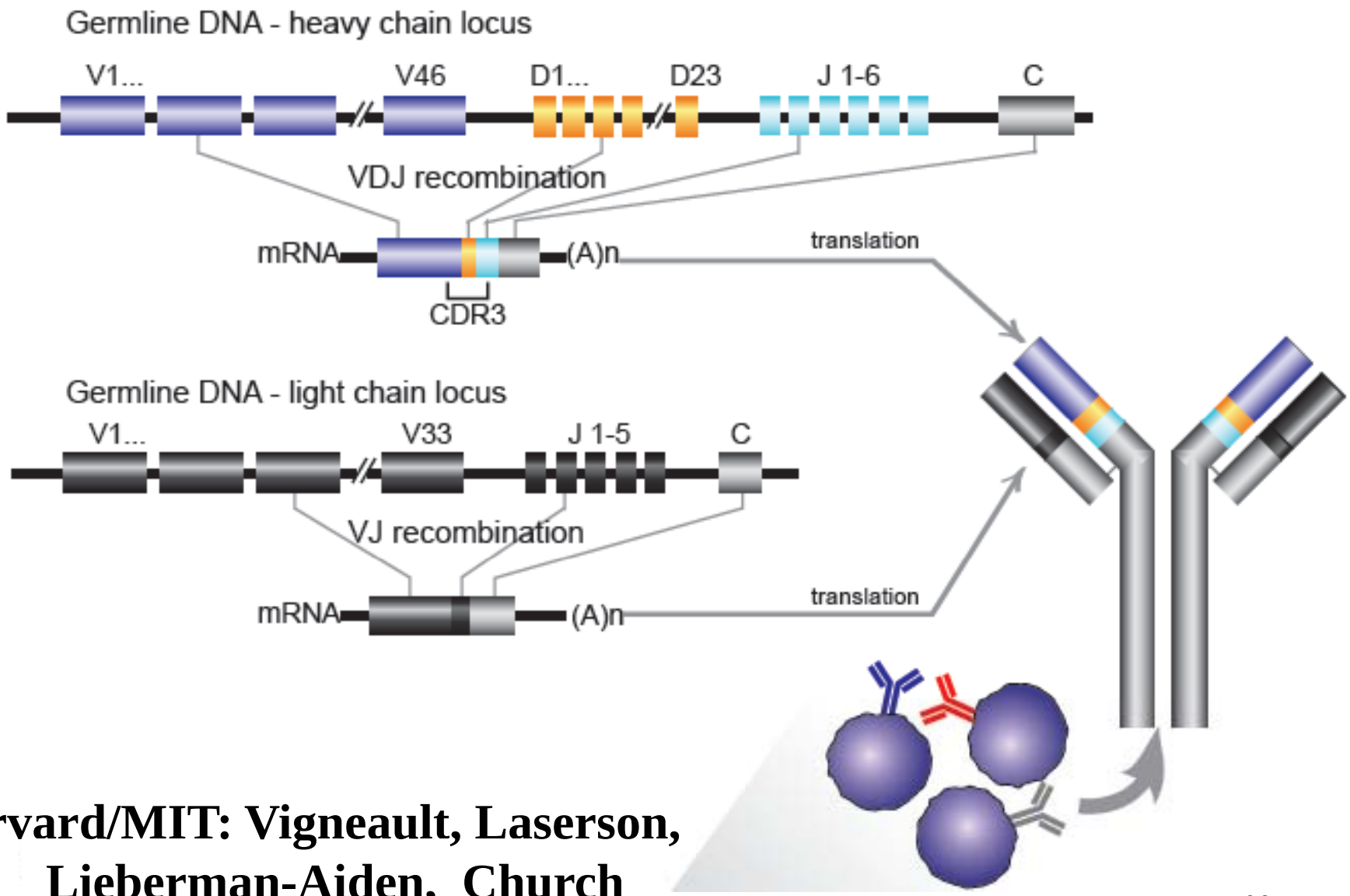
The New England Journal of Medicine

Microbiome vs Immunome

Microbe tests: Detect Drug resistance spectrum
Earlier warning (e.g. meningitis)

Immune tests: Focus on response to exposure
Longer times to detect exposure (e.g. HIV, TB)

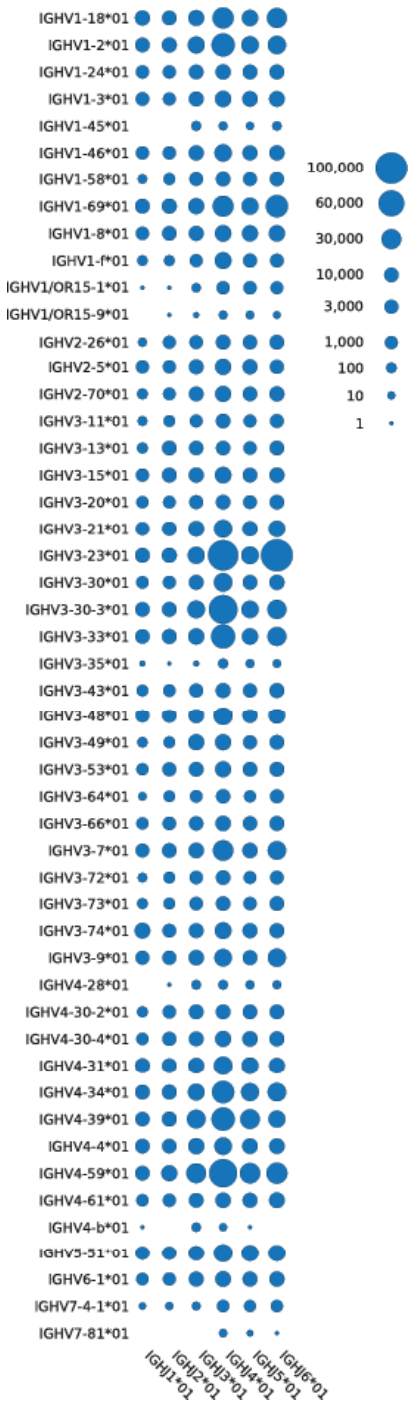
PGP Immunome time series

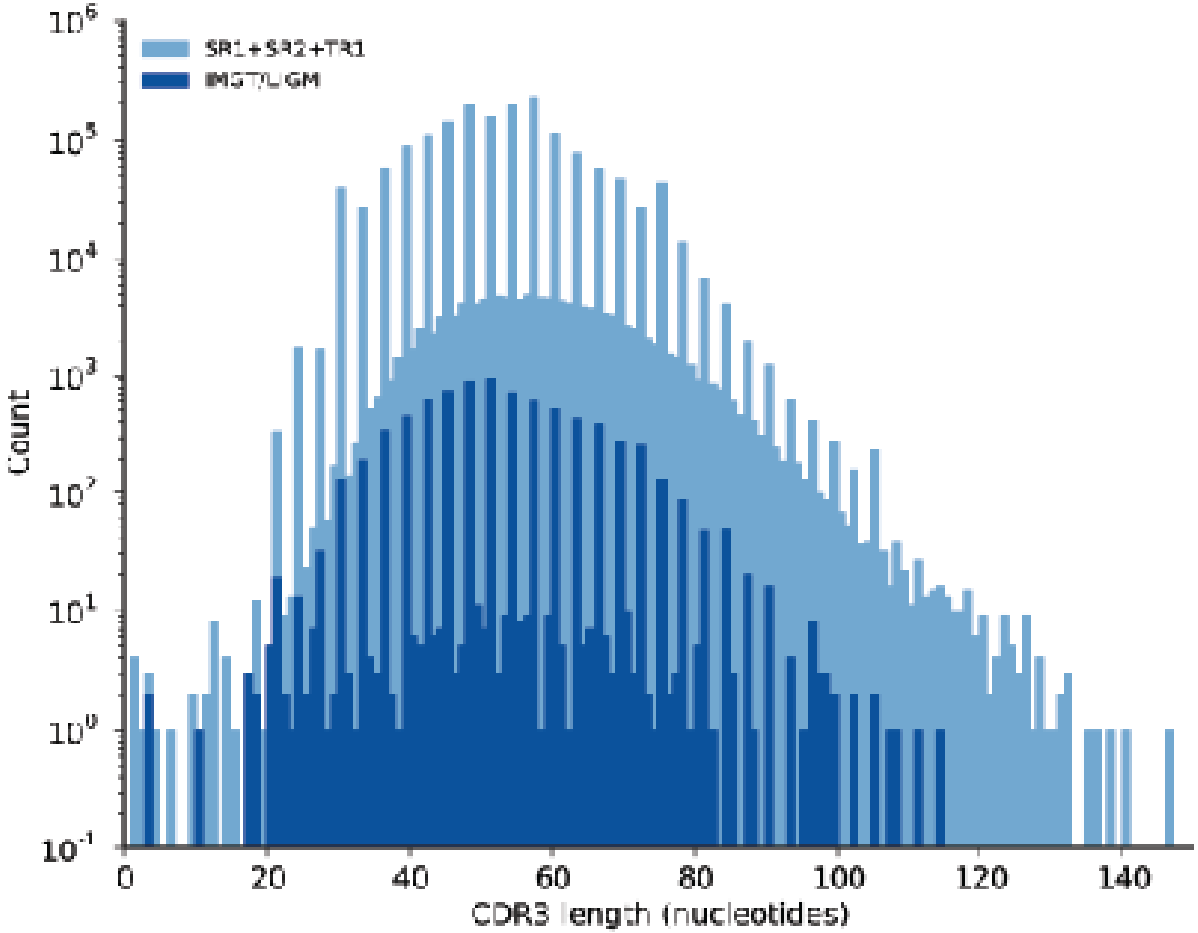


Harvard/MIT: Vigneault, Laserson, Lieberman-Aiden, Church

Roche: Egholm, Simen

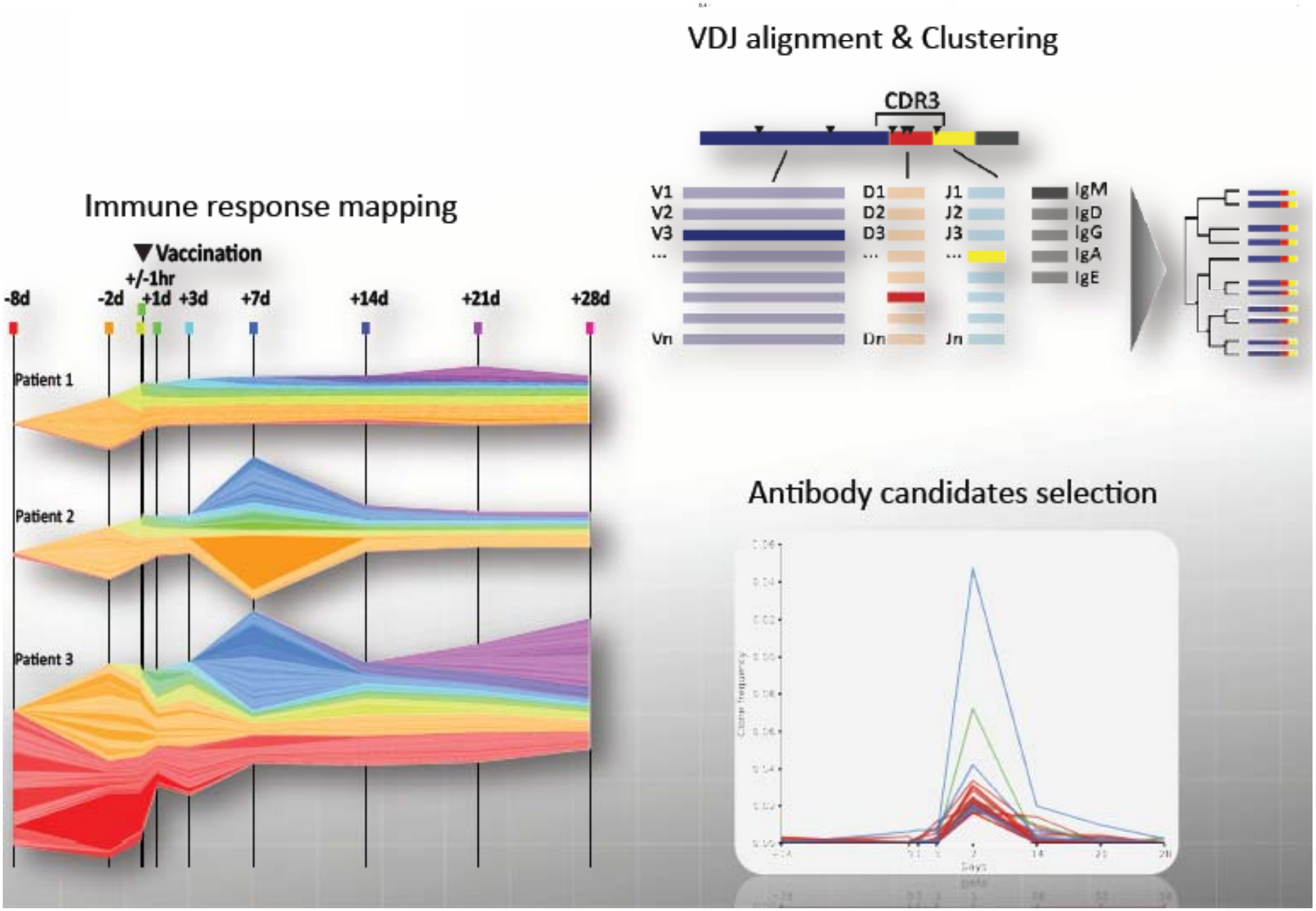
PGP CDR3 size distribution



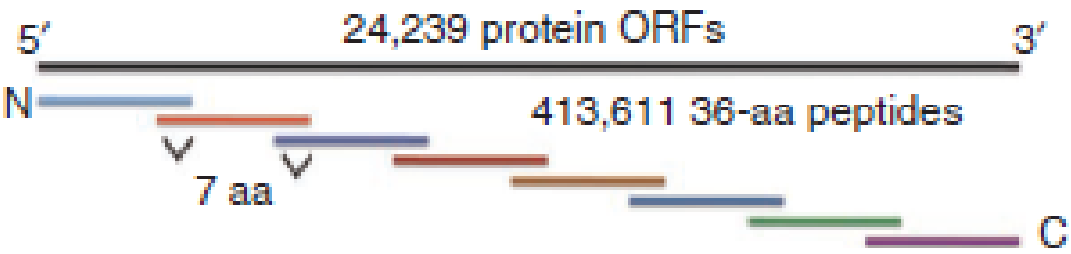


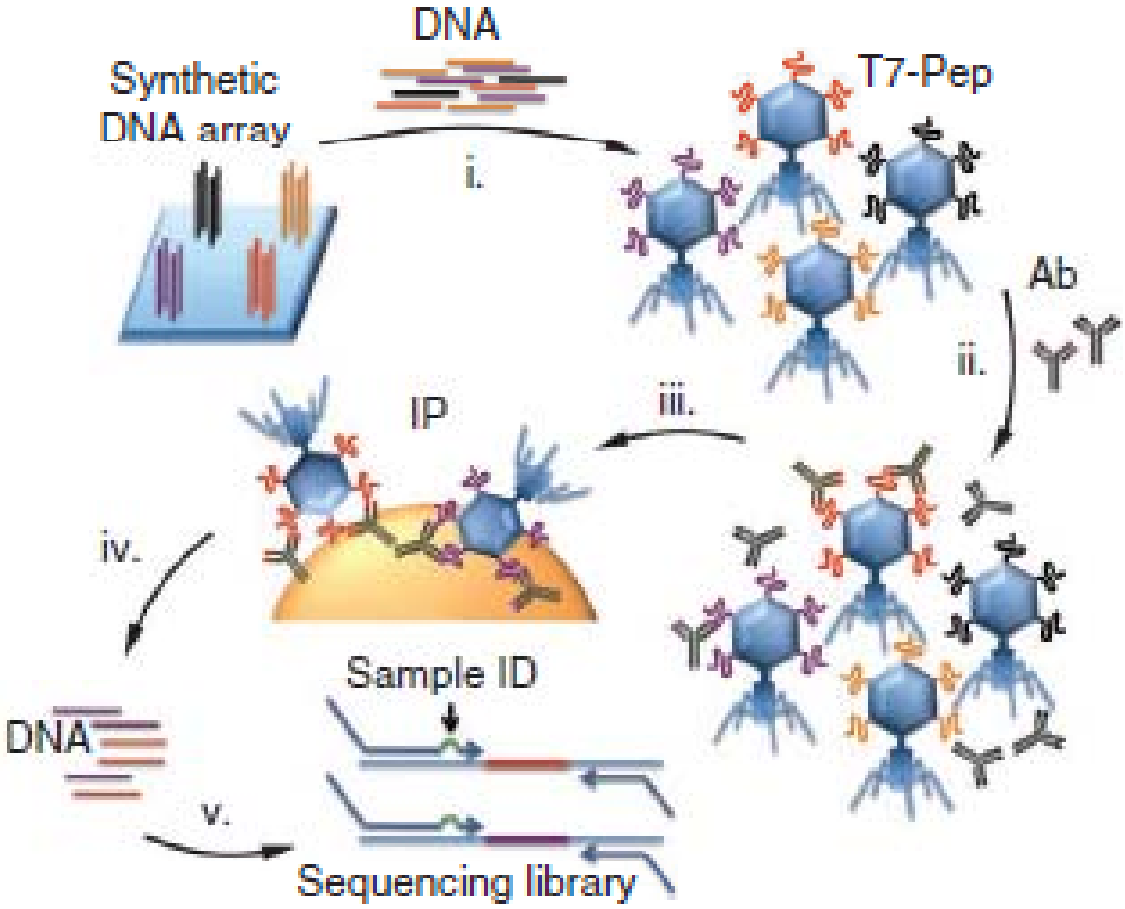
Laserson, Vigneault

PGP Vaccination 3 year time series.



Antigen Libraries





Larman et al
Nature
Biotech 2011

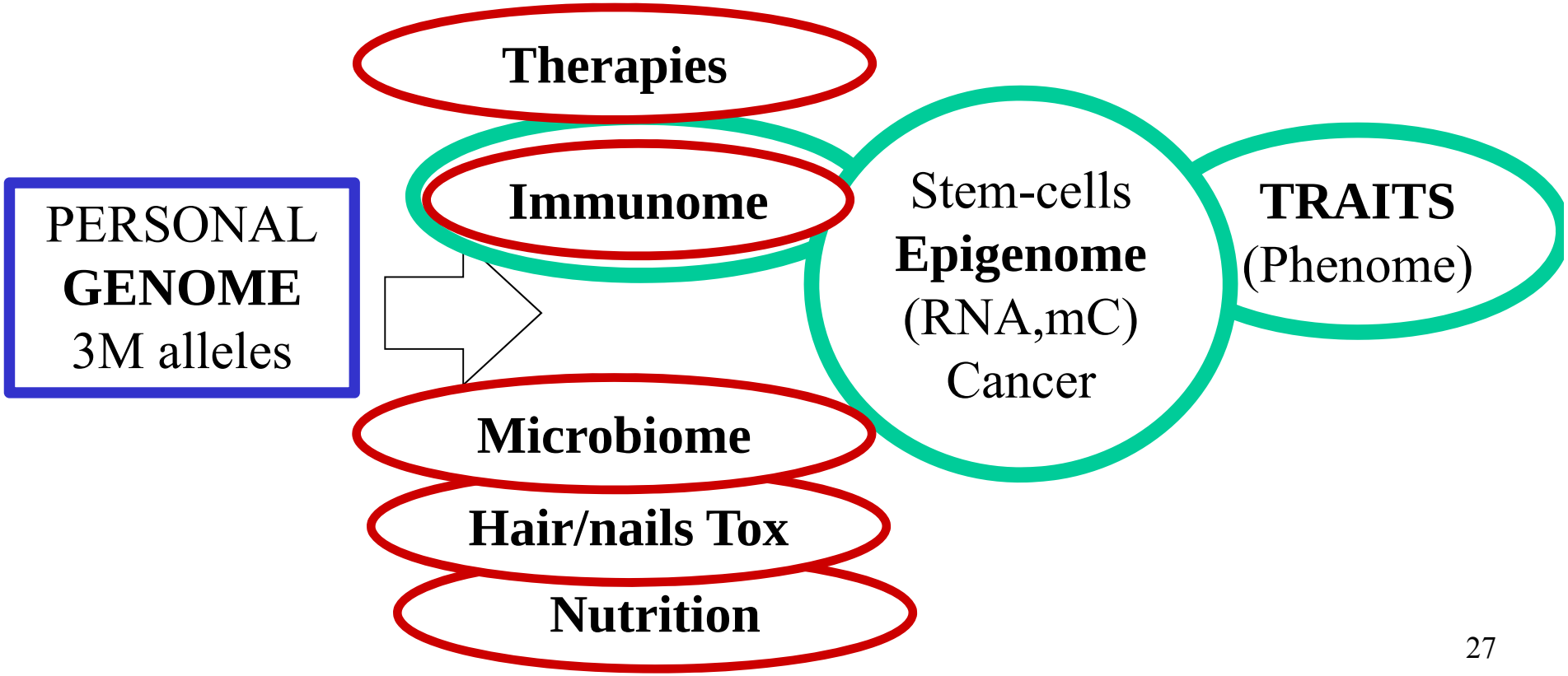
2011: What's next

1. Handheld, no prep/library/amplification
2. In situ : 3D/4D tissues
   (cancer, inflammation, infection)
3. Interpretation & integration software
4. Great cohorts to test drive tech & personalized medicine

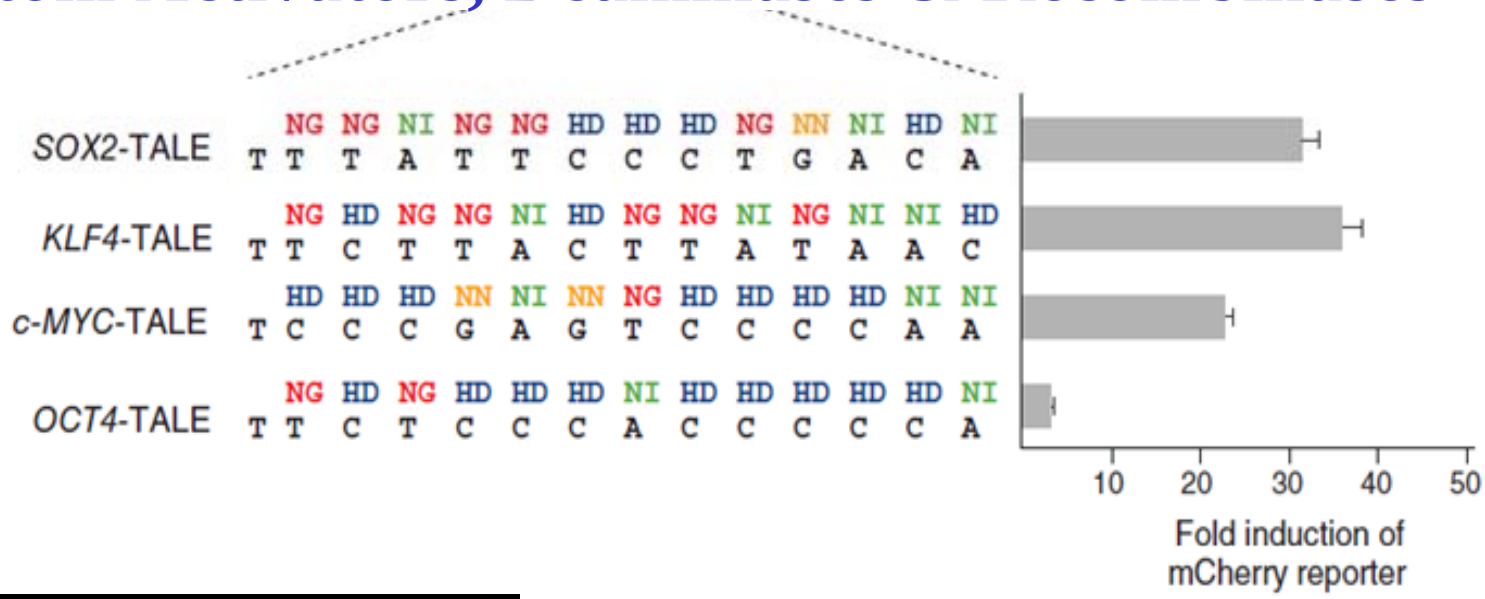
Genomes + Environments = Traits

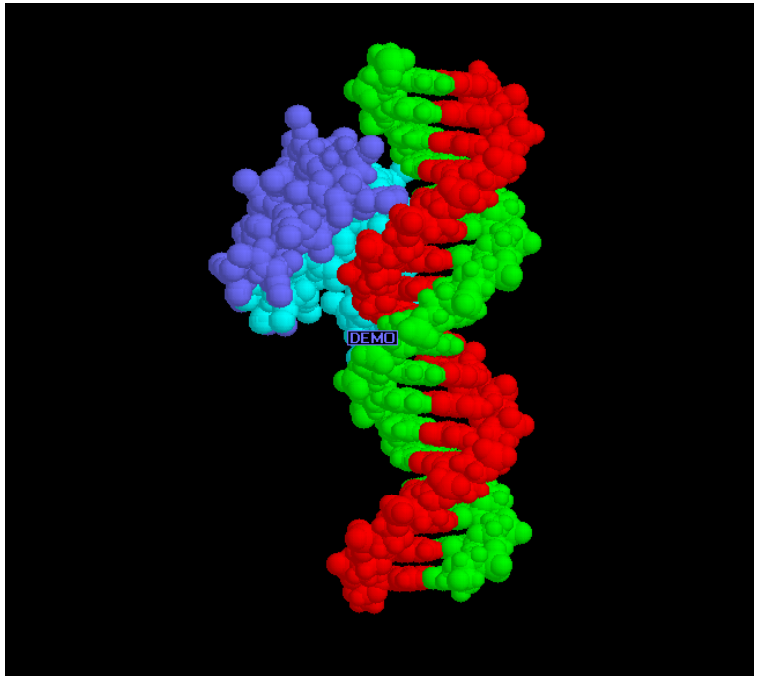
PersonalGenomes.org

Evidence.personalgenomes.org



Technology for Reading &Writing Human Genomes
Custom Activators, Deaminases & Recombinases



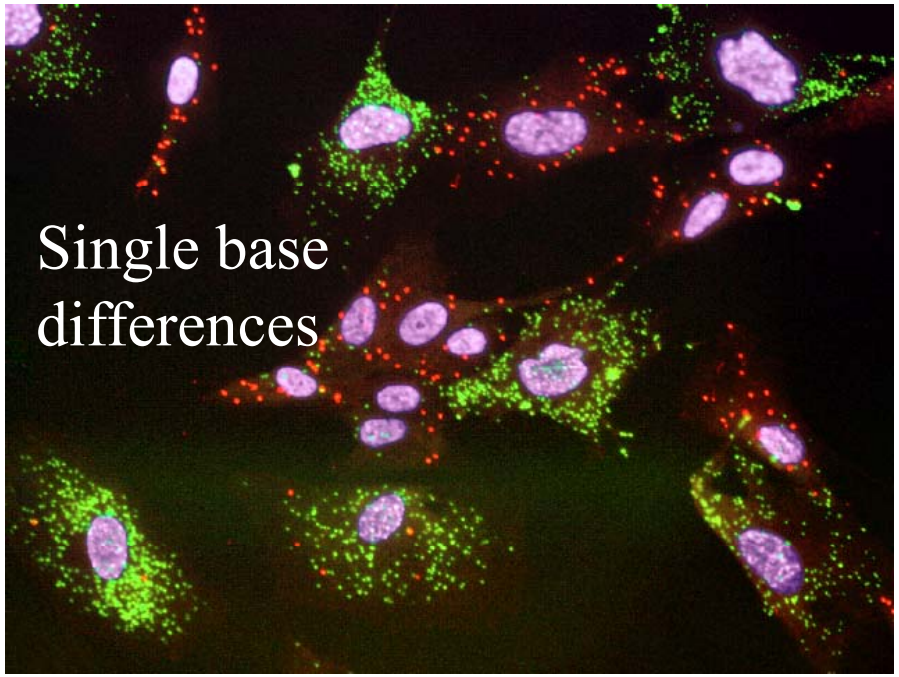


Zhang, Cong, et al.
Nat Biotech 2011

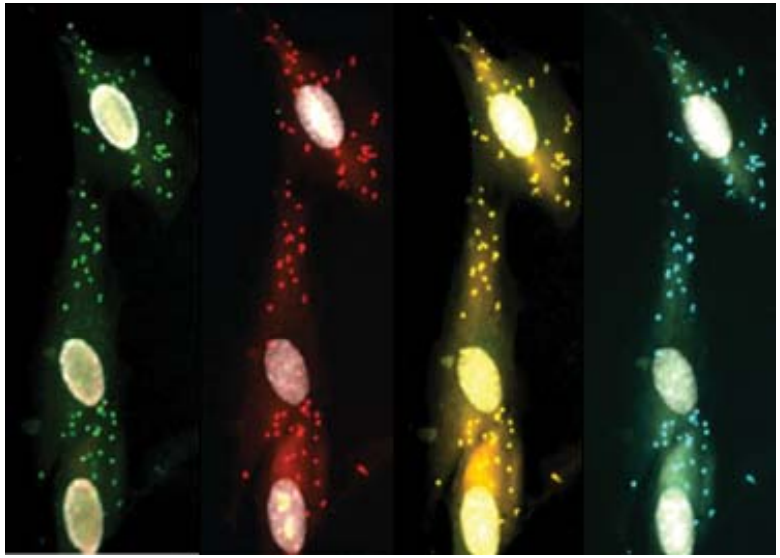
2 TALE domains binding to 2 bp
Neves, et al. pdb 2010 2kq5
Boch et al Science 2009

Toward comprehensive single cell in situs

2 kb Lee ,Yang, Nilsson: multiplex in situ RNA
100 kb Drmanac: Long Fragment Reads (LFR)
2 Mb Wu: Bind & Snap libraries
6 Gb Wu: Oligo Paints in nuclei



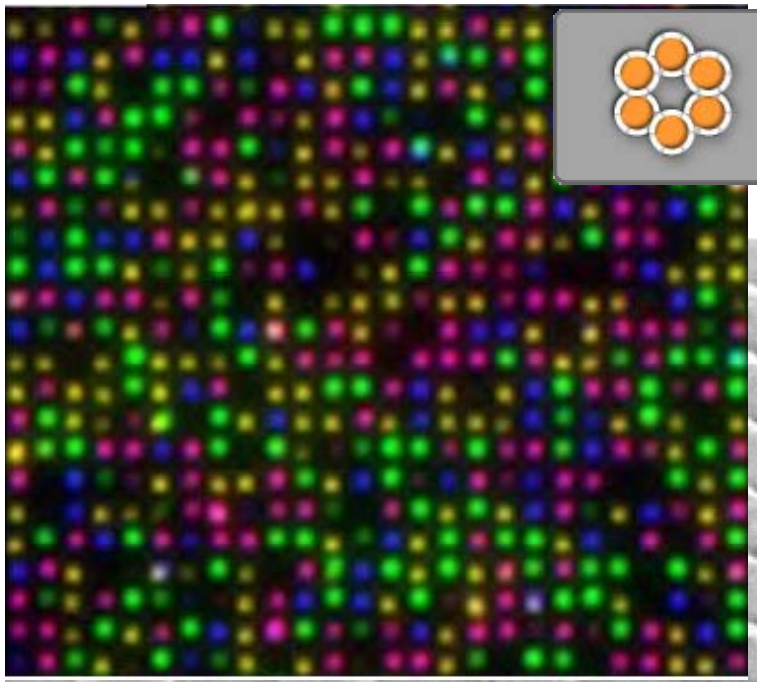
4 base reads

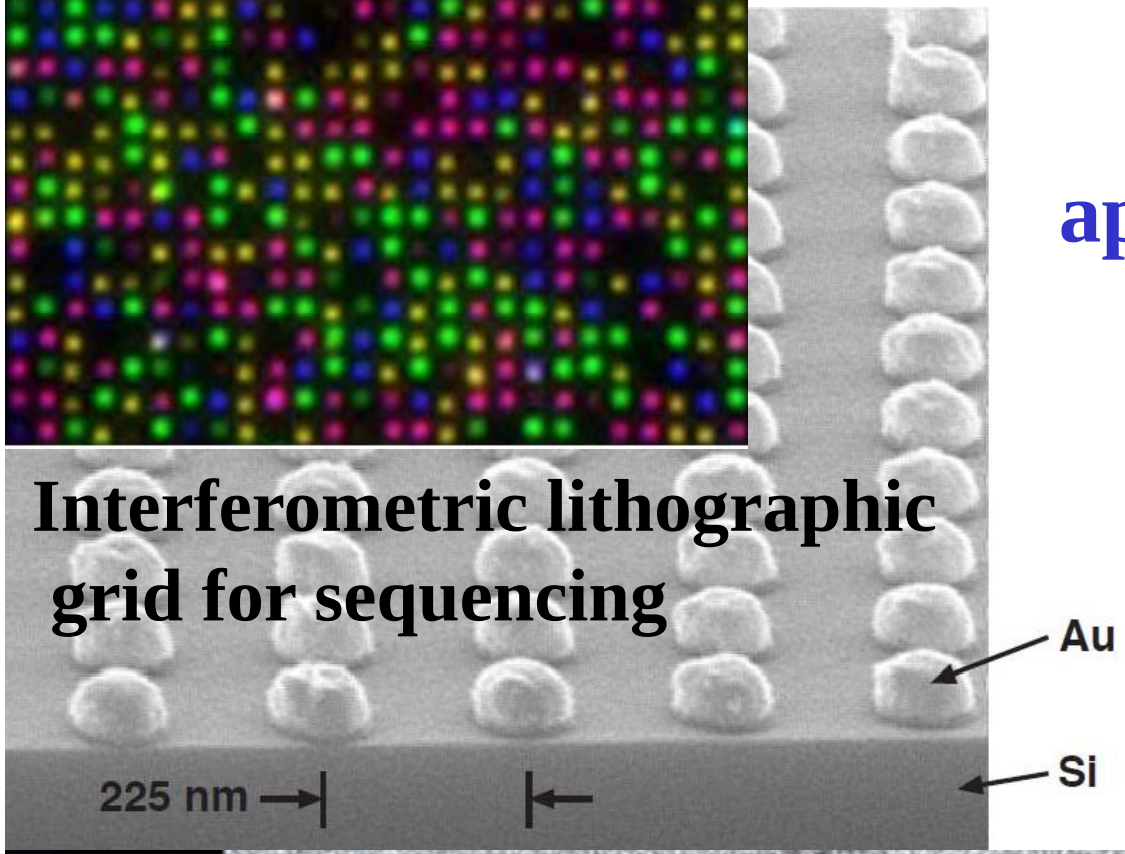


caDNAno

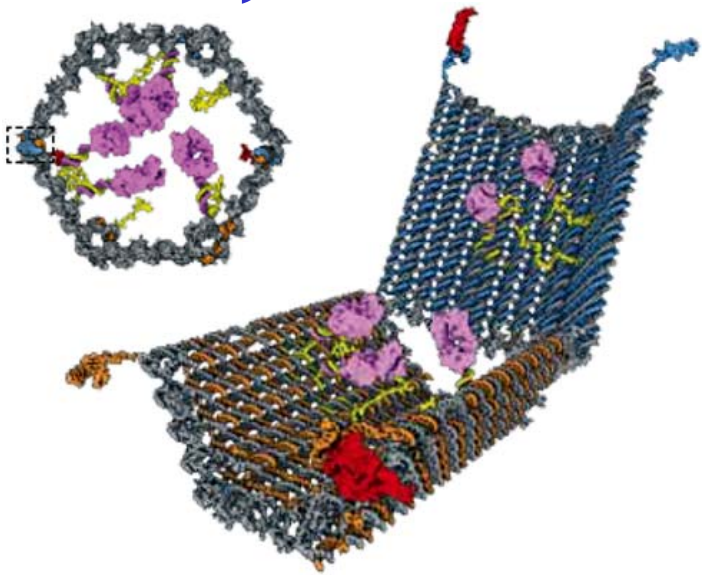
open-source software for design of three-dimensional DNA origami

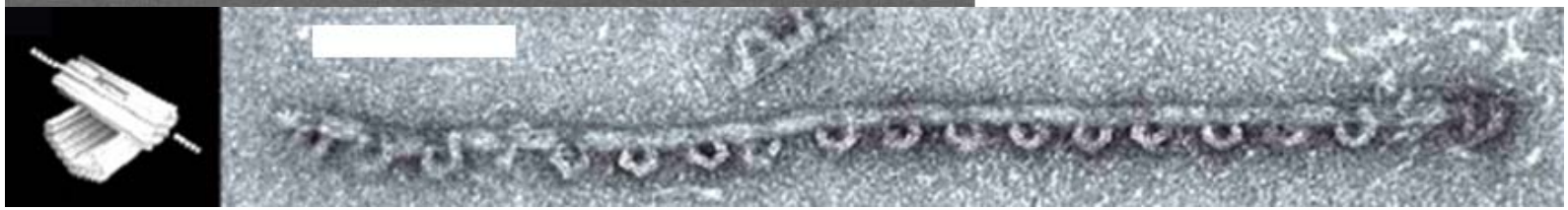
Bridging atom-to-mm aptamers, antibodies

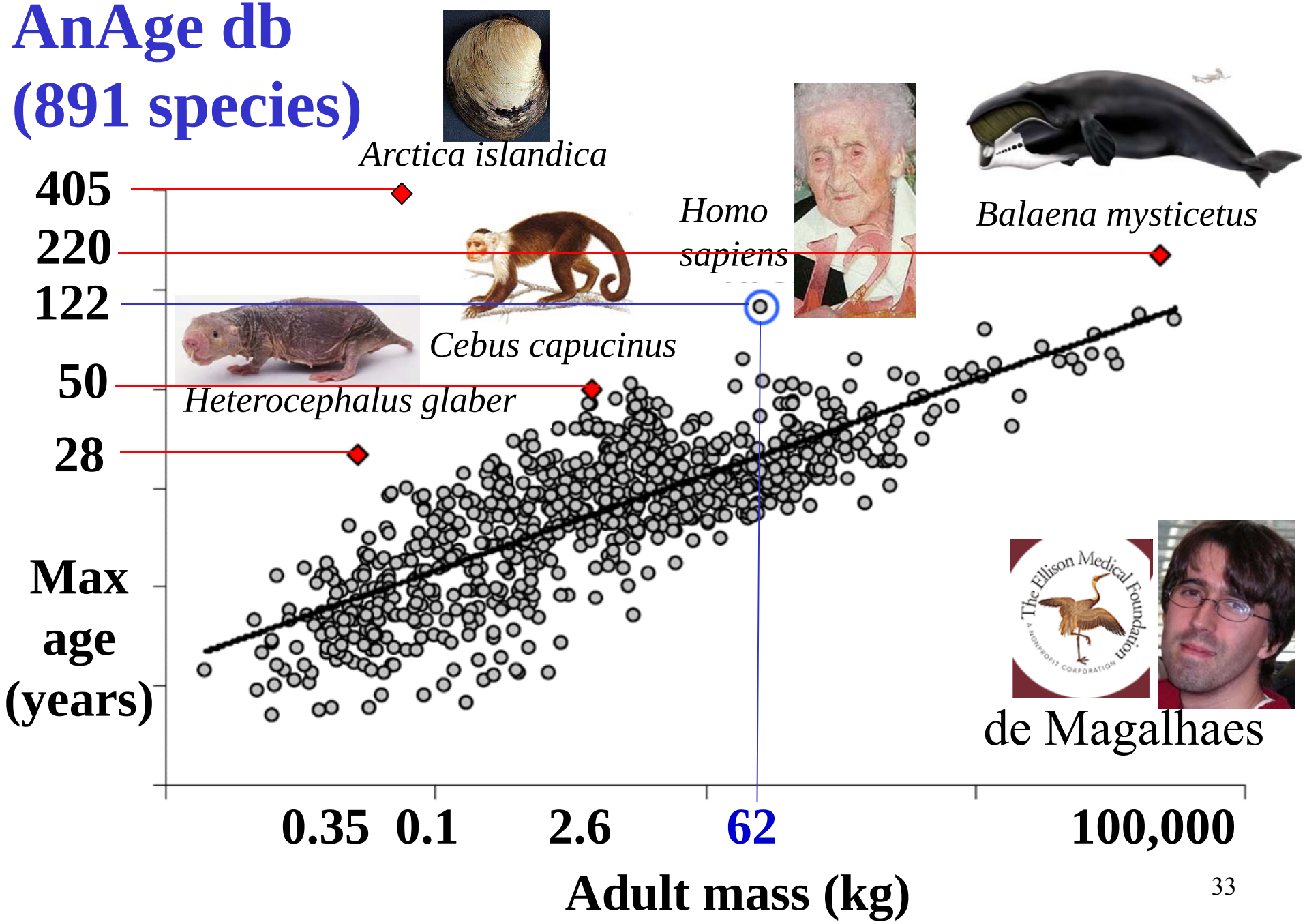




Interferometric lithographic grid for sequencing





Edison : Narcolepsy

AnAge db (891 species)