Science advances one funeral at a time

Planck

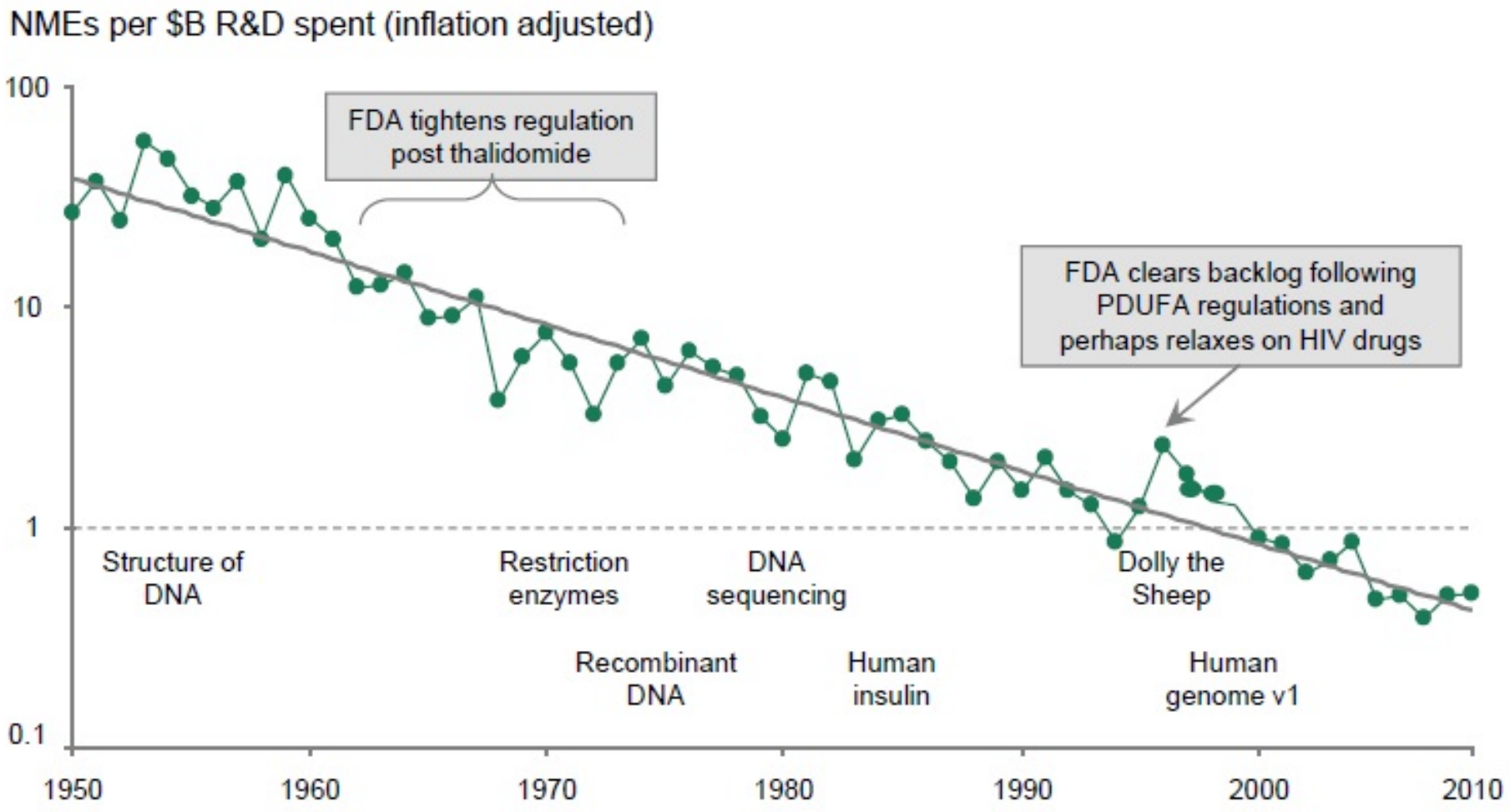
Something is wrong with science and medicine…..

>$250B a year invested in biomedical research

For many diseases, we still don't even understand molecular mechanisms, let alone how to design a therapeutic strategy

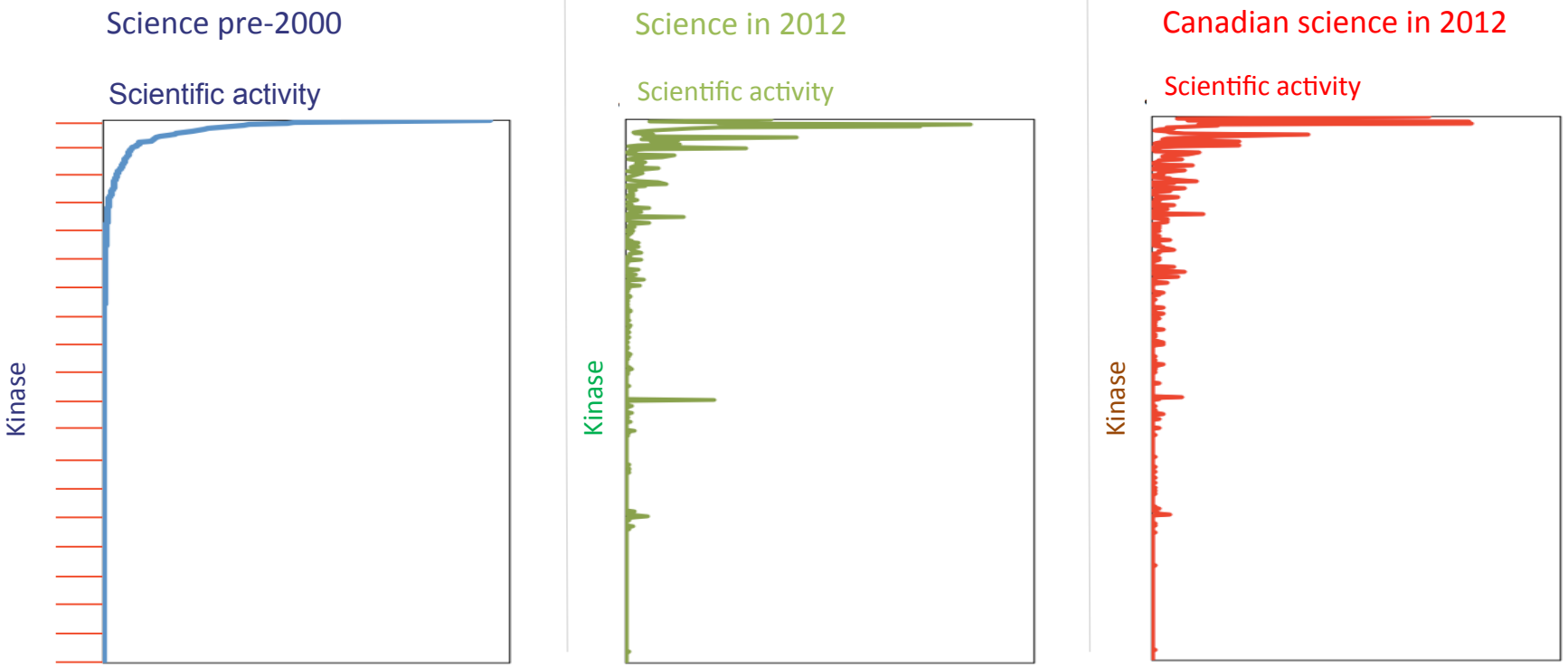
Medicines are not affordable for most people in the world

Something is wrong with industry…..



Why?

Science resists change and is redundant



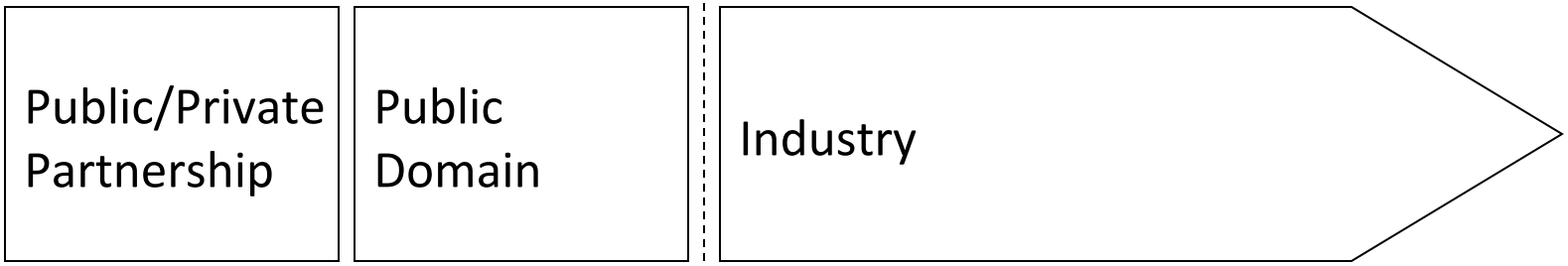
SGC at a glance

- Operations started in June 2004
- Government agencies, Wellcome Trust, Gates Foundation, charities & leading pharma companies
- +280-strong team in Oxford, Toronto, Stockholm, Campinas, Chapel Hill & Frankfurt (plus extended network)
- Open Access Policy:
  - Promptly placing results, reagents and know-how in the public domain
  - SGC scientists never file patents

Open structural biology

- Our core strength
- >1,500 human proteins in public domain all pre-publication
- 14% of world all-time output

Open chemistry industry partnership concept



Research tools

SGC
Screening
Structure
Cell activity

Pharma
Chemistry

Academics use them

No IP
No restrictions
Publication

Industry takes ideas and develops drugs

(re)Screening
Chemistry
Lead optimization
Pharmacology
DMPK
Toxicology
Chemical development
Clinical development

Creative commons

Proprietary

Open Chemistry speeds drug discovery

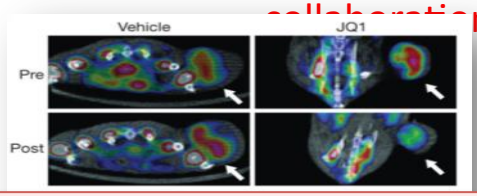
6 Months | 11 Months | 1 Month | 2 Years and 2 months | 6 Months | 3 Months

July 2009

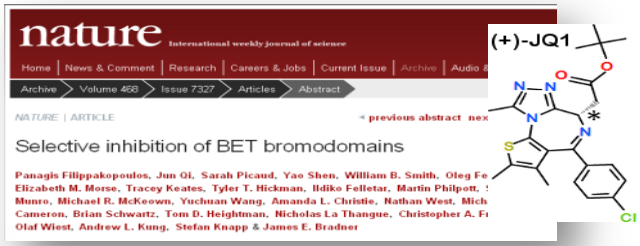
GSK informs SGC about Mitsubishi compound

Jan 2010

Oxford and Harvard start collaboration



Dec 2010



Co -publication of JQ1 probe (SGC; cancer) and

Jan 2011

July 2011

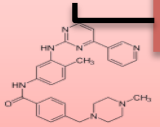
Broad interest from

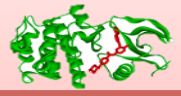
Oct 2011

Mar 2012

GSK carries out first in man (for open access - discovered indication!)

Glivec (Tk_{inh}) discovered





1992 ⟷ 1998

First-in-man study

6yrs

SGC

I’MPATIENT

Open access enabling early-stage drug discovery by patient & disease foundations

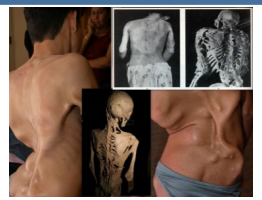
I'MPATIENT programme partnerships

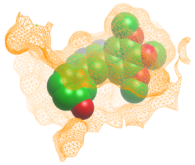
"Stone-Man Syndrome"

fopaction Fibrodysplasia Ossificans Progressiva

Friends of Oliver

\+ SGC

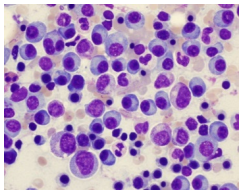




Ultra-rare disease
No treatment
SGC co-dev. compounds.
assays & models

Multiple Myeloma

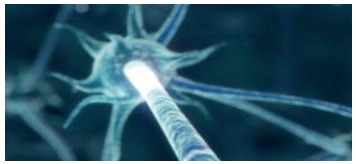
MyelomaUK + SGC



Relapses
Need to identify novel targets for new treatments
Myeloma UK already established Translational Research Programme & Clinical Trials Network

Brain Tumour Charity

The BRAIN TUMOUR CHARITY + SGC



Novel tissue platform and follow-up med chem to generate open clinical compounds for DIPG

Huntington's Disease

CHDI FOUNDATION
Accelerating therapeutic development for Huntington's disease
\+ SGC

To rapidly discover & develop drugs that delay or slow Huntington's disease

To jointly explore the role of epigenetic regulation in HD and novel proteins identified by CHDI network

I'MPATIENT

Fibrodysplasia Ossificans Progressiva (FOP): From gene to clinical candidate

SGC

Gene → Mechanism → Pre-clinical → Clinical candidate

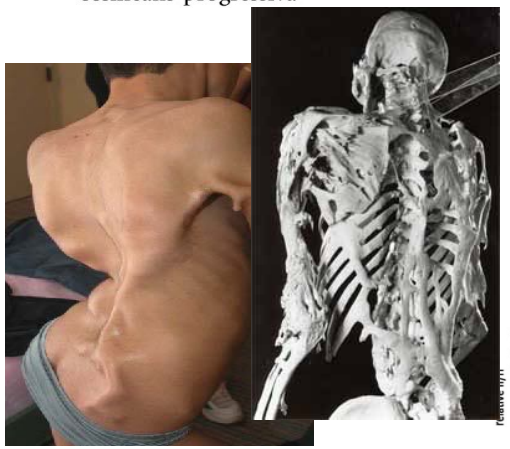
Apr 2006 — 3 years — **Apr 2009** — 3 years — **2012-2013** — 2 years — **2015**

6 years

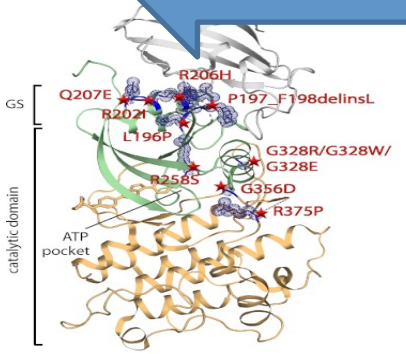
Gene causing FOP was discovered

nature genetics

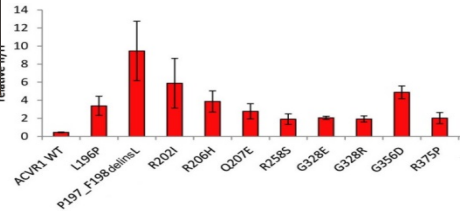
A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva



Structure solved; mutations mapped

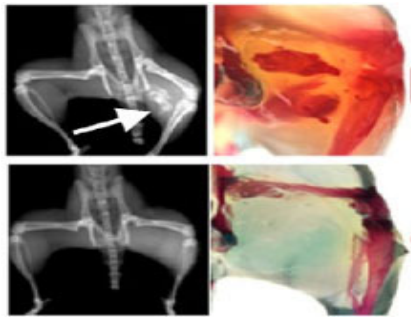


Kinase gain of function

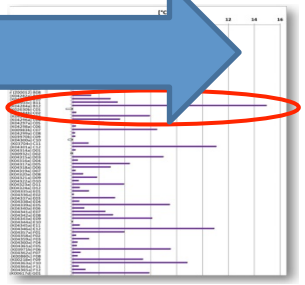


New tool compounds & animal models

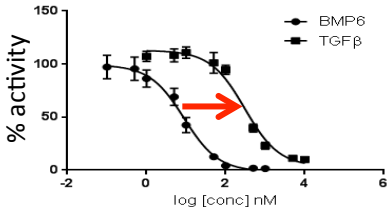
Tool compounds



Clinical study being designed



Potent and selective



Alex N Bullock

UNC Rare Disease Catalyst

- Partnership with disease foundation
- Co-recruitment of Fellow who will make a career in that disease research
- Fellow will be expected to create research tools for public domain
  - These tools will be used for disease understanding
- Fellow will hold monthly Webinar with patient groups to chat science

Open Lab Notebooks

Aims:

- Open access science
- Collaborative and interactive
- Real-time and honest reporting
- Accessible to all

Lab Scribbles

Real-time open access science

About Lab Scribbles | Huntington's Disease | Bio | Contact

Purifying full-length huntingtin protein from bacul… expression system for EM analysis

September 21, 2016 Leave a comment

Things are moving fast in the lab which is exciting as it means the project i… quickly too. However, it does mean that I now have lots of data to share in t… thanks to very generous sharing of reagents from Dr. Ihn Sik Seong, we are… Read More ….

Huntingtin methylation analysis by mass spectrom…

August 30, 2016 Leave a comment

For the past week or so I have been continuing to conduct an analysis of po… modifications or PTMs of the huntingtin protein. After the protein is expre… often chemically modified by small moieties which can affect its fold and f… In my last post I looked at Read More ….

Huntingtin phosphorylation analysis by mass spect…

August 5, 2016 2 Comments

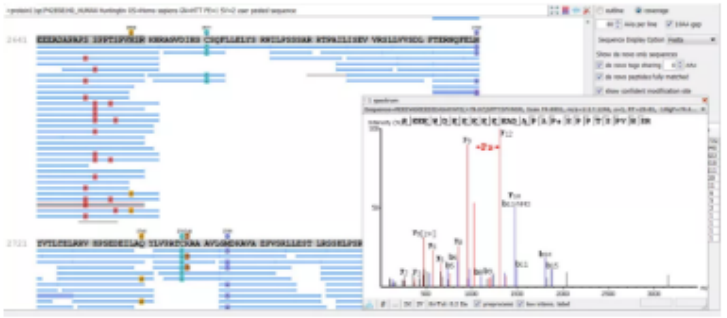
For the past week or so I have been conducting an analysis of post-translati… of the huntingtin protein. After the protein is expressed in the cell, it is the… modified by small moieties which can affect its fold and function. In this in… looking at the phosphorylation of the Read More ….

Huntingtin phosphorylation analysis by mass spectrometry

August 5, 2016 racheljaneharding 2 Comments

For the past week or so I have been conducting an analysis of post-translational modifications of the huntingtin protein. After the protein is expressed in the cell, it is then often chemically modified by small moieties which can affect its fold and function.

In this instance, I have been looking at the phosphorylation of the protein through reanalysis of the peptides seen in the previous mass spectrometry experiments conducted as part of the domain mapping investigations. All of this work was done using the huntingtin protein sample derived from HEK293 cells, kindly provided by Stefan Kochanek and Bin Huang.



An example spectra showing phosphorylation on S2652.

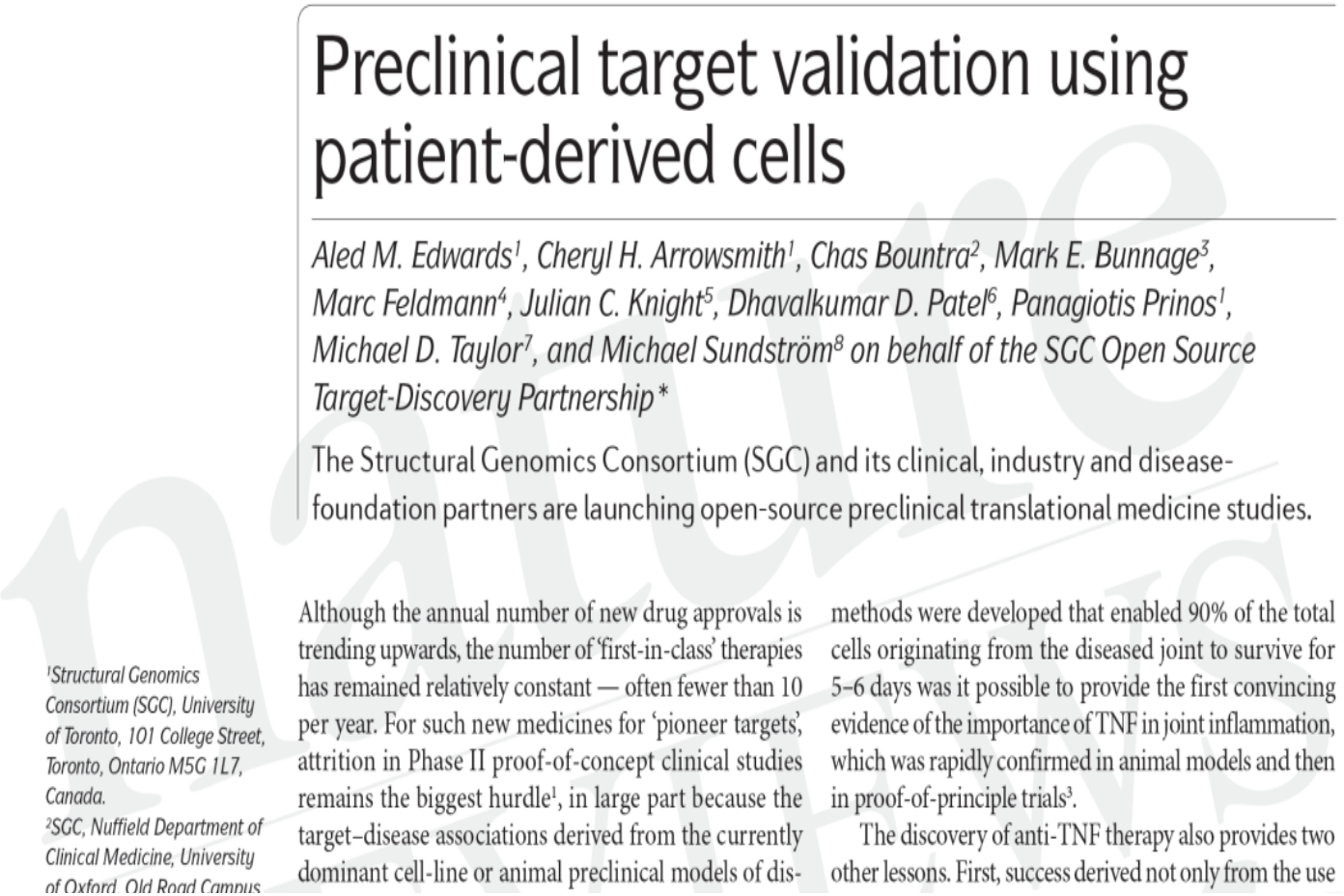
Many phosphorylations can be found in the protein sample. A total of 89 different sites were detected, many of which have been previously reported but some we are reporting for the first time. All of the data can be downloaded and read on Zenodo.

It is important to note that the protein used in these experiments is derived from an environment most unlike that of native huntingtin in neuronal cells, so this work shows only the potential for these sites to be modulated by phosphorylation, not that they actually are under physiological conditions. Further experiments will definitely be needed to validate any of these sites for functional, structural or disease relevance. None-the-less, a good starting point.

Can we convince Universities and Hospitals to be Open?

Open assays from patient cells

- Oxford
- Karolinska
- Toronto
- McGill
- ….



COMMENT

Preclinical target validation using patient-derived cells

*Aled M. Edwards[1], Cheryl H. Arrowsmith[1], Chas Bountra[2], Mark E. Bunnage[3], Marc Feldmann[4], Julian C. Knight[5], Dhavalkumar D. Patel[6], Panagiotis Prinos[1], Michael D. Taylor[7], and Michael Sundström[8] on behalf of the SGC Open Source Target-Discovery Partnership**

[1]Structural Genomics Consortium (SGC), University of Toronto, 101 College Street, Toronto, Ontario M5G 1L7, Canada.
[2]SGC, Nuffield Department of Clinical Medicine, University of Oxford, Old Road Campus

The Structural Genomics Consortium (SGC) and its clinical, industry and disease-foundation partners are launching open-source preclinical translational medicine studies.

Although the annual number of new drug approvals is trending upwards, the number of 'first-in-class' therapies has remained relatively constant — often fewer than 10 per year. For such new medicines for 'pioneer targets', attrition in Phase II proof-of-concept clinical studies remains the biggest hurdle[1], in large part because the target–disease associations derived from the currently dominant cell-line or animal preclinical models of dis-

methods were developed that enabled 90% of the total cells originating from the diseased joint to survive for 5–6 days was it possible to provide the first convincing evidence of the importance of TNF in joint inflammation, which was rapidly confirmed in animal models and then in proof-of-principle trials[3].

The discovery of anti-TNF therapy also provides two other lessons. First, success derived not only from the use

OPEN INSTITUTIONS

SGC

INSTITUTE

Montreal institute going 'open' to accelerate science

By Brian Owens | Jan. 21, 2016

Guy Rouleau, the director of McGill University's Montreal Neurological Institute (MNI) and Hospital in Canada, is frustrated with how slowly neuroscience research translates into treatments. "We're doing a really shitty job," he says. "It's not because we're not trying; it has to do with the complexity of the problem."

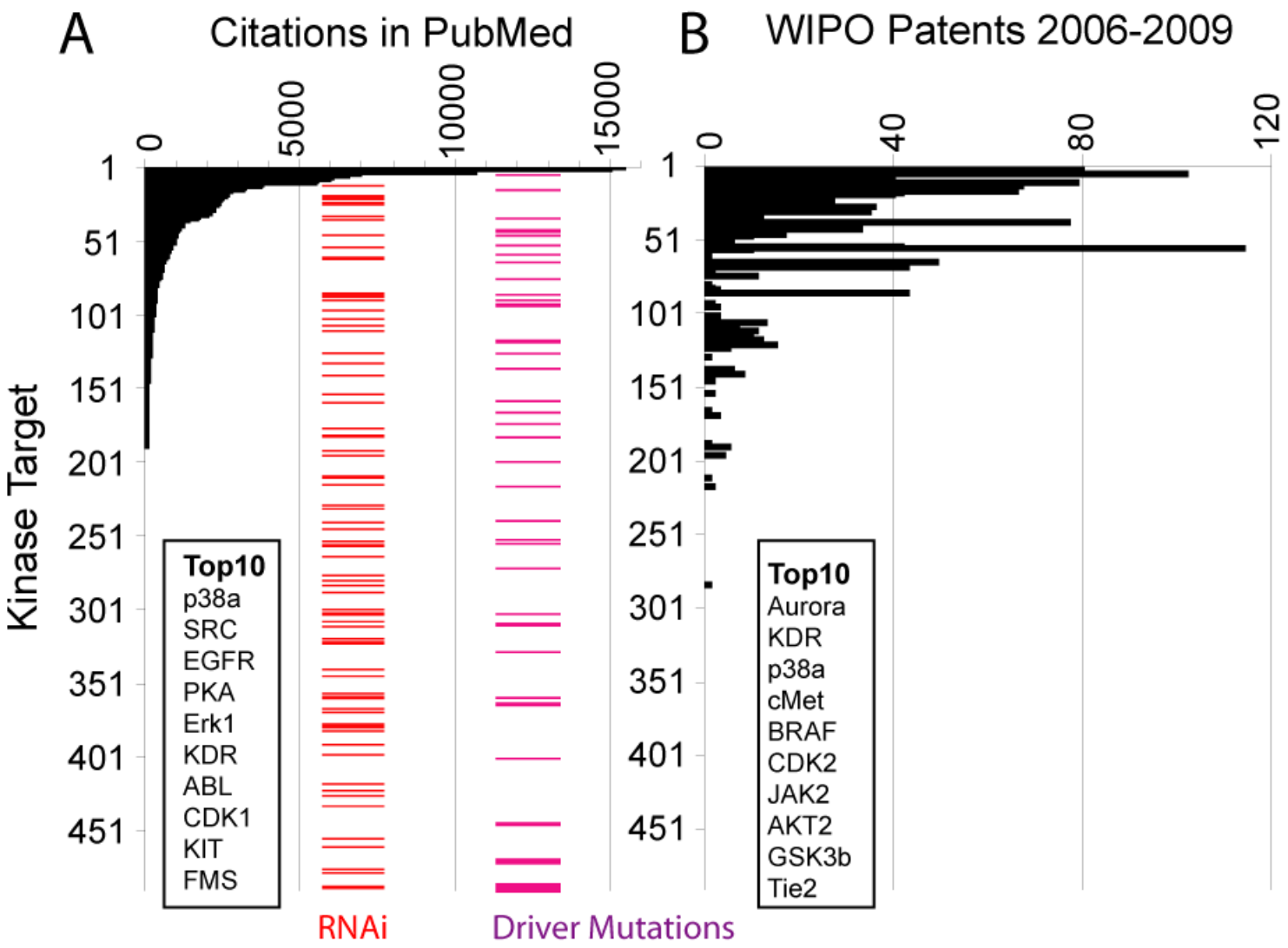
"It comes down to what is the reason for our existence? It's to accelerate science, not to make money."

"Shitty reagents generate shitty science. They waste money and waste careers," says biochemist Aled Edwards….

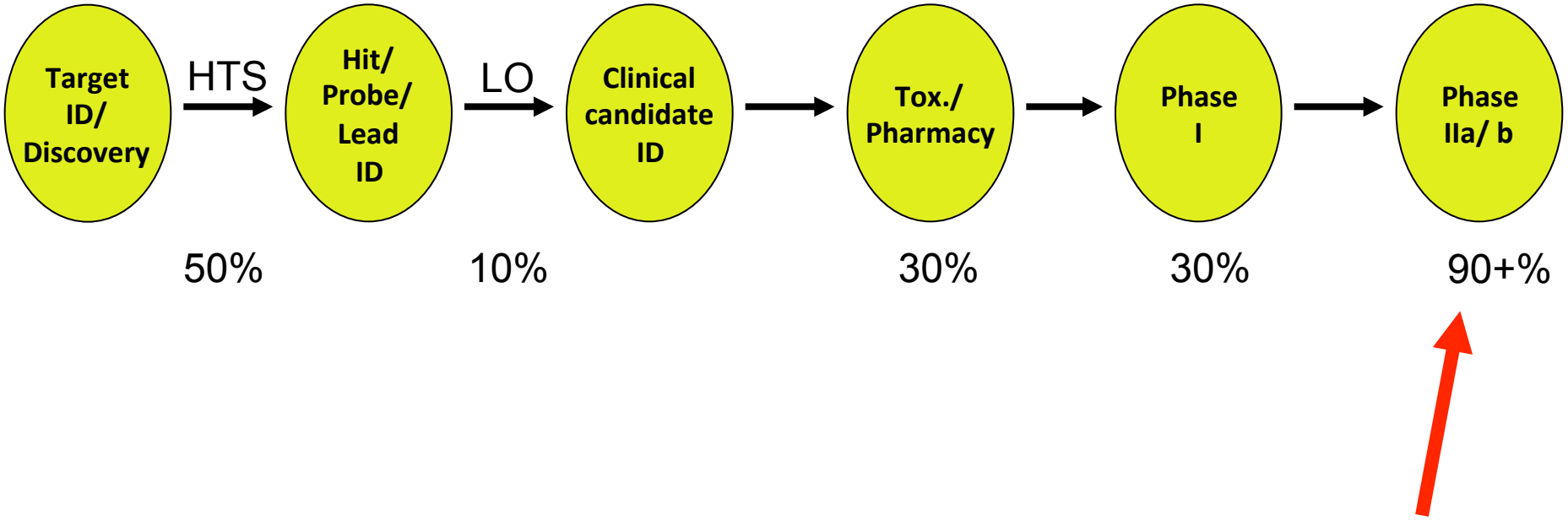
www.thesgc.org

Can we increase productivity of drug discovery by making it open?

Industry does redundant science

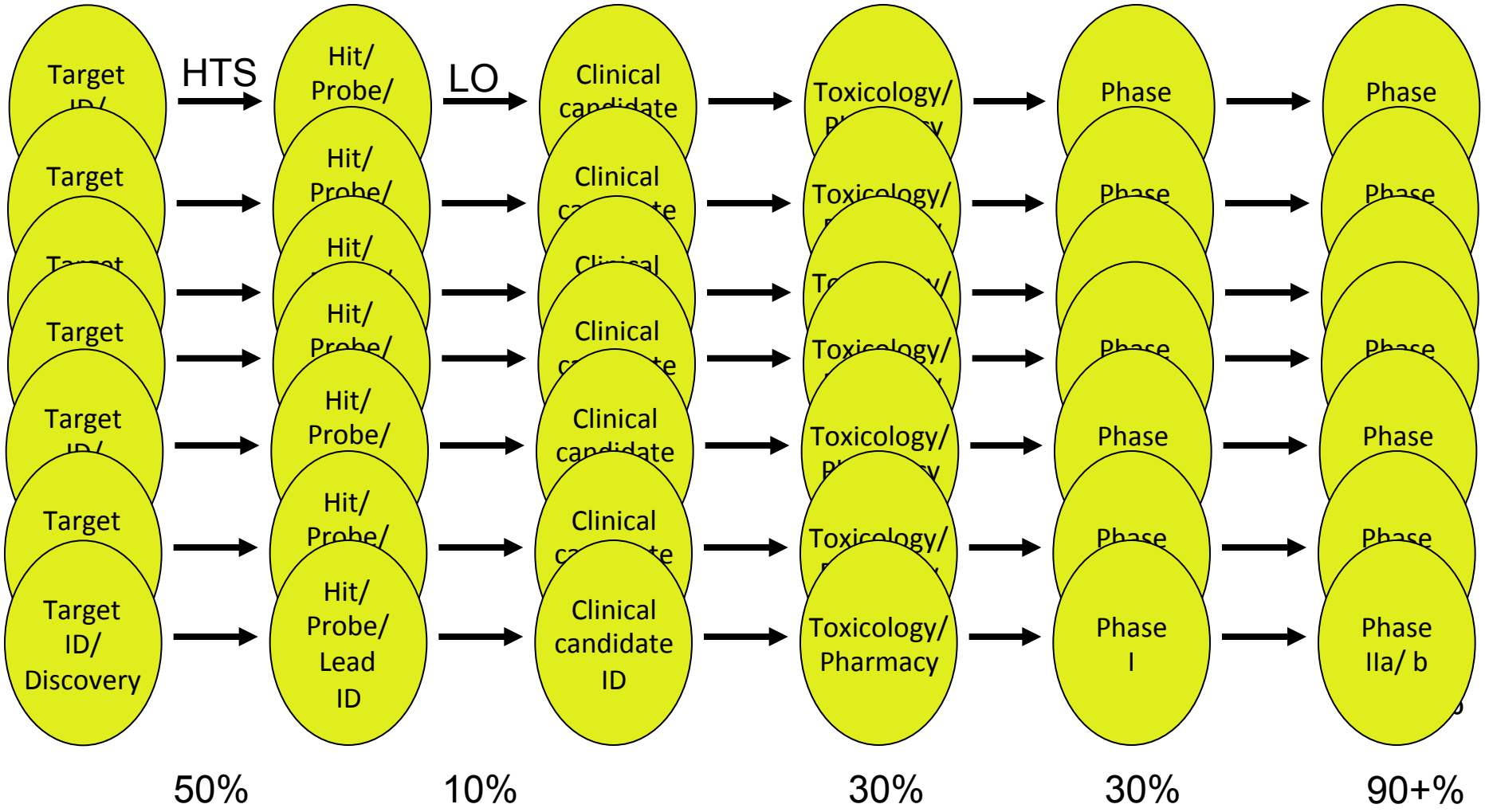


The big issue with drug discovery



…we can generate "safe" molecules, but they are not developable in chosen patient group

Industry also runs redundant clinical trials

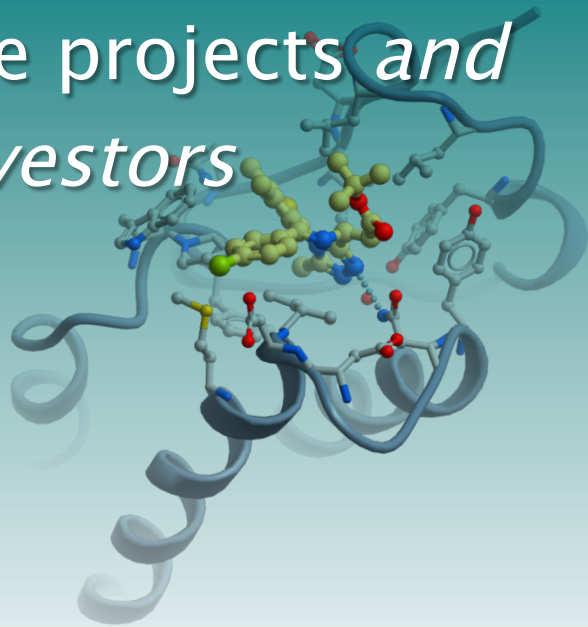


We need more new ideas with proof of concept

Open drug discovery business model

Hypothesis:

Running *bona fide* drug discovery projects in the open (i.e. no patents) will be more cost-effective, will reduce duplication, will be more reproducible can focus on higher-risk, innovative projects *and will generate healthy returns for investors*



Concept

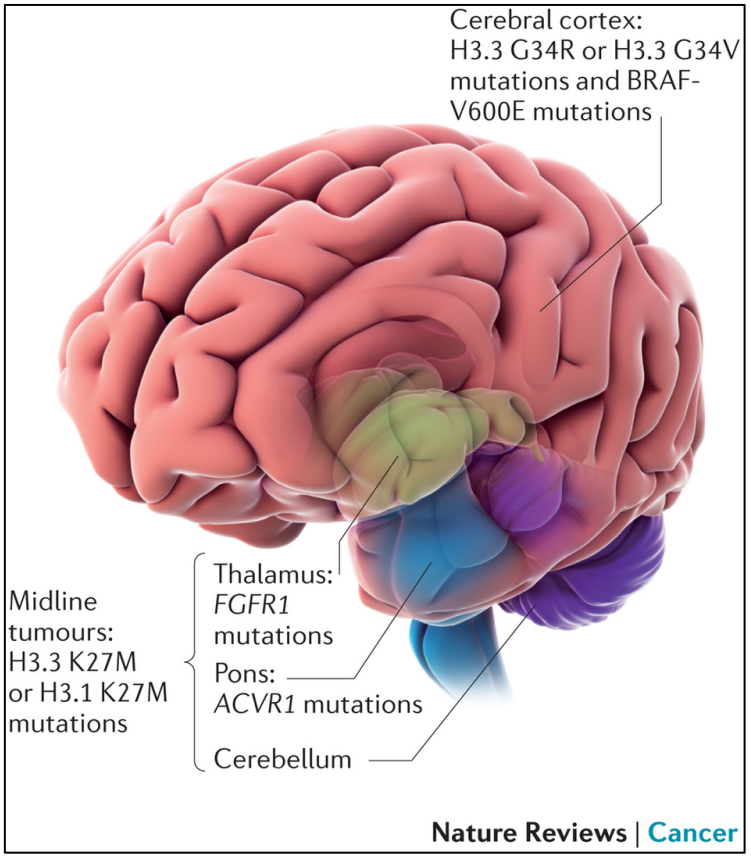
Start a virtual company, building from our (open science) Stand Up 2 Cancer project

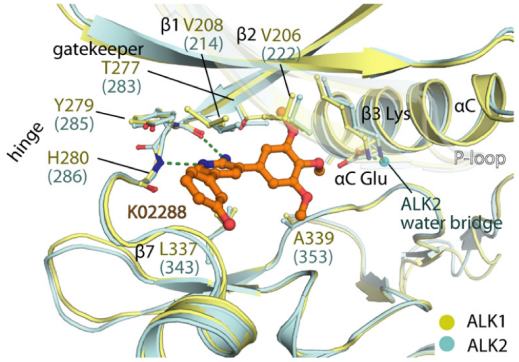
Generate drug that works in small pediatric oncology trials

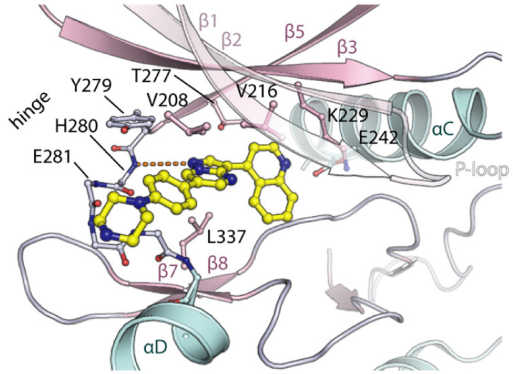
License drug (open) & regulatory documents (proprietary) to large pharma to test and then make/distribute

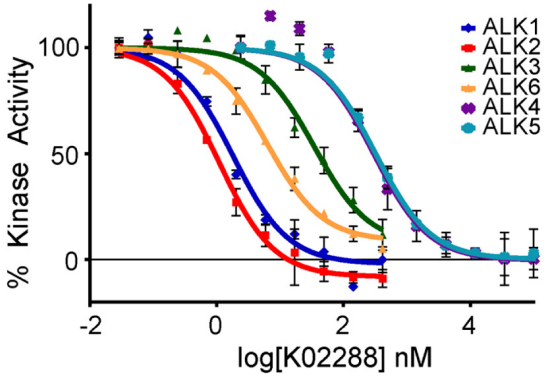
Meds4Kids

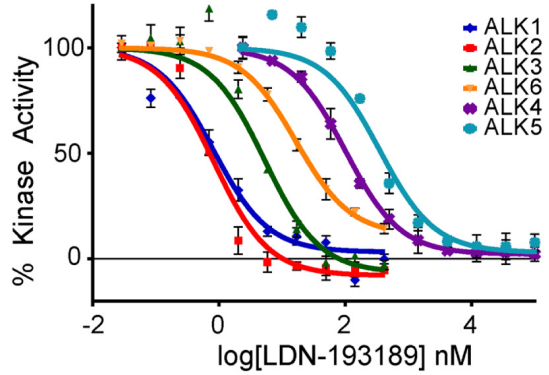
Targeting the Drivers of Incurable Paediatric Cancers





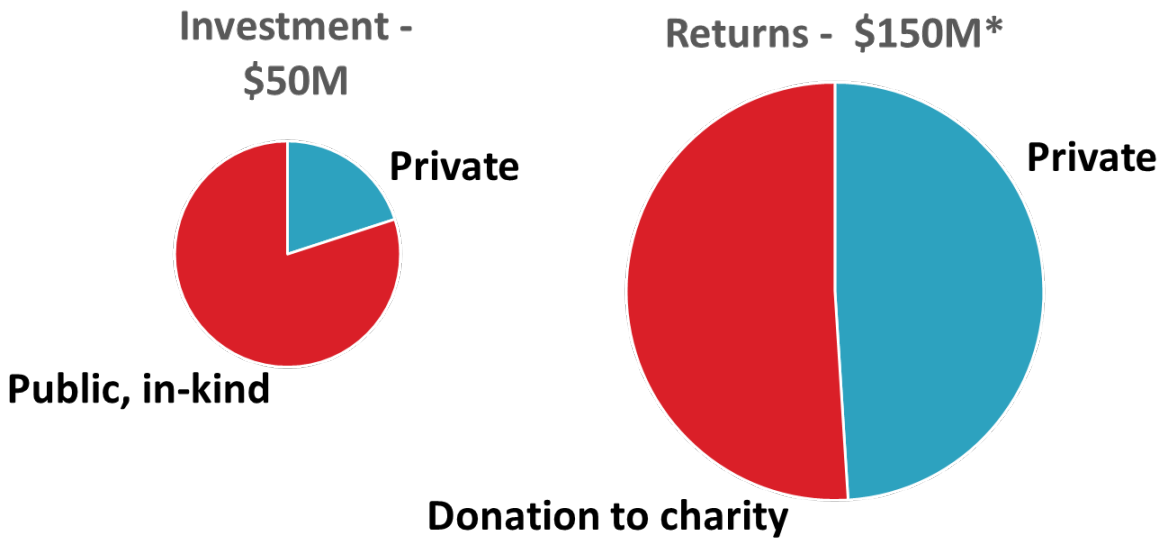






A Simple Exit Strategy with Significant Returns

- Primary exit strategy is to sell the asset after clinical PoC (4-6 years)
- Conservative calculated IRR of ~20%



Donation to charity will feed the open science project pipeline and enable the start of additional open drug discovery projects

** Does not price in the FDA Voucher that is granted for getting a pediatric drug approved*