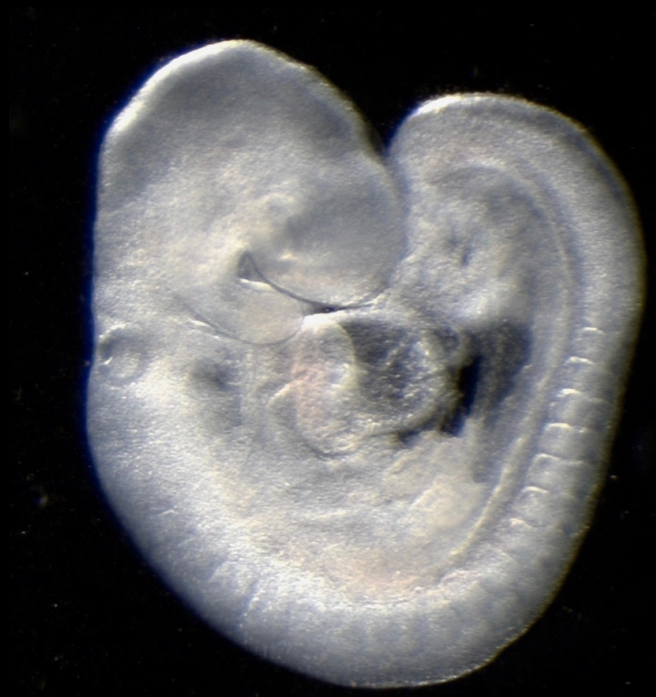
A Nonlinear Story of Development

Questioning Assumptions and Following Curiosity

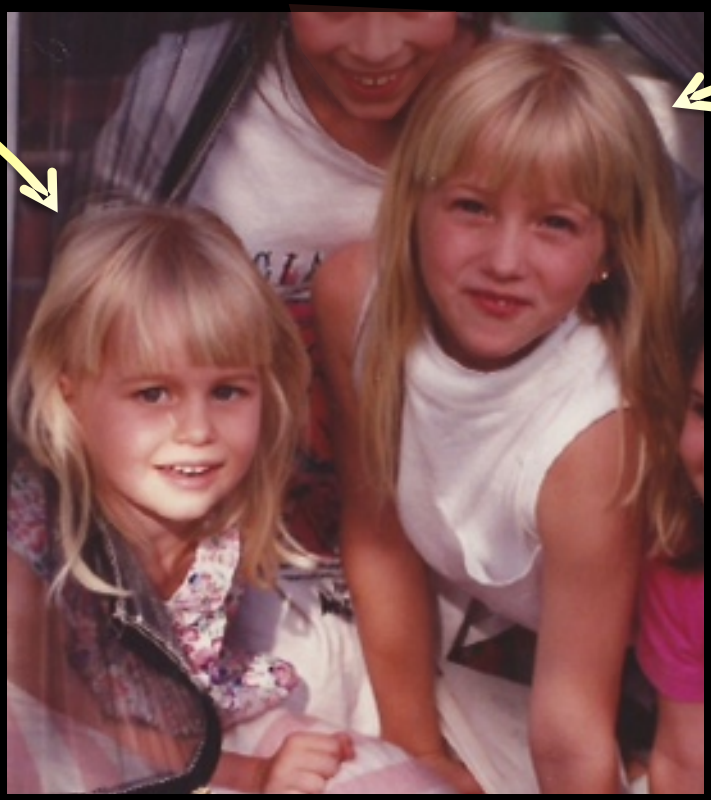


Daisy Robinton, Ph.D.

University of California, Los Angeles

March 5, 2020

Me



Lily


Jordan Fischer
HC70A 2006


LAW


HC70AL 2006
UCLA

HC70A, 2008


HC70A, 2008


HC70A, 2009

Imposter syndrome is real

REVIEW

doi:10.1038/nature10761

The promise of induced pluripotent stem cells in research and therapy

Daisy A. Robinton[1–5] & George Q. Daley[1–5]

The field of stem-cell biology has been catapulted forward by the startling development of reprogramming technology. The ability to restore pluripotency to somatic cells through the ectopic co-expression of reprogramming factors has created powerful new opportunities for modelling human diseases and offers hope for personalized regenerative cell therapies. While the field is racing ahead, some researchers are pausing to evaluate whether induced pluripotent stem cells are indeed the true equivalents of embryonic stem cells and whether subtle differences between these types of cell might affect their research applications and therapeutic potential.

CellPress

Cancer Cell

Article

Lin28b Is Sufficient to Drive Liver Cancer and Necessary for Its Maintenance in Murine Models

Liem H. Nguyen,[1,8] Daisy A. Robinton,[2,8] Marc T. Seligson,[2,8] Linwei Wu,[1,3] Lin Li,[1] Dinesh Rakheja,[4] Sarah A. Comerford,[5] Saleh Ramezani,[6] Xiankai Sun,[6] Monisha S. Parikh,[1] Erin H. Yang,[1] John T. Powers,[2] Gen Shinoda,[2] Samar P. Shah,[2] Robert E. Hammer,[7] George Q. Daley,[2,*] and Hao Zhu[1,*]

Developmental Cell

Short Article

CellPress

The Lin28/*let-7* Pathway Regulates the Mammalian Caudal Body Axis Elongation Program

Daisy A. Robinton,[1,2,3,4] Jérome Chal,[4,5,6] Edroaldo Lummertz da Rocha,[1,3,4] Areum Han,[1,2,3,4] Alena V. Yermalovich,[1,2,3,4] Masayuki Oginuma,[4,5,6] Thorsten M. Schlaeger,[1,4] Patricia Sousa,[1,2,3,4] Antony Rodriguez,[7] Achia Urbach,[8] Olivier Pourquié,[4,5,6] and George Q. Daley[1,2,3,4,9,*]

(You can call me Dr. Daisy)

REVIEW

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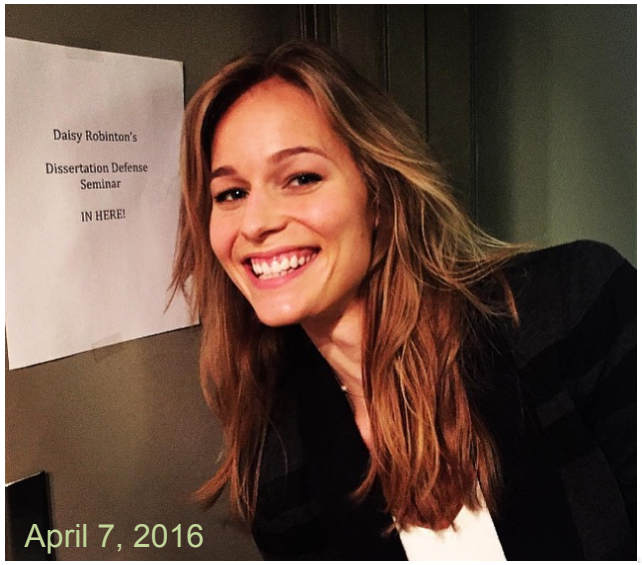

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Even you can be a scientist.

Even you can be a ~~scientist~~.

artist
writer
lawyer
storyteller
entrepreneur

Why pick just one…?

What if you could start over and take the career path most different from the one you're on? Let us help you.

The Labor Department keeps detailed and at times delightfully odd records on the skills and tasks required for each job. Some of them are physical: trunk strength, speed of limb movement, the ability to stay upright. Others are more knowledge-based: economics and accounting, physics, programming. Together, they capture the essence of what makes a job distinctive.

We've used these records to determine what each job's polar opposite would be.

Enter any job. We'll tell you its opposite:

The opposite job of a biological scientist is a model.

Pursuing opposites leads to a wide breadth of skill development

The opposite job of a biological scientist is a model.

	Biological Scientists use these skills the most		Models use these skills the most
1	Interpreting the meaning of information for others	1	Ability to maintain balance
2	Biology	2	Gross body coordination
3	Thinking creatively	3	Trunk strength
4	Mathematics	4	Ability to reach with arms, hands and legs
5	Interacting with computers	5	Performing general physical activities
6	Inductive reasoning	6	Performing for or working directly with the public
7	Ability to organize groups in different ways	7	Technology design
8	Processing information	8	Stamina
9	Analyzing data or information	9	Fine arts
10	Written comprehension	10	Dynamic strength

…and filling in skill gaps that a single professional pursuit can leave open

Biological Scientists use these skills the least		Models use these skills the least	
1	Static strength	1	Monitor processes, materials or surroundings
2	Ability to react quickly in response to signals	2	Identifying objects, actions and events
3	Ability to reach with arms, hands and legs	3	Making decisions and solving problems
4	Public safety and security	4	Processing information
5	Ability to to time movements in anticipation of moving objects	5	Estimating the quantifiable characteristics of products, events or information
6	Performing general physical activities	6	Finger dexterity
7	Customer and personal service	7	Getting information
8	Reaction time	8	Pattern recognition
9	Handling and moving objects	9	Near vision
10	Ability to coordinate two or more limbs	10	Information ordering

DAVID SALAFIA/REEBOK

Developmental biologist Daisy Robinton earns extra cash by modelling for athletic companies such as Reebok.

OUTSIDE THE LAB

Side jobs for scientists

Paid work beyond the bench can offer a welcome source of income to cash-strapped junior researchers and provide opportunities for career development.

BY ELIE DOLGIN

Daisy Robinton expected to study mouse models of development when she started her PhD seven years ago, not to become a model herself. She quickly found success in her research, showing that a gene involved in embryonic-stem-cell differentiation can also initiate liver cancer in later life (L. H. Nguyen *et al. Cancer Cell* **26,** 248–261; 2014), and co-authoring the most-cited review paper of all time on reprogrammed stem cells (D. A. Robinton and G. Q. Daley *Nature* **481,** 295–305; 2012).

But Robinton also found herself struggling to live on her modest PhD stipend, and started to look for extra work. That's why in many Reebok stores today, a billboard bearing her life-size likeness is on display, strategically positioned to best display the company's latest product. Robinton now spends around two days each month at photo shoots, mostly for athletic-apparel companies. During her PhD programme, that work paid enough to nearly double her modest income, and it continues to ease her way financially while she completes her postdoc in neurodevelopment at Boston Children's Hospital in Massachusetts.

Robinton is one of many early-career researchers who take on jobs outside the lab to help balance the books. "Being able to supplement my income instead of increasing my debt load was a big deal," says Robinton. She makes up for lost research hours by working more on evenings and at weekends, and declines fashion work that cuts into her lab time. "My number-one priority will always be my science," she says.

Her attitude is the right one for any junior researcher considering work outside the lab, says Alaina Levine, a science and engineering careers consultant in Tucson, Arizona. Graduate students and postdocs need to think strategically, Levine says, about whether a side gig will support their overall career plan (or at least their happiness and well-being) and whether they realistically have the time.

In addition to extra cash, a part-time second job can yield opportunities for skill development and professional advancement, Levine adds. Yet any such work must come in lieu ▶

Cross-pollination of ideas

Practicing communication of your work

Testing your assumptions

Transferring skills from one context to the next

Create new avenues of motivation and inspiration

Bootstrapping energy

Explore your Curiosity and NETWORK!

GET
GENOMES • ENVIRONMENTS • TRAITS
CONFERENCE

Genomes
Environments
Traits

Jordan

Jamie

Weird and Wonderful

Forbes 30 UNDER 30

SCIENCE

Discovering new worlds, in our cells and outer space

Edited by Alex Knapp, Matt Perez and Sarah Hedgecock

COUPLE THINKERS

Sharing science with the world

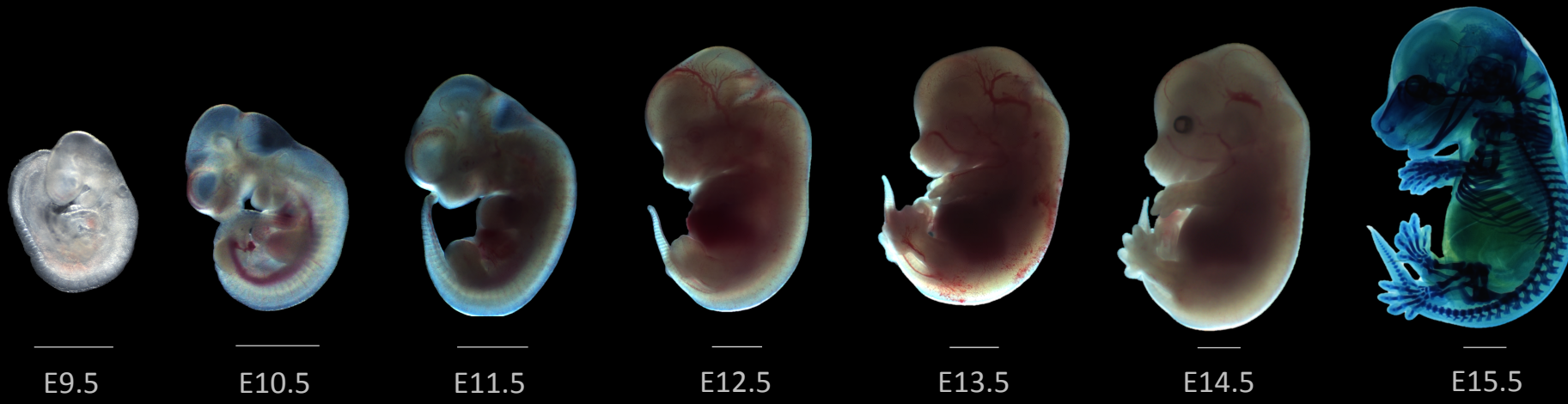
Building bridges and expanding impact

Building relationships across industries

Bringing science to influencers and beauty brands

Wearing Multiple Hats

E = embryonic day after fertilization



Science Writer & Strategist

BrainMind

Biology & Innovation Consulta

lululemon athletica

Model

New York Models, SLU, Maggie Inc

Visting Fellow

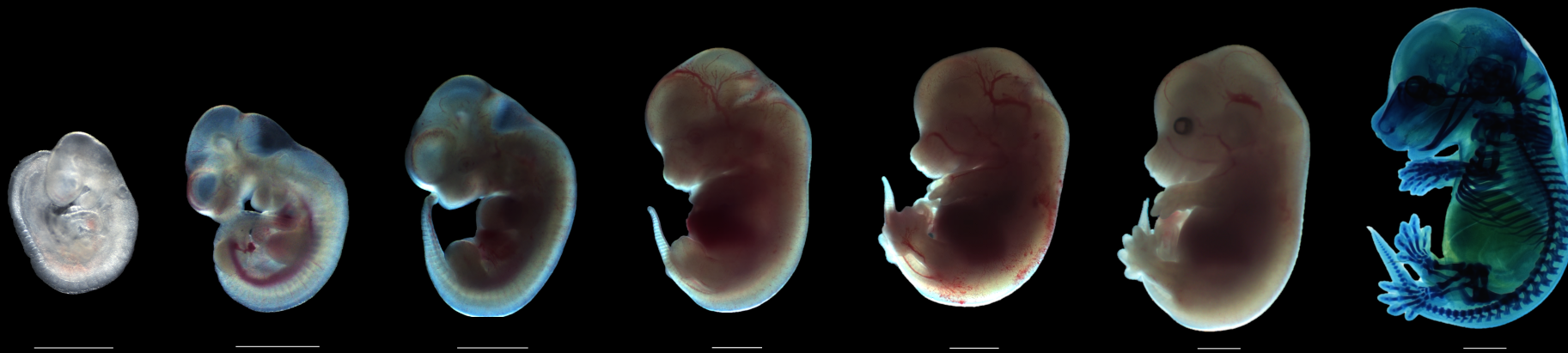
Weill Cornell School of Medicine

Scientist in Residence

Cambria Biosciences

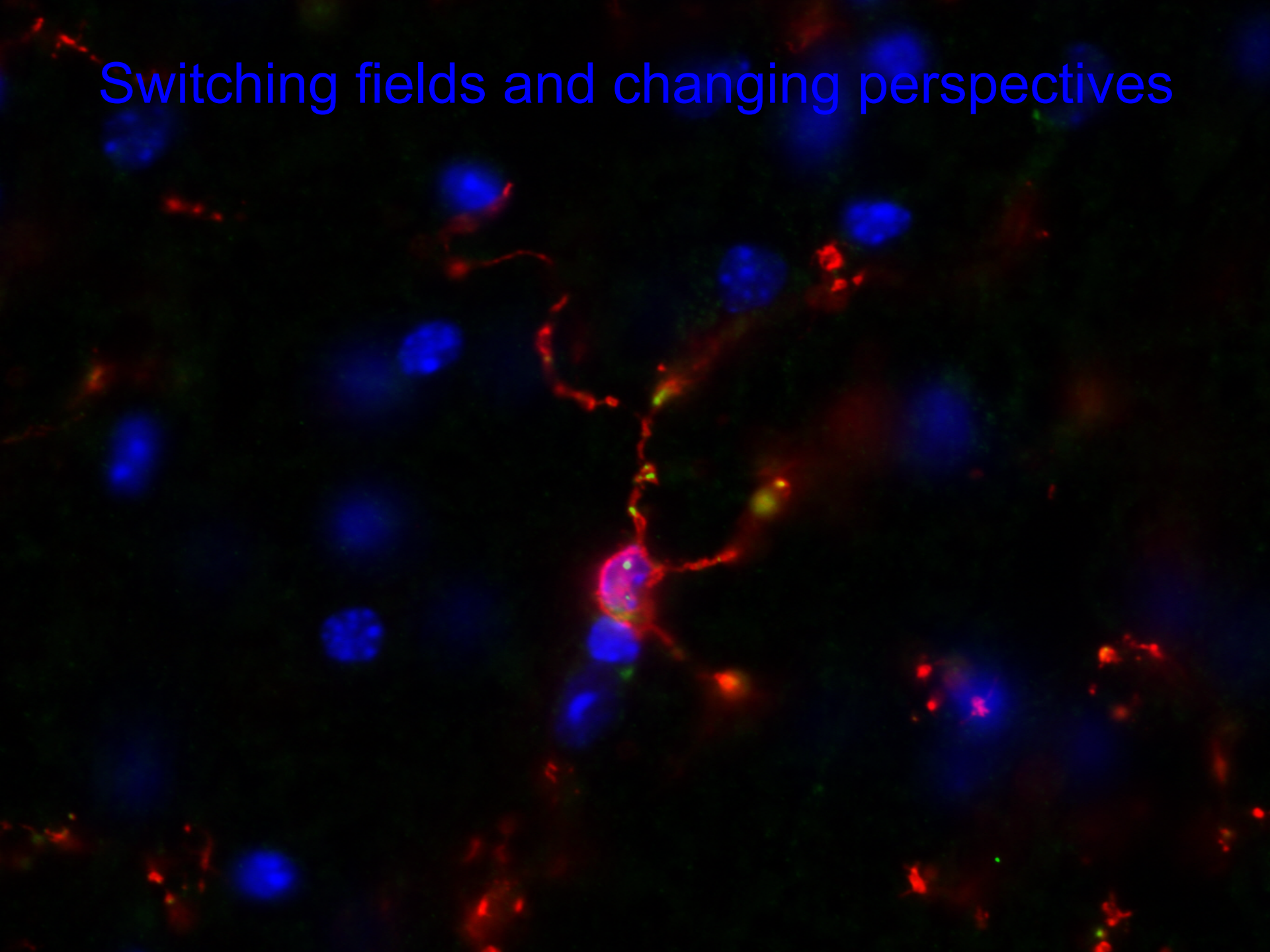
Molecular Biologist

Embryonic Development of the Mouse

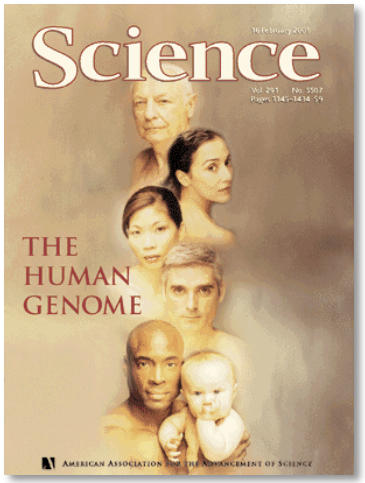


E = embryonic day after fertilization

Switching fields and changing perspectives



From Genomes to Genomic Therapeutics



~ 6,000
Diseases caused by genetic mutations

~ 95%
Have no approved therapy

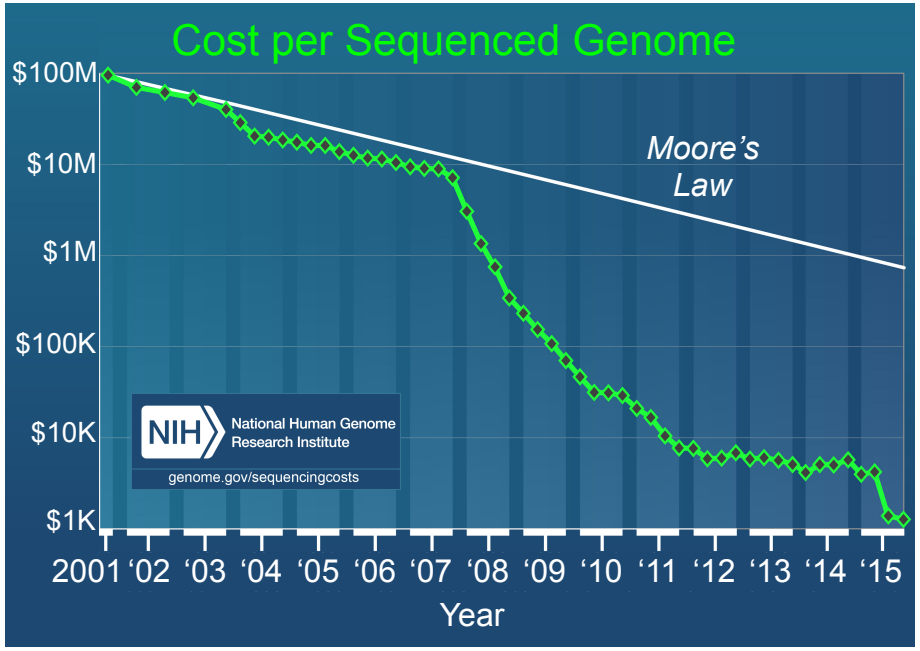
Each GWAS association offers a potential clue about disease mechanisms.

National Human Genome Research Institute

NHGRI GWAS Catalog. Welter et al, 2014

Alkes L. Price et al. Proc. R. Soc. B 2015

We have entered the age of the *Genetic Revolution*



The next wave of discovery in common diseases is likely to be driven by the growth of large population biobanks that combine:

genome-wide genetic information
with
extensive phenotypic information,
and in some cases –
lifestyle,
diet,
and other environmental exposures,

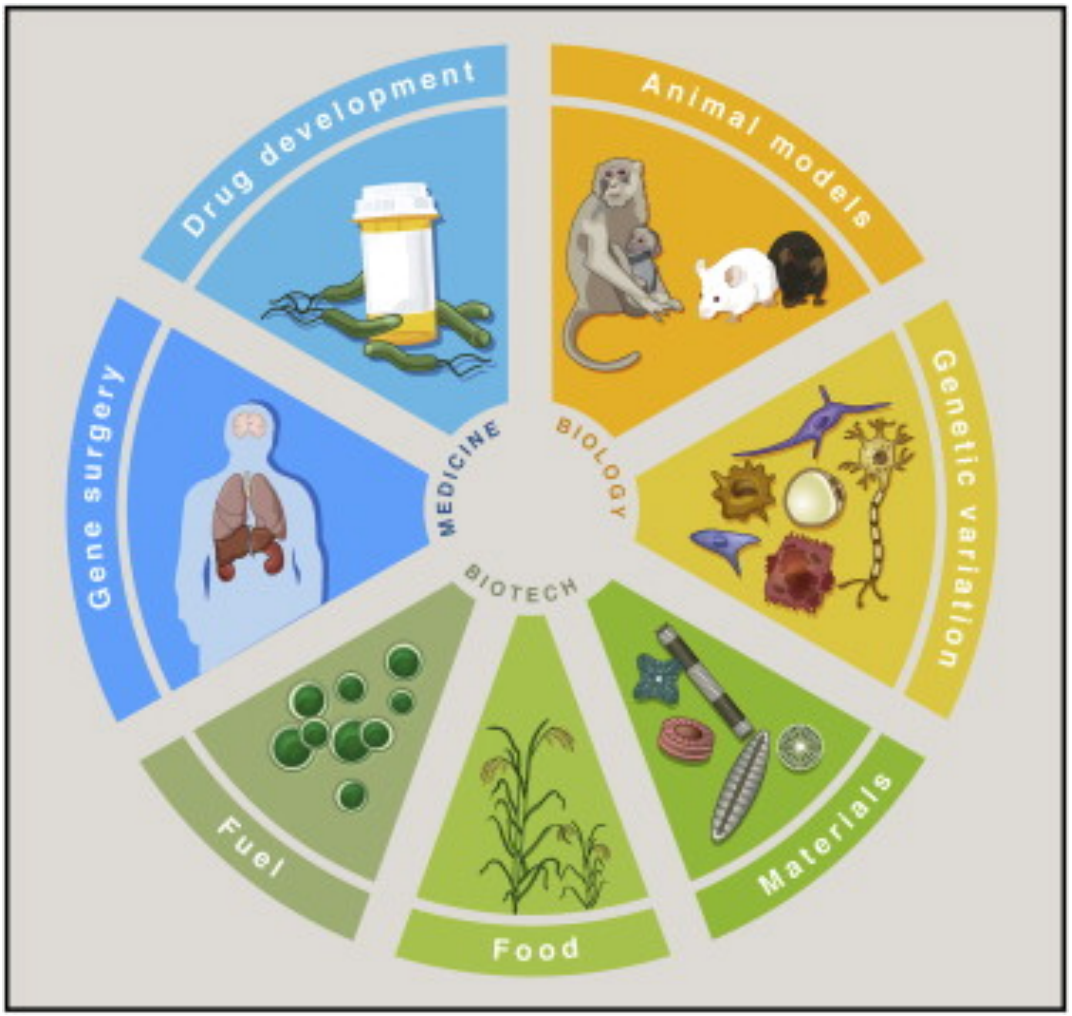
all measured on the same individuals.

NHGRI GWAS Catalog. Welter et al, 2014

Alkes L. Price et al. Proc. R. Soc. B 2015

CRISPR-Cas9 has Transformed Biology

Ease of use & efficiency has led to the wide adoption of this technology in research and beyond.



Wang et al, *Science* 2014

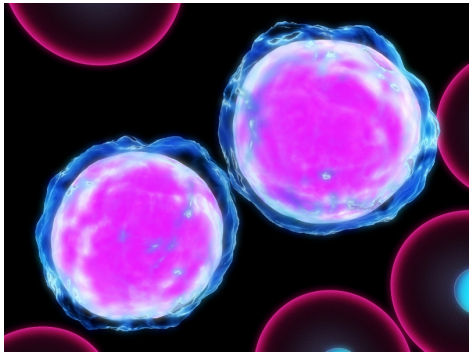
Targeted genome editing has rapidly accelerated our ability to assess gene function

http://www.publicdomainpictures.net/

*Capability to introduce targeted alterations into *ANY specific DNA sequence with high efficiency*

- **This capability did not exist before for most organisms/cell types**
- Broadly useful for practicing reverse genetics
- Also has therapeutic potential for wide range of inherited diseases

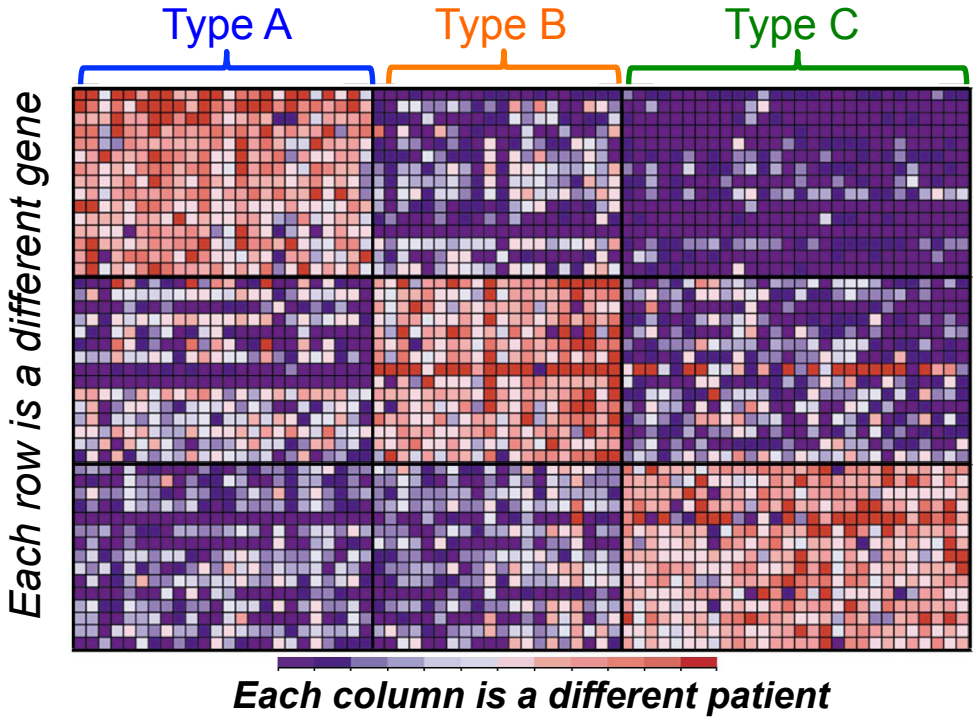
Genetic Diagnostics Enable Personalized Medicine



Leukemia cells

Extract RNA

Detect gene expression



Patients of type A, B, or C leukemia exhibit different gene expression patterns (RNA levels).

Treatment is specific to each type of leukemia; successful treatment requires early and accurate diagnosis

Diagnosis based on these levels is 95% accurate.

Slide adapted from Prof. David Liu

Traditional vs. Personalized Medicine

- Traditional medicine: diagnose based on symptoms, family history, and laboratory data; treat with the therapies thought to best fight the diagnosed disease

- Personalized medicine: diagnose as above, but **also use the patient's DNA sequence**; treat with the therapies thought to best fight the diagnosed disease given the patient's genetic makeup

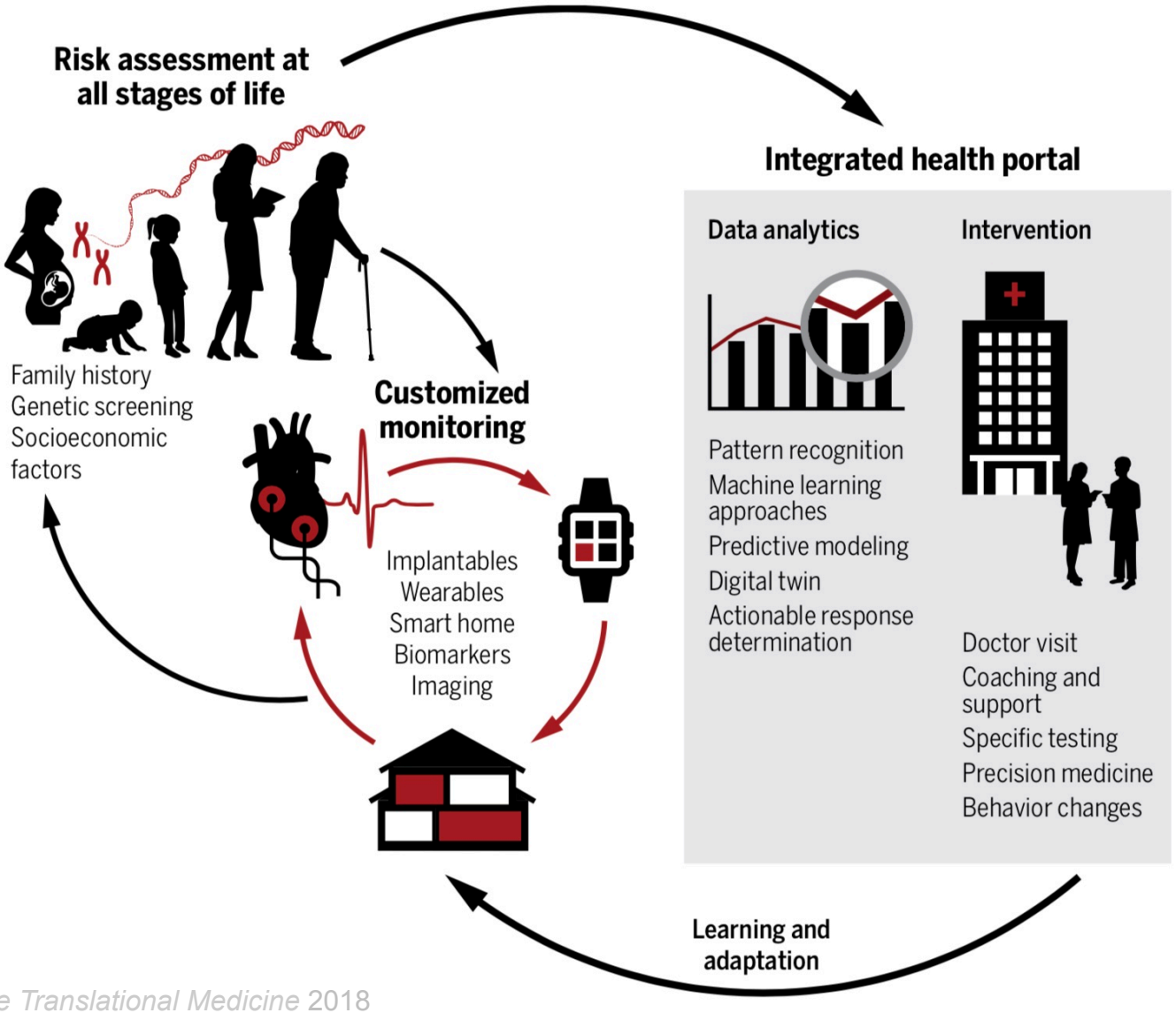
Is a drug likely to be toxic to **me**?

What is **my risk** of developing a certain disease?

Which drugs will be effective in treating **my disease**?

Slide adapted from Prof. David Liu

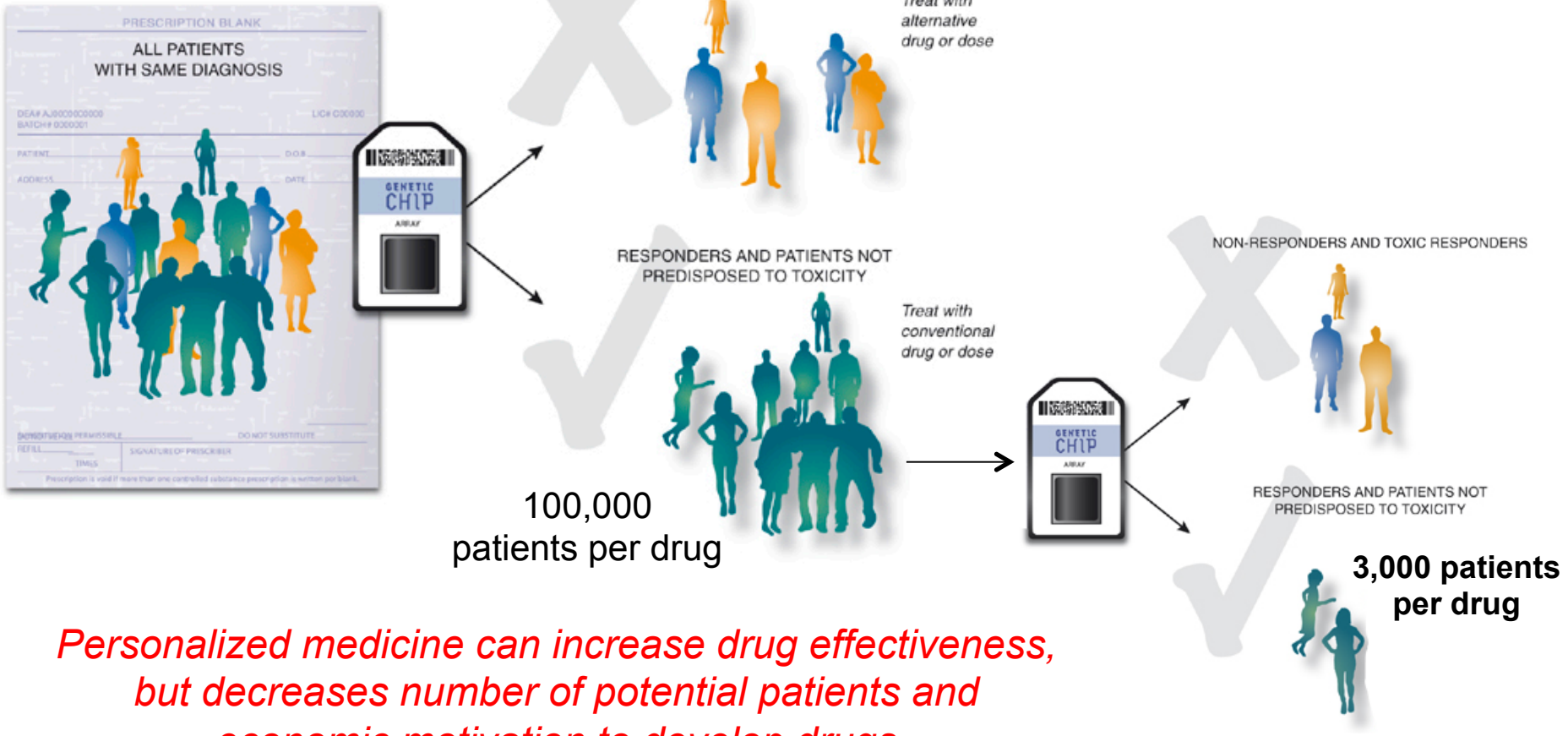
Gene editing is ushering in an era of *Precision Health* and Predictive or Preventative Medicine



Gambhir et al, *Science Translational Medicine* 2018

Personalized medicine and the economics of drug development

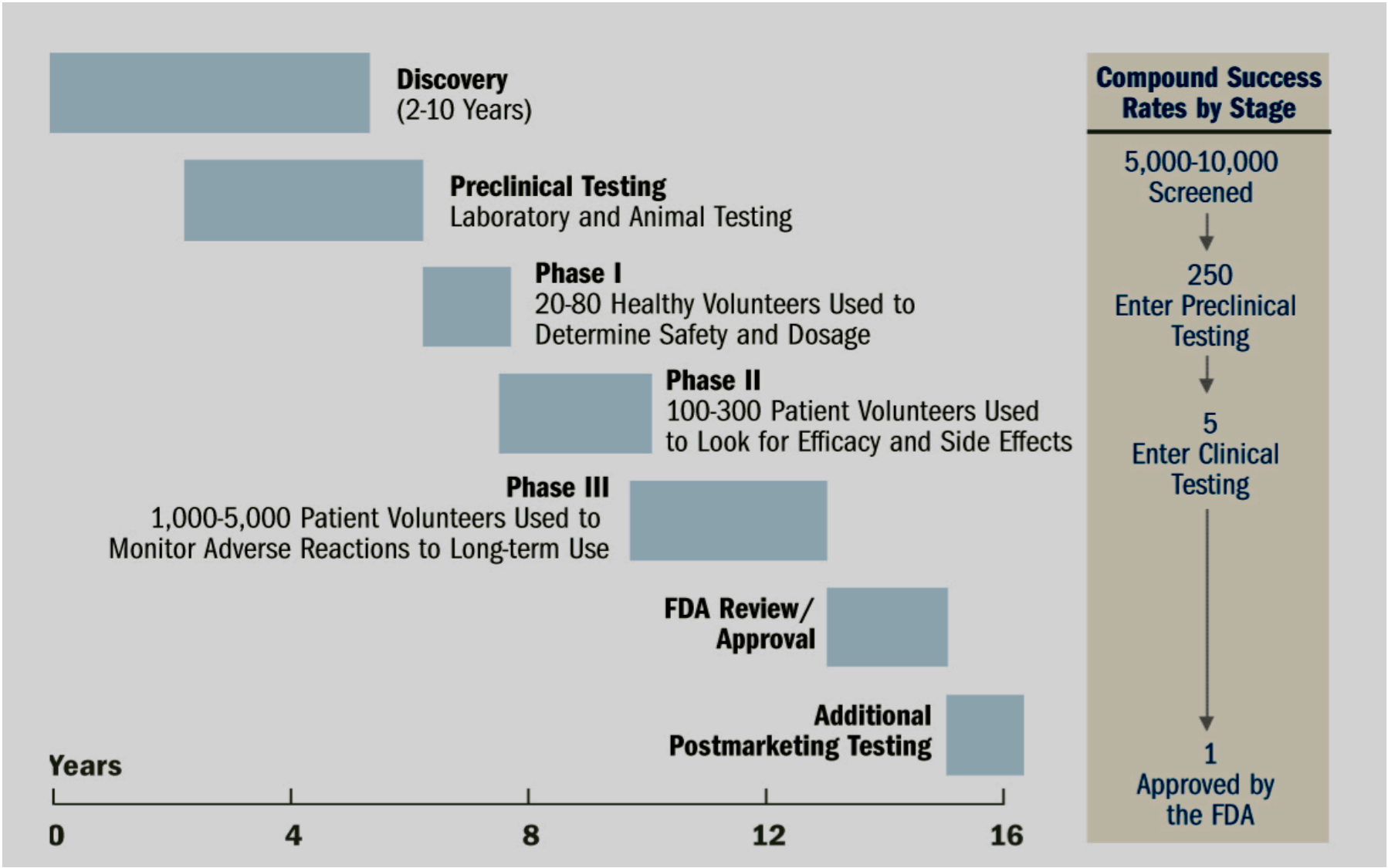
500,000 patients,
all taking one drug



Personalized medicine can increase drug effectiveness, but decreases number of potential patients and economic motivation to develop drugs

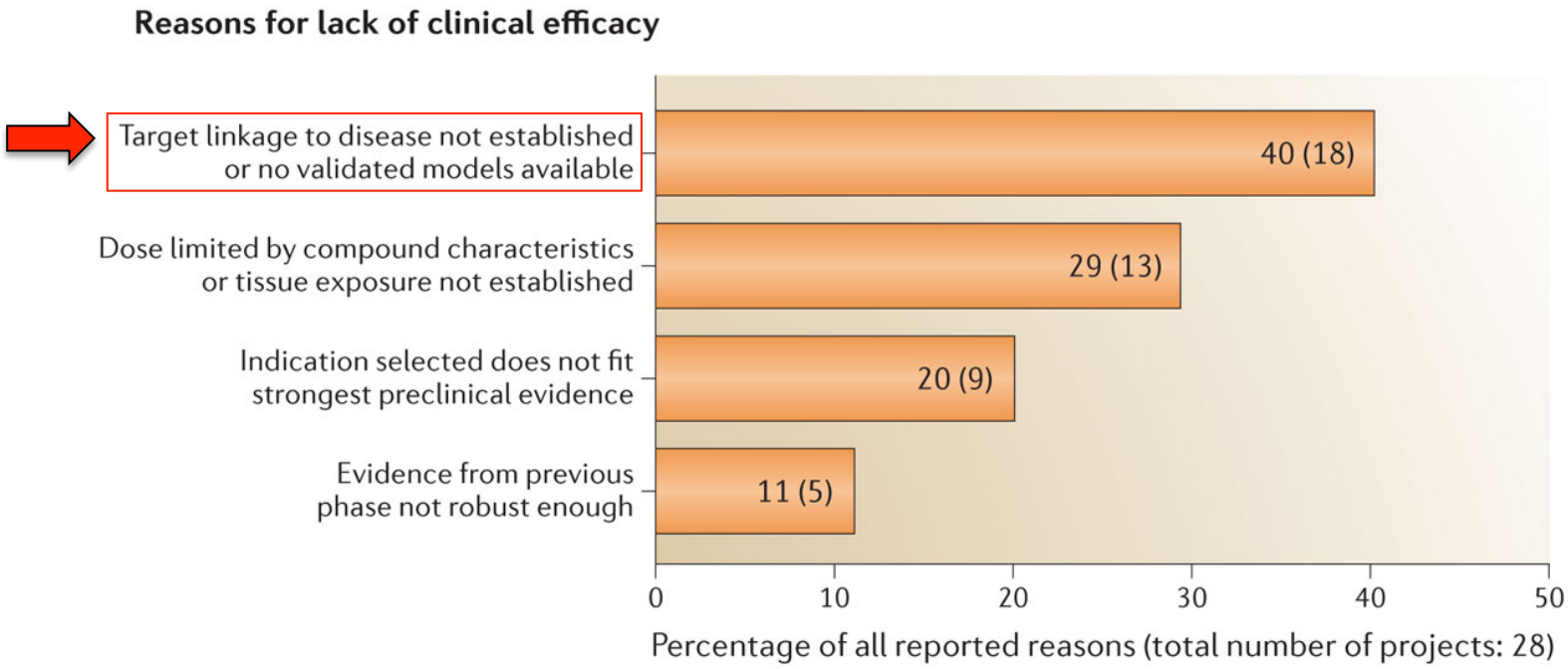
Slide adapted from Prof. David Liu

Drug Development is Very Difficult



Slide adapted from Prof. David Liu

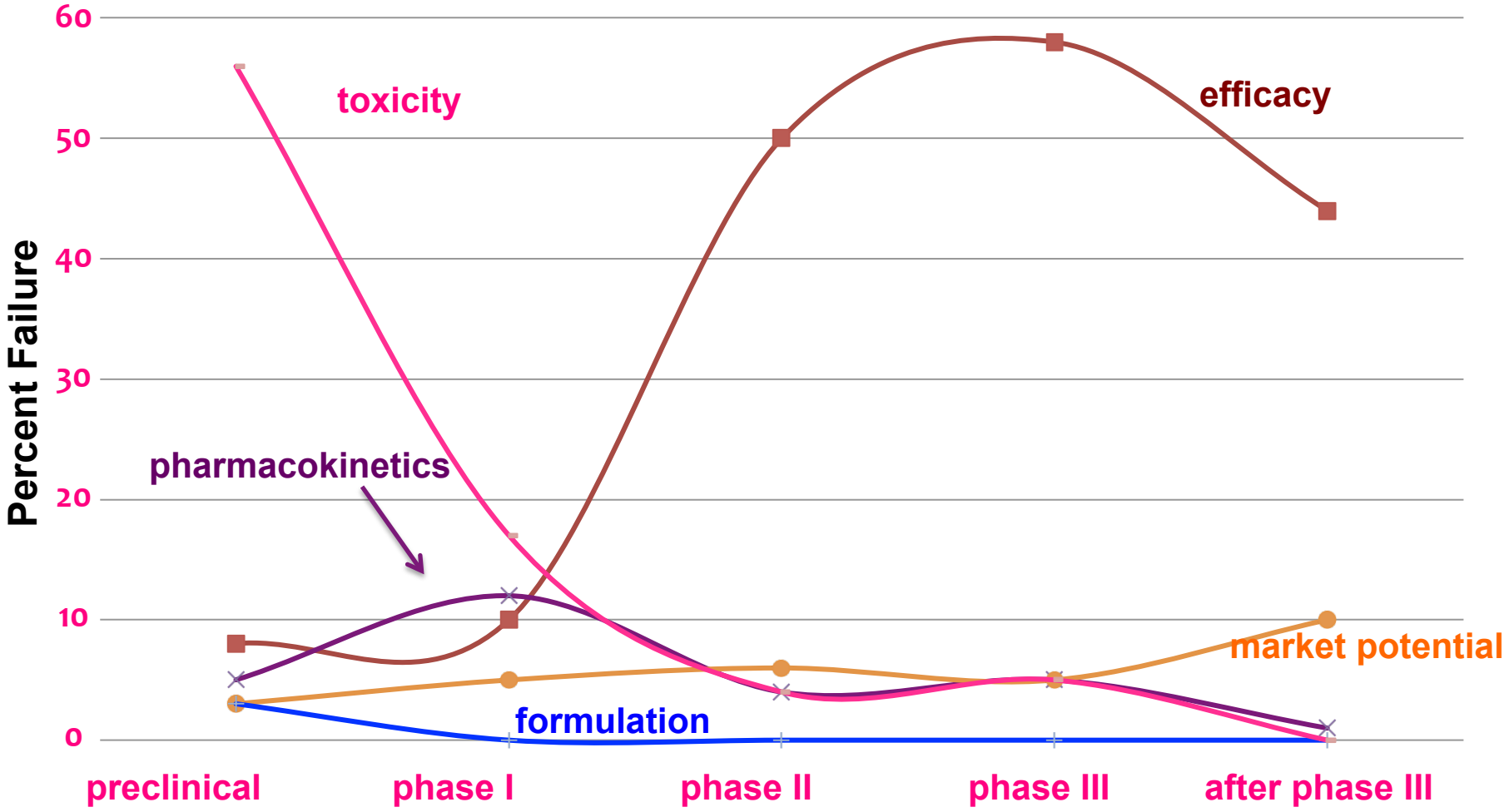
Most failure is attributed to poor preclinical models



Less than 5% of potential drugs are successful in reaching the market.
It is argued that most of this failure is due to the
inadequacies of preclinical models of disease, and
our **lack of understanding of human biology**.

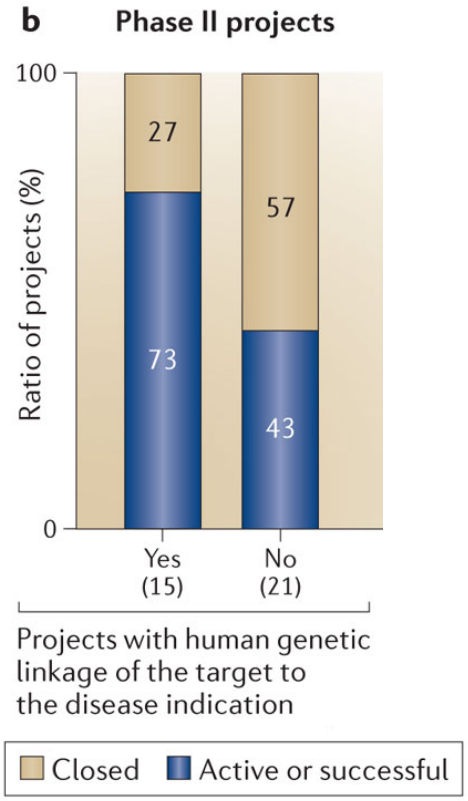
Cook et al, *Nature Reviews*, 2014

Why most candidates fail clinical trials



Slide adapted from Prof. David Liu

Genetic linkage of drug target to disease indication improves success rate



"**73%** **of projects with some genetic linkage of the target to the disease were active or successful** in Phase II compared with 43% of projects without such data."

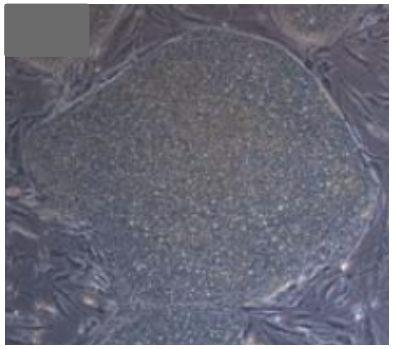
With growing datasets, genetics will be helpful in **stratifying patient populations for a more personalized treatment course,** rather than a "one size fits all" approach

Cook et al, *Nature Reviews*, 2014

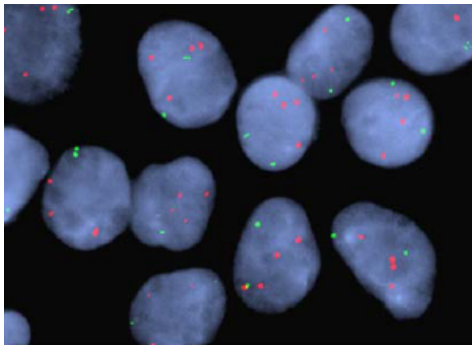
Using CRISPR to make customized cell lines

- Previously not possible to ***efficiently*** modify mammalian cells genetically
- Wide variety of cells have been modified including ESCs, iPSCs, HSCs, and many somatic cells
- Can now create mutated lines for <u>drug screening, disease modeling, or genetic analysis</u>
- Can *correct* disease mutations in patient-derived cell lines

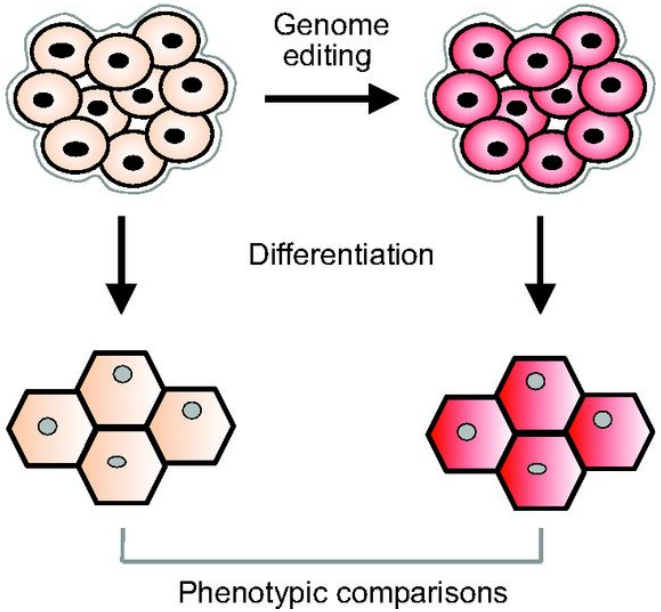
Learning about human biology in humans instead of animal models



Sebastiano et al., Stem Cells 2011



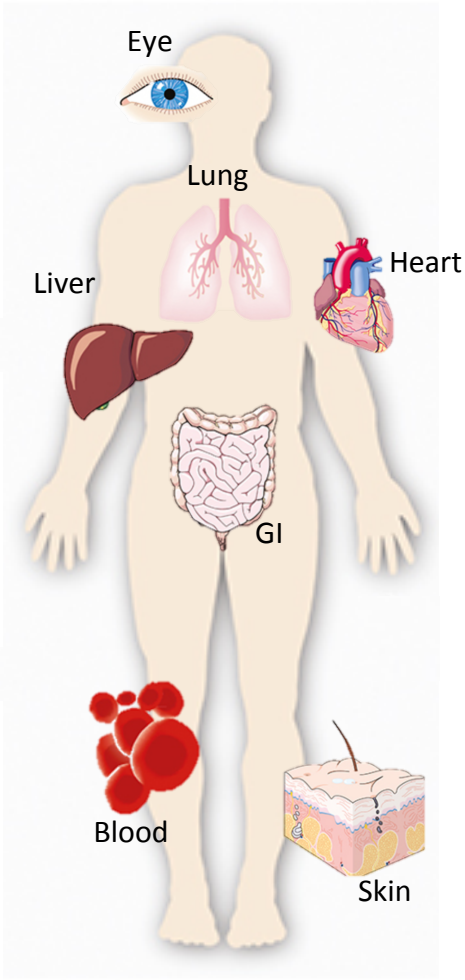
Maeder et al., *Mol Cell* 2008



from Musunuru K, *Dis. Model. Mech*. 2013

Slide adapted from Prof. David Liu

How are we moving forward with actual gene editing of humans?



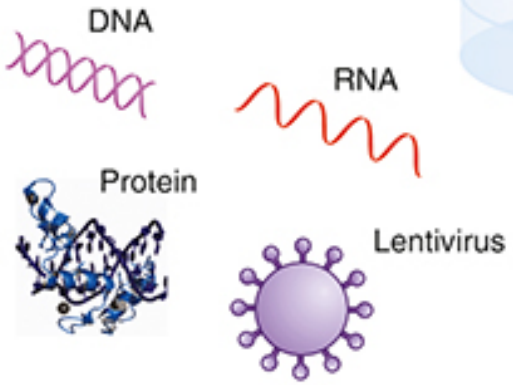
Maeder & Gersbach, *Mol Ther* 2016

How are we moving forward with actual gene editing of humans?

Ex Vivo
(Outside the body)

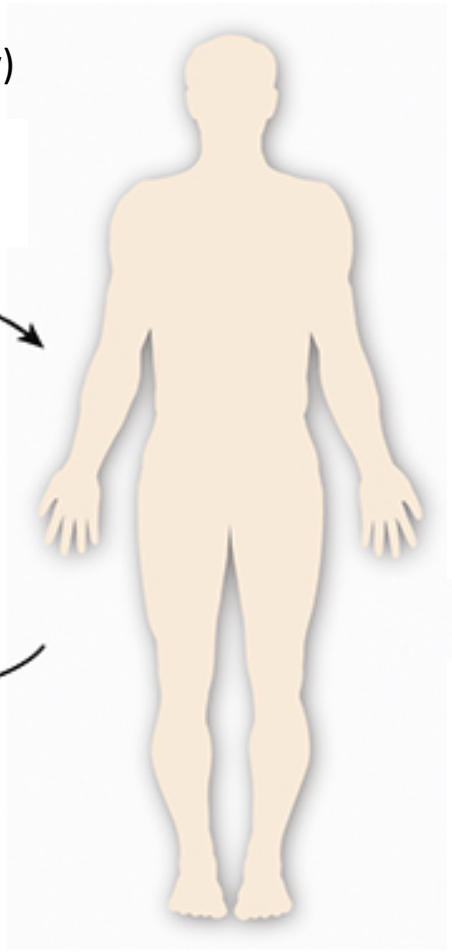
Put modified cells
back into the patient

Modify the cells with engineered
CRISPR-Cas9 for Genome Editing



(Tools we use to modify cells)

Remove cells
from the patient



Maeder & Gersbach, *Mol Ther* 2016

"In vivo" gene editing is much more challenging…

Delivery is a major challenge

Eye

Retinal Dystrophies

Liver

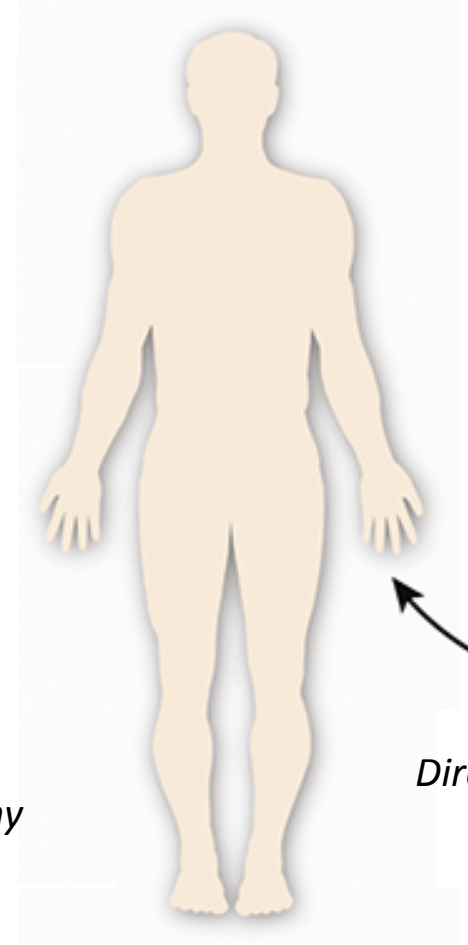
Hemophilia
MPS

Lung

Cystic Fibrosis

Muscle

Duchenne Muscular Dystrophy



In Vivo
(Inside the body)

Direct delivery of gene editing tools into the patient

Maeder & Gersbach, *Mol Ther* 2016

NEWS · 22 JANUARY 2019

CRISPR-baby scientist fired by university

Investigation by Chinese authorities finds He Jiankui broke national regulations in his controversial work on gene-edited babies.

Fewer Restrictions Allowing for Faster 'Progress'

China has less intensive regulation –

>11 genome editing clinical trials underway with at least 86 cancer patients treated

"China shouldn't have been the first one to do [a human genome editing trial] … but there are fewer restrictions."

Dr. Shixiu Wu | Leader of China's first trial at Hangzhou Cancer Hospital

WSJ Report highlights instances of less stringent, inconsistent review processes for human trials faced by Chinese researchers compared with their Western counterparts.

US operations face hospital review boards, ethics committees and government agencies before receiving approval.

Are there problematic elements to this differential regulatory structure between countries?

What about when disparate rules are made across countries, and/or inside vs outside the US?

“Asilomar 2015”

1970’s

Copyright © National Academy of Sciences

Key Ethical Considerations

Safety

Weighing benefits vs unintended risks

Germline Editing

Informed Consent

Incorporating Societal Values

Into clinical applications and policy discussions

Governing

Potential for differential regulation across nations

Access, Justice and Equality

Who can afford it? Does it deepen socioeconomic inequality?

China, the US and the UK agree that viable human embryos can be used for ***research***

NEWS | IN FOCUS

BIOTECHNOLOGY

Embryo editing gets green light

UK decision sets precedent for research on editing genomes of human embryos.

At the international Summit on Human Gene Editing in 2015, scientists from the US, the UK and China were in agreement that **viable human embryos can be used for research**, but it would be **unacceptable to alter the DNA of these embryos in clinical settings**.

The successful applicant is developmental biologist Kathy Niakan, at the Francis Crick Institute in London. Her team plans to use the CRISPR–Cas9 technique in healthy human embryos to alter genes that are active just after fertilization. The researchers will stop the experiments after seven days, when the embryos will be destroyed.

Callaway, *Nature* Feb 2016

What does the future hold?

What does it mean to change your genetic destiny?

Image: Dr. Jack Kreindler

The future of *in vivo* gene editing…
Gene Vaccines!

nature
International journal of science

OUTLOOK · 07 MARCH 2018

A CRISPR edit for heart disease

A one-off injection to reduce the risk of cardiovascular disease is now a prospect thanks to advances in gene editing.

Consider this scenario: it's 2037, and a middle-aged person can walk into a health centre to get a vaccination against cardiovascular disease. The injection targets cells in the liver, tweaking a gene that is involved in regulating cholesterol in the blood. The simple procedure trims cholesterol levels and dramatically reduces the person's risk of a heart attack.

**Some experts think this could become a reality within 5-10 years!*

Today's standard-of-care versus the future

OUTLOOK · 07 MARCH 2018

A CRISPR edit for heart disease

A one-off injection to reduce the risk of cardiovascular disease is now a prospect thanks to advances in gene editing.

Standard of Care TODAY

Current antibody-based therapies can cut the risk of heart attack by 27% and stroke by 21%, when administered in combination with statins. Lifestyle changes also important.

Treatment:

Regular infusions of drugs for the rest of a patient's life

Cost:

US $14,500/year

Gene Vaccines in 2037 – who should receive these?

OUTLOOK · 07 MARCH 2018

A CRISPR edit for heart disease

A one-off injection to reduce the risk of cardiovascular disease is now a prospect thanks to advances in gene editing.

Should this type of treatment be administered to at-risk patients only?

Standard of Care 2037

Gene vaccine entailing a single injection of gene editing molecules targeted to the liver. Follow-up blood test to evaluate efficacy. Lifestyle…?

Treatment:
Single injection followed by efficacy screening
Cost:
$$$?

"You don't necessarily want to treat people who haven't got a disease yet"
Karel Moons, *clinical epidemiologist*

Safety Considerations – Somatic Approach

Do the benefits of genome editing justify the risks?

How does gene editing compare to the risk in current therapeutic strategies?

Disease Type

Disease Progression

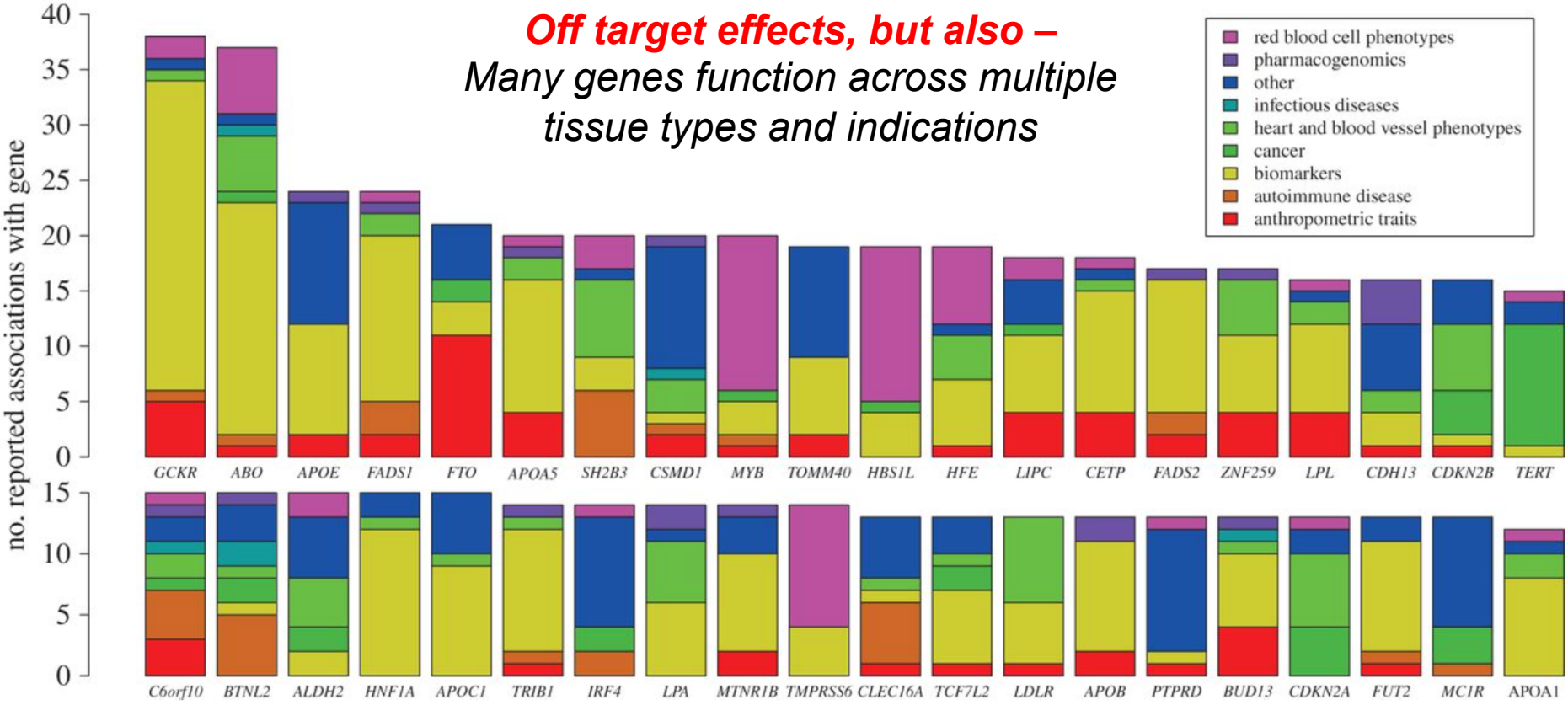
Types of Cells/Tissue Treated

Mode of Therapeutic Application

Other Therapeutic Options

Likely Off-target Sites for Site to be Edited

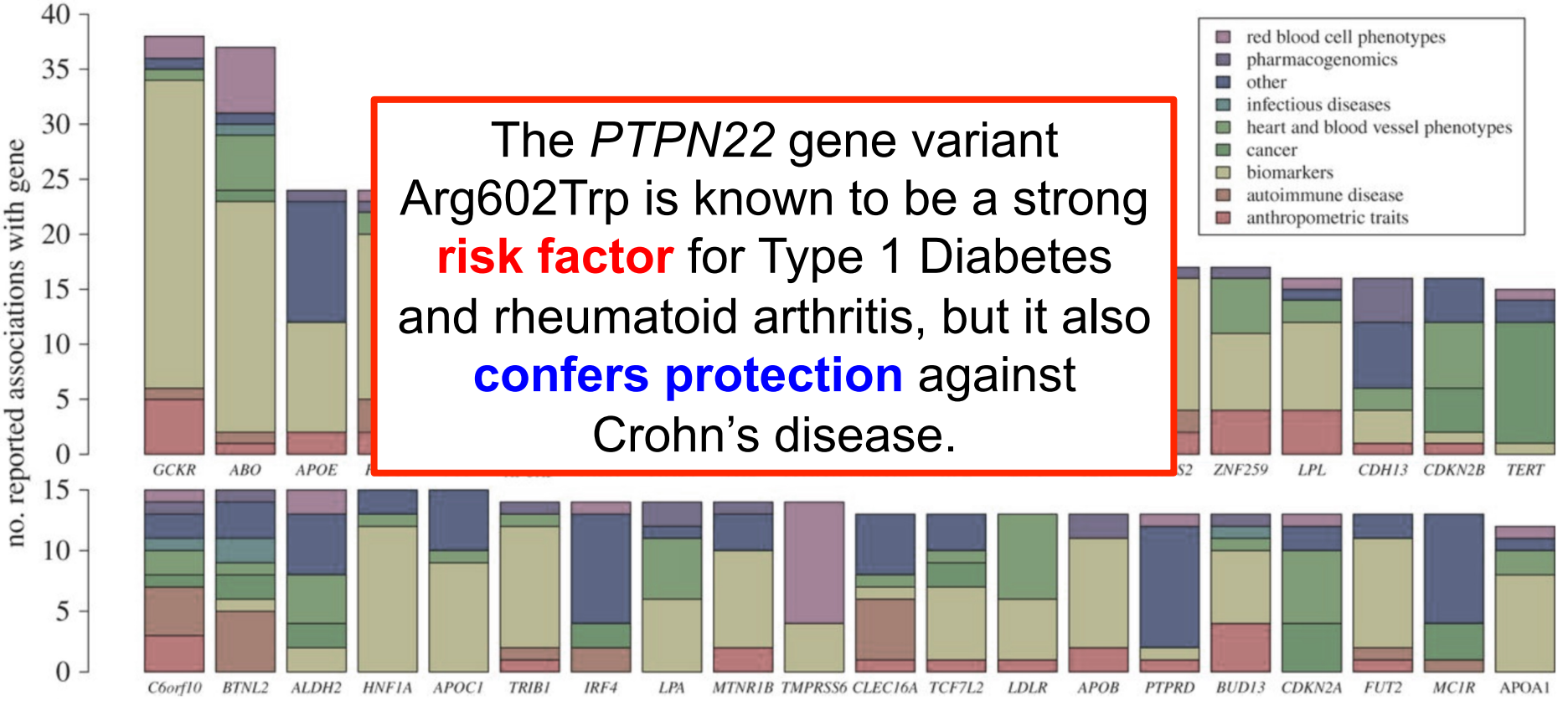
To keep in mind as we embark into gene editing therapeutics…



Barplot of the 40 genes in the NHGRI GWAS catalog (2014) that have the highest number of associations where they are listed as the reported gene.

Price et al, Proc Royal Soc B, 2015

Many genes function across multiple tissue types and indications



The *PTPN22* gene variant Arg602Trp is known to be a strong **risk factor** for Type 1 Diabetes and rheumatoid arthritis, but it also **confers protection** against Crohn's disease.

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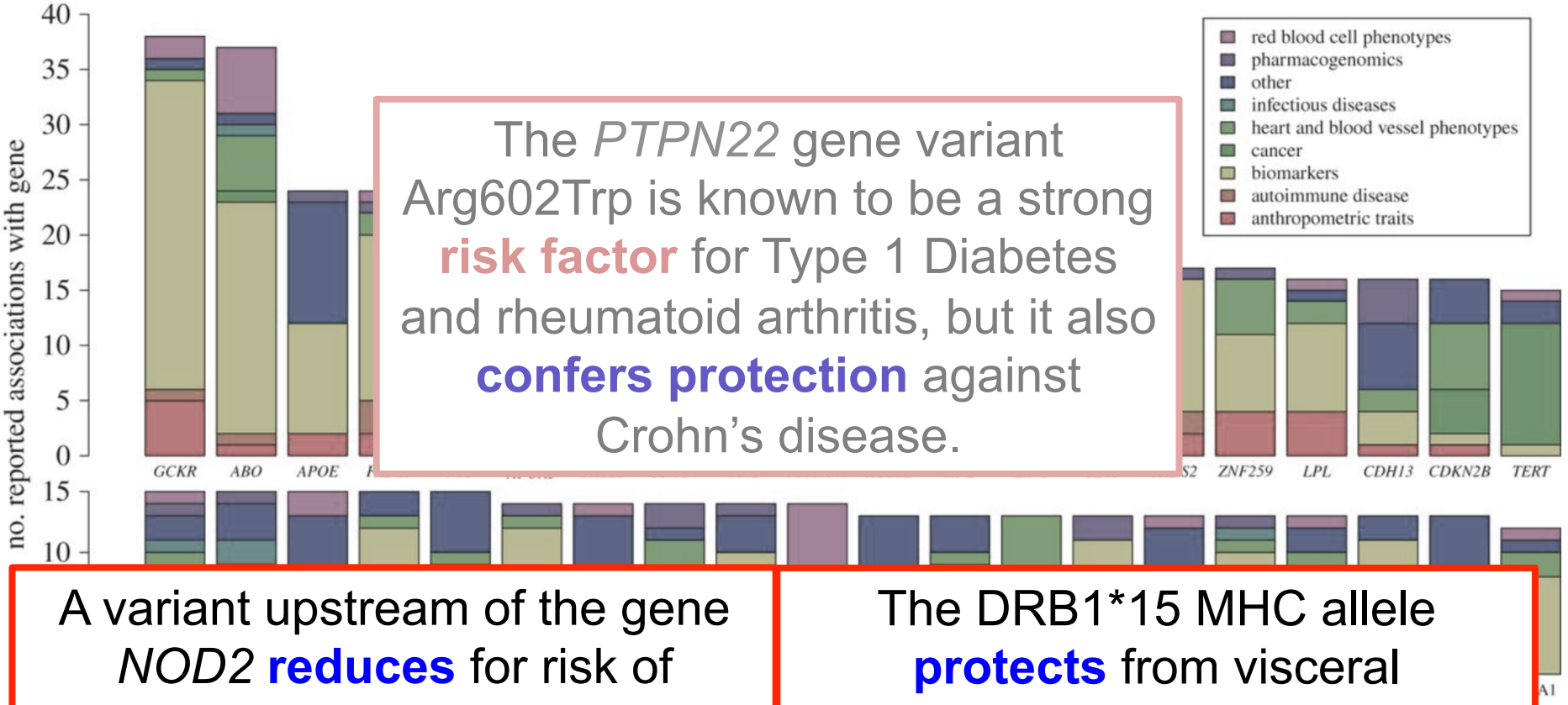
Pleiotropy can potentially lead to conflicting evolutionary pressures



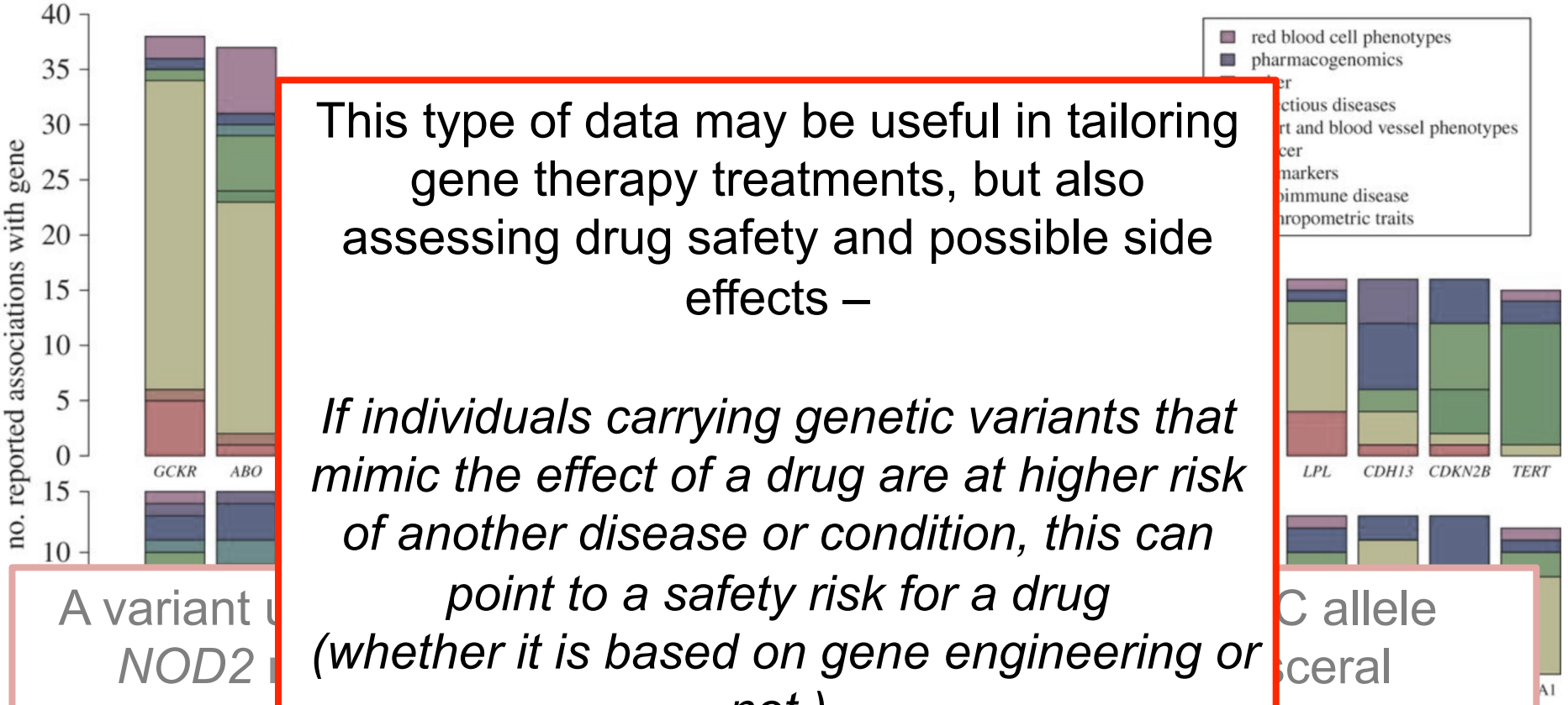
The *PTPN22* gene variant Arg602Trp is known to be a strong **risk factor** for Type 1 Diabetes and rheumatoid arthritis, but it also **confers protection** against Crohn's disease.

A variant upstream of the gene *NOD2* **reduces** for risk of inflammatory bowel disorder but **increases** risk of leprosy.

The DRB1*15 MHC allele **protects** from visceral leishmaniasis and leprosy, but **increases** risk of MS.

Price et al, Proc Royal Soc B, 2015

Pleiotropy can potentially lead to conflicting evolutionary pressures



This type of data may be useful in tailoring gene therapy treatments, but also assessing drug safety and possible side effects –

If individuals carrying genetic variants that mimic the effect of a drug are at higher risk of another disease or condition, this can point to a safety risk for a drug (whether it is based on gene engineering or not.)

A variant u… *NOD2* … inflammato… increases risk of leprosy.

…C allele …sceral …prosy, but increases risk of MS.

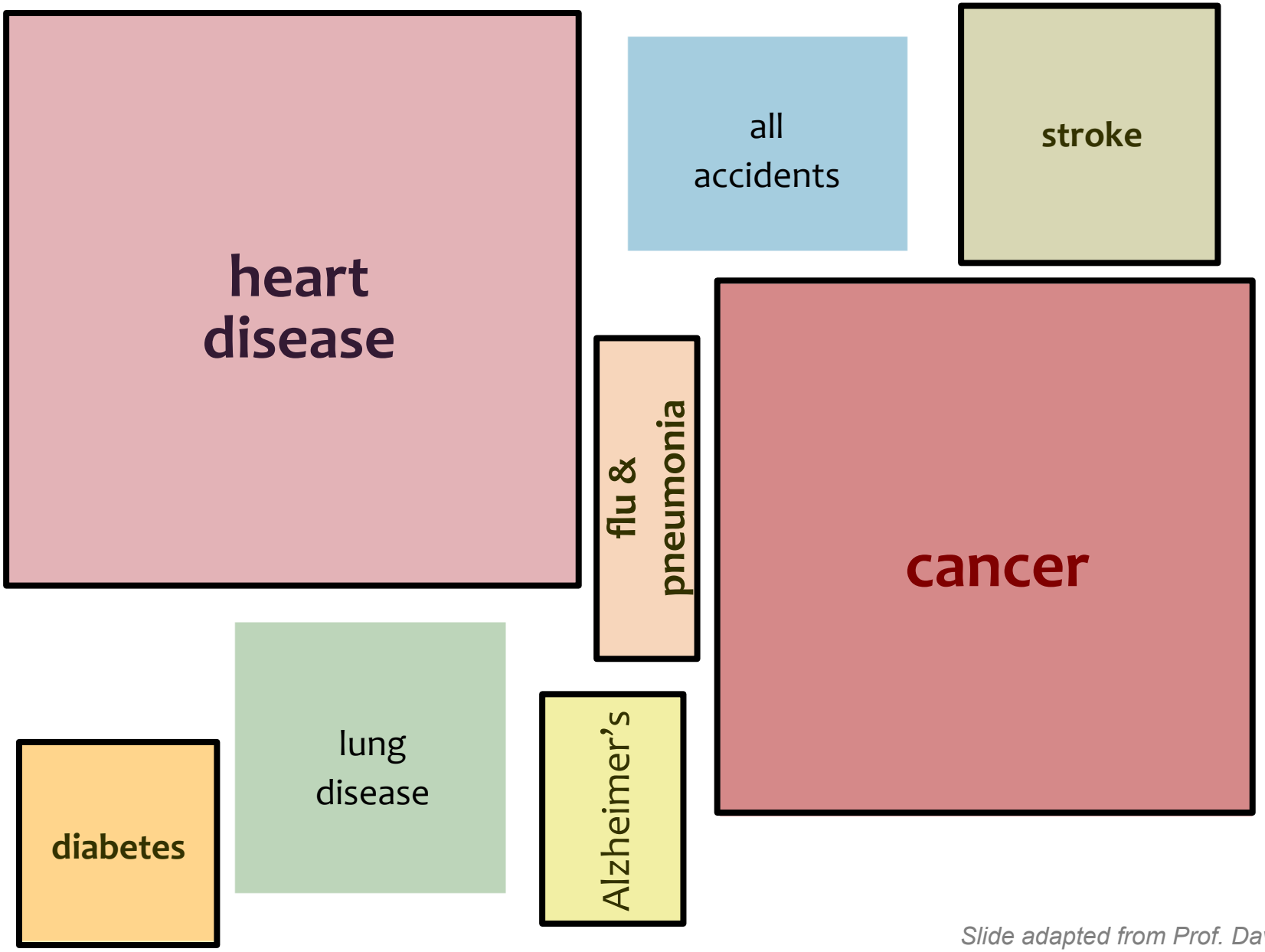
Price et al, Proc Royal Soc B, 2015

Assuming moderate risk, would you be open to gene therapy treatment to prevent diseases you are at risk for before their typical age of onset?

Keep in mind: *many commonly drugs have mild to moderate risk (birth control pills & blood clots, arthritis meds & liver damage, etc)*

Do you think safety testing needs to be modified for therapies designed for healthy people versus ill people?

As we get ahead of age-related diseases, will we also prolong human life?



Slide adapted from Prof. David Liu

Can we treat aging as a disease?

"We take disease seriously, whereas we view processes of aging as simply being natural."

Irwin Rosenberg, Tufts University

LIFE EXPECTANCY:

1837 → ~ 45 years

2015 → ~87 years

Fighting the inevitability of ageing

The debilitating loss of muscle and strength that comes with age is being recognized as a disease that could be treated.

"We know we're an increasingly ageing population… One of the challenges for us is how to make sure that those added years are quality years."

Elaine Dennison, Epidemiologist

Liam Drew, *Nature* 2018

Would you want to live to be 150?

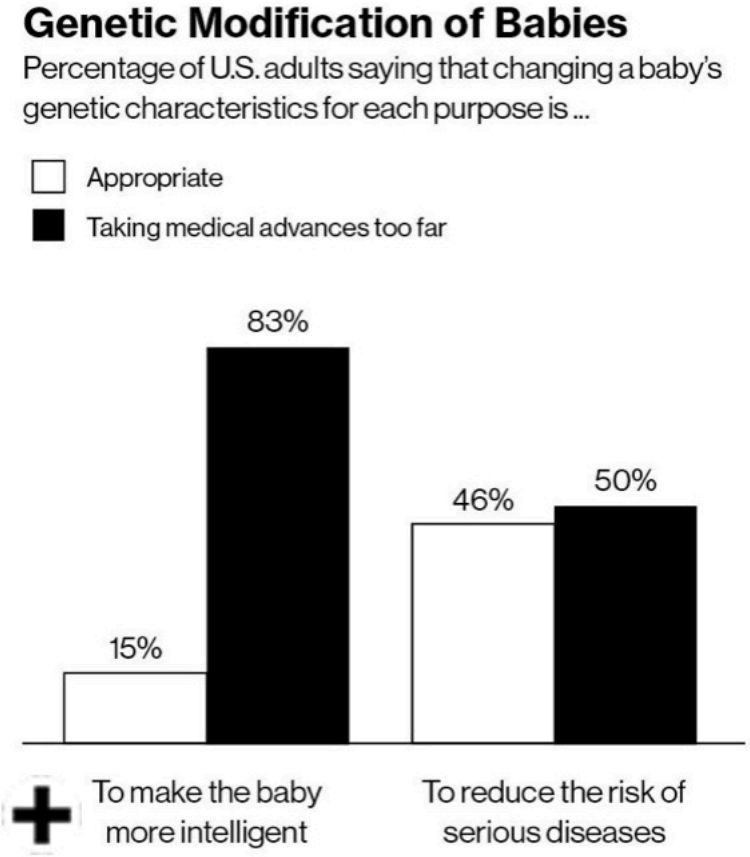
What does the future hold for genetic engineering of humans?

It is becoming possible to correct disease genes
(and pass those genetic fixes on to future generations)

How does informed consent work in this context?

Intervention to protect people from long-term disease can begin at, or even before, birth.

Germline Editing – Where do we draw the line?



Updated figures suggest over 60% of the population agrees with disease-treating genome editing

"If germ-line engineering becomes part of medical practice, it could lead to transformative changes in human well-being, with consequences to people's life span, **identity**, and economic output."

If you could choose to enhance protective traits in you or your offspring, would you?

A Regalado. *Engineering the Perfect Baby.* MIT Tech Review 2015

Who should decide what traits we can and cannot edit in human embryos?

A. The parents
B. Scientists and/or medical doctors
C. Bioethicists
D. State and/or Federal government
E. All of the above

A number of genes could offer protective enhancements

George Church: “In addition to common variants of small impact and rare deleterious variants, there are rare protective gene variants of large impact.”

LRP5 (G171V/+) – Extra-strong bones

MSTN (-/-) – Lean muscles

SCN9A (-/-) – Insensitivity to pain

ABCC11 (-/-) – Low odor production

CCR5, FUT2 (-/-) – Virus resistance

PCSK9 (-/-) – Low coronary disease

APP (A673T/+) – Low Alzheimer’s risk

GHR, GH (-/-) – Low cancer

SLC30A8 (-/+) – Low T2 Diabetes

IFIH1 (E627X/+) – Low T1 Diabetes

Will it be possible to “install” genes that offer lifelong protection against infection, Alzheimer’s, and maybe effects of aging?

If you could choose to enhance yourself via gene editing in you or your offspring, would you?

How would you feel knowing your parents engineered you to enhance particular traits?

Positively

I am the product of their creation (genetically and creatively)

Negatively

Others have no right to alter my unique genetic heritage

Will we one day directly alter human evolution?

Can we eradicate diseases like Huntington's the same way we've eradicated many diseases with vaccines –
"prevent the propagation of human disease in future generations"

"You can't retract a designer baby"

Would you support a “reproductive quarantine” for individuals who have unexpectedly deleterious outcomes of germline genetic engineering?

What types of human germline modifications do you think are acceptable?

A. Genetic disorders with no treatment options
B. Genetic disorders with treatment options
C. Trait enhancement
D. A, B and C
E. None of the above

Which concerns you most in relation to the use of genome editing of embryos for non-therapeutic modifications?

A. Loss of human diversity
B. Eugenics
C. Both concern me equally
D. Something else

CRISPR-Cas9 has gone Hollywood

What is the role of entertainment in biotechnology?

Science

Jennifer Lopez set to produce NBC bio-terror drama *C.R.I.S.P.R.*

By **Jessica Boddy** | Oct. 19, 2016 , 11:00 AM

She's still Jenny from the block, but now **Jennifer Lopez is also the executive producer of a new drama called *C.R.I.S.P.R.***, *The Hollywood Reporter* writes. Each episode of the new J Lo–produced show, slated to air on NBC, will investigate a criminal bio-attack based on the CRISPR gene-editing technique, from a genetic assassination attempt on the president to the framing of an unborn child for murder. If the project moves forward (the script is still being written), the drama will center on a scientist and her former mentor as they battle for control over the human genome, the culmination of which could mean life or death for the entire human race. Don't stress over a real-life CRISPR though —these days, the technique is being used to **engineer pasta dishes**, not frame murders.

How does pop-culture’s influence on emerging science and technology impact public opinion or sentiment?

Our visions of technology and design and entertainment and creativity have to be married with visions of humanity, compassion, and justice. And more than anything, for those of you who share that, I've simply come to tell you to keep your eyes on the prize, hold on.

Bryan Stevenson | *Human Rights Lawyer*

Thank you!

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