N E W L A Y O U T

1,000,000,000 *CHF investment*

7,000,874 *hours of work*

6,587 *experiments*

423 *researchers*

1 *medicine*

Health Hackathon

14 & 21.12.2023

With Prof Susan M Gasser and Prof Olivier Michielin

THE MAKING OF AN INNOVATIVE MEDICINE

Introductory workshops on translational biomedical research and drug discovery and development

BIO-698 resumes Thursday September 21. 2023
4:15 PM @ AAC 108

EPFL

Sciences de la Vie -SV

Prof Roger G. Clerc

The Making Of An Innovative Medicine – course schedule

Thursday's @ 4-6 PM except 14.12/21.12.23 @2-6 PM

Session 1: **Scope of the course _ general organization _ case study**
21.09.23 *Embracing a career at the heart of biomedical research !?*
AAC108

Session 2: **Historical perspective: the modern pharmacy**
28.09.23 *Advent of modern medicines - placebo controlled drug development*
AAC108

Session 3: **Introduction to translational research: crossing the bridge**
05.10.23 *A chasm has opened wide between biomedical research and patients in need*
AAC014

Session 4: **Therapeutic target identification I & II**
12-19.10.23 *"me too" vs a wealth of innovative targets _ small MW cpds vs biologicals*
AA014 AAC108 *Early front loading of biomarker identification for cohort stratification*

Session 5: **Structure based drug design _medicinal chemistry_low/high throughtput**
26.10.23 **screening assays_ multiple parallel parameters optimization MDO**
AAC108 *Setting up screening assays, the robotics, the million cpds librairies*

Session 6: **Therapeutic modalities peptides and biologicals: today's -**
02.11.23 **tomorrow's pharmacy NBEs**
AAC108 *Challengies (cost of goods - healthcare payers) and opportunities*

The Making Of An Innovative Medicine - course schedule

Thursday's @ 4-6 PM except 14.12/21.12.23 @2-6 PM

Session 7: **Personalized Healthcare PHC _ precision medicine**
09.11.23 *How PHC started: from a single case to a paradigm change*
AAC108

Session 8: **Pharmacogenetic polymorphisms, Pharmacogenomics**
16.11.23 *Interindividual variability toxicity in response to medicines*
AAC014

Session 9: **In vivo pharmacology, investigative toxicology with Dr Nathalie Brandenberg PhD**
23.11.23 *Pre[illegible] research ends up with IDB's, FDA guidelines [illegible]*

Session 10: **Clinical research_ phase 0, phase I, II, III, IV**
30.11.23 *The long and complex experimental procedures with human patients*
AAC108

Session 11: **[illegible]ectual property _ integrity in research_my genome [illegible] genomes**
07.12.23 *Why are patents essential to new medicine/biotech development*
AAC108

Session 12: **Health Hackathon – Hacking medicine I with Dr Greg Michielin MD PhD**
14.12.23 *Pitches –building teams – hacking problem - 5Ws – brainstorm*
starts @ 2PM ! MED21522

Session 13: **Health Hackathon – Hacking medicine II with Prof O. Michielin MD - Prof SM Gasser PhD judges**
21.12.23 *Building up solutions – make it better - final presentations*
starts @ 2PM ! AAC231

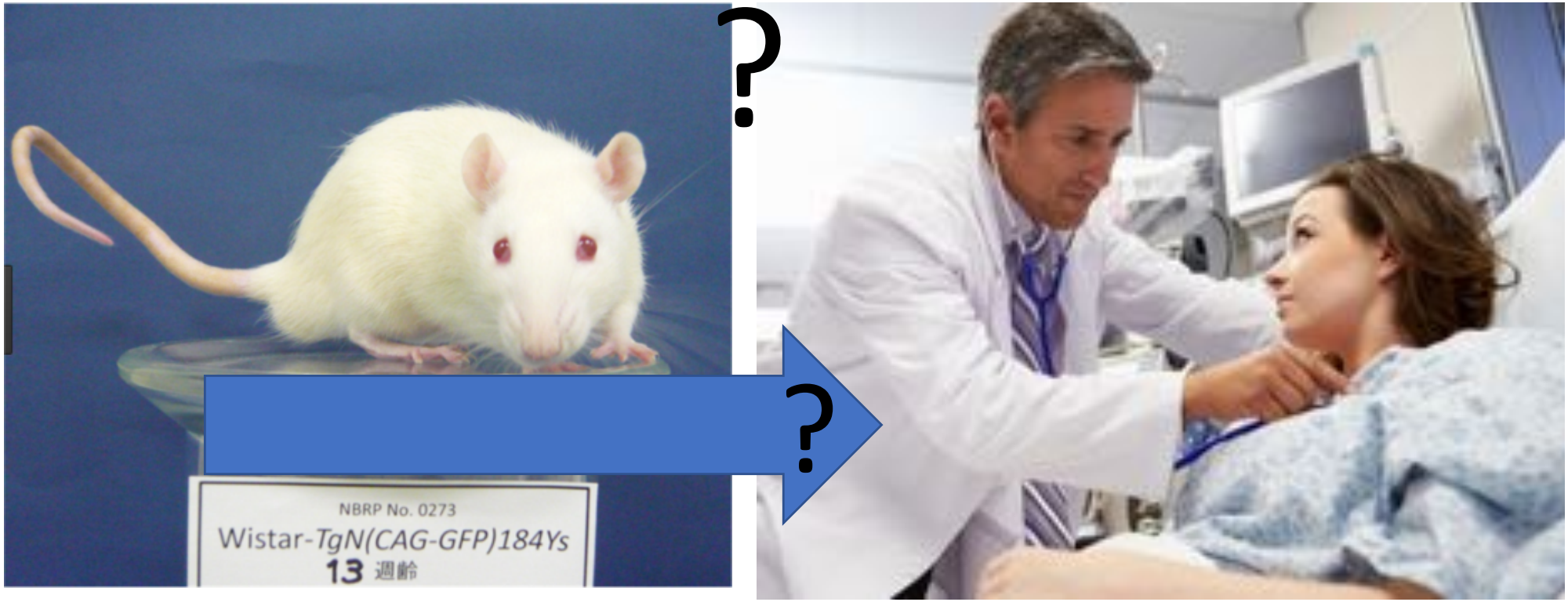
WORKSHOP LISTING - THE MAKING OF AN INNOVATIVE MEDICINE BIO698			
! NON EXHAUSTIVE LISTING - SUGGESTIONS WELCOME !			
sessions	no	workshops	speaker/s
S02 (28-09-23) ! AAC108 !			
historical medicines	1	vaccine discovery : E. Jenner and smallpox	Danica M
with Nobel laureates while	2	penicilin: impact, whose invention ?	
hopping on giant shoulders	3	prozac at the core of psychiatry	
	4	lipitor/statins at last a blockbuster	
	5	artemisinin and malaria	Umair
	6	cyclosporin from soil sample to blockbuster	Umair
S03 (5-10-23) ! AAC014 !			
translational research	7	expanding the scope of targeted therapies	
an emerging field	8	chronotherapy	Pitt
S04 (12-10-23) ! AAC014 !			
therapeutic target identification	9	rare diseases repurposing medicines	Adrien
S04b (19-10-23) ! AAC108 !	10	nocosomial inf/MRSA/phage antibacterials	Georges
therapeutic target identification	11	Crispr/Cas9 gene editing huntington disease	Pitt
	12	AI in drug discovery	Simon
S05 (26-10-23) ! AAC108 !			
structure based drug design	13	macrocycles and non druggable targets	Masota
	14	chemoproteomics - NMEs	Nico G
	30	AIDS HIV from deadly virus to chronic disease	Camilla
S06 (02-11-23) ! AAC108 !			
therapeutic modalities - NBEs	15	therapeutic peptides/incretins	Tim
	16	biologicals on the rise MABs medicines	Nico G
	16	RNA therapeutics, antisense medicines	
S07 (9-11-23) ! AAC108 !			
PHC personalized healthcare	17	BRCA1 preventive surgery/tumor board	Nikita
Human genomics	18	SOPHiA Genetics - GWAS	
	19	disease enabling biomarkers/micro RNAs	Isika
S08 (16-11-23) ! AAC014 !			
pharmacogenetic polymorphism	20	NextGenSequencing - precision medicine	Hien
	21	deCODE Inc pharmgenomic/iceland genealogy	
S09 (23-11-23) ! AAC108 !			
in vivo pharmacology	22	thalidomide repurposing mulitple myeloma	
toxicology	23	organoids come of age CFTR patients	Nathalie B
S10 (30-11-23) ! AAC108 !			
clinical research	24	AI medicine 2.0	Simon
	25	most common genetic defect : cystic fibrosis	.
	26	sex bias in preclicnial and clinical research	Weilin
	27	placebo/nocibo effects	Tim
S11 (07-12-23) ! AAC108 !			
intellectual property/integrity	28	SMA gene therapy - pay for performance	Abtin
	29	biopatents - 23 and Me - my genome	Khosiyat
S12 (14-12-23) starts @ 2PM		Hacking medicine	all + invitees
! MED21522!			
S13 (21-12-23) start @ 2 PM		Hacking medicine	all + invitees
! AAC231 !			

Workshops _ The Making Of An Innovative Medicine

(today's class)

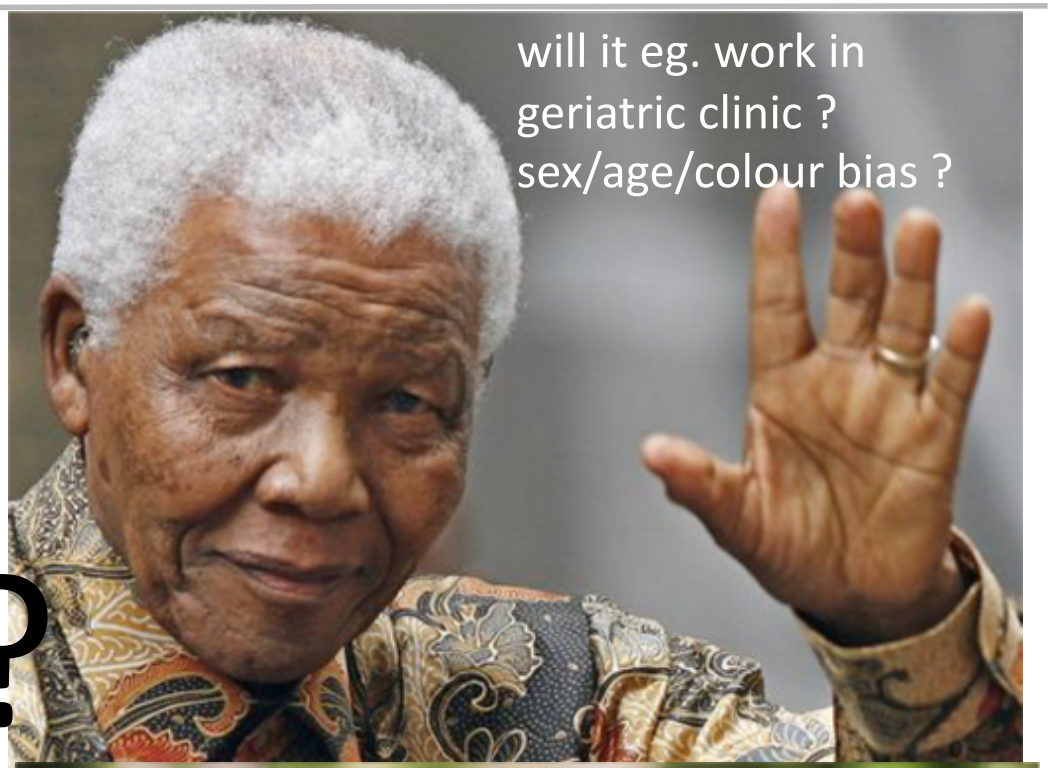
- Clinical research_early and late clinical trials of novel medicines (internal conference website ICH)
- Submit the IND (to authority and ethics body)investigational new drug application IDB
- First-in-human FIH trials
- Placebo - Nocebo

- Now that it works in the rat, will it work in human ? individualized cohorts ?



Clinical development – an experiment with human subjects

- Or else...all these efforts only good for the rats ?



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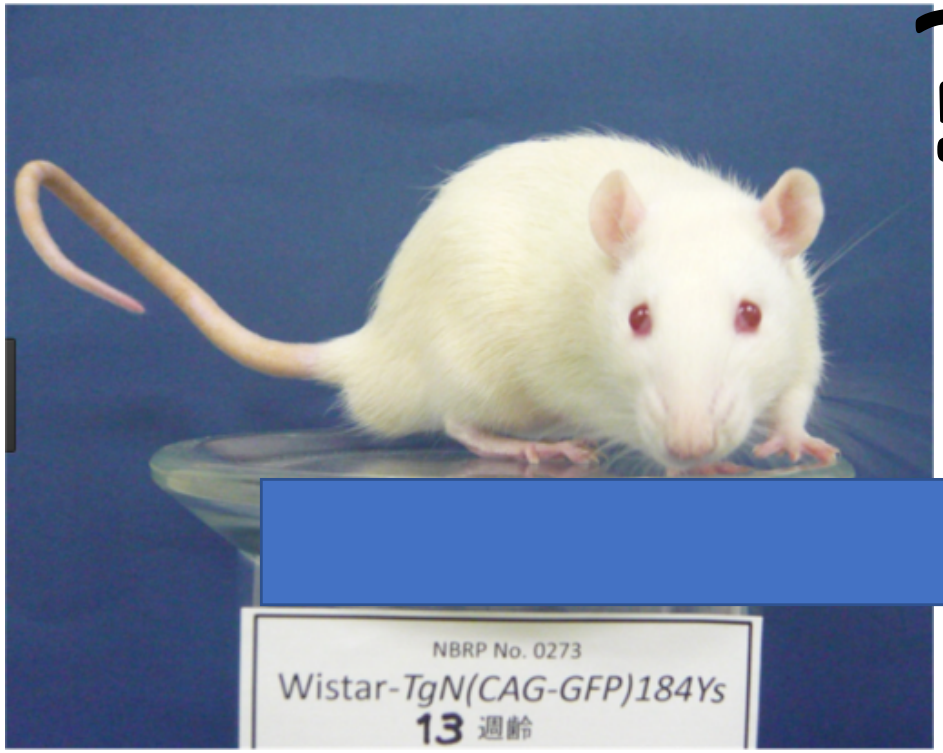
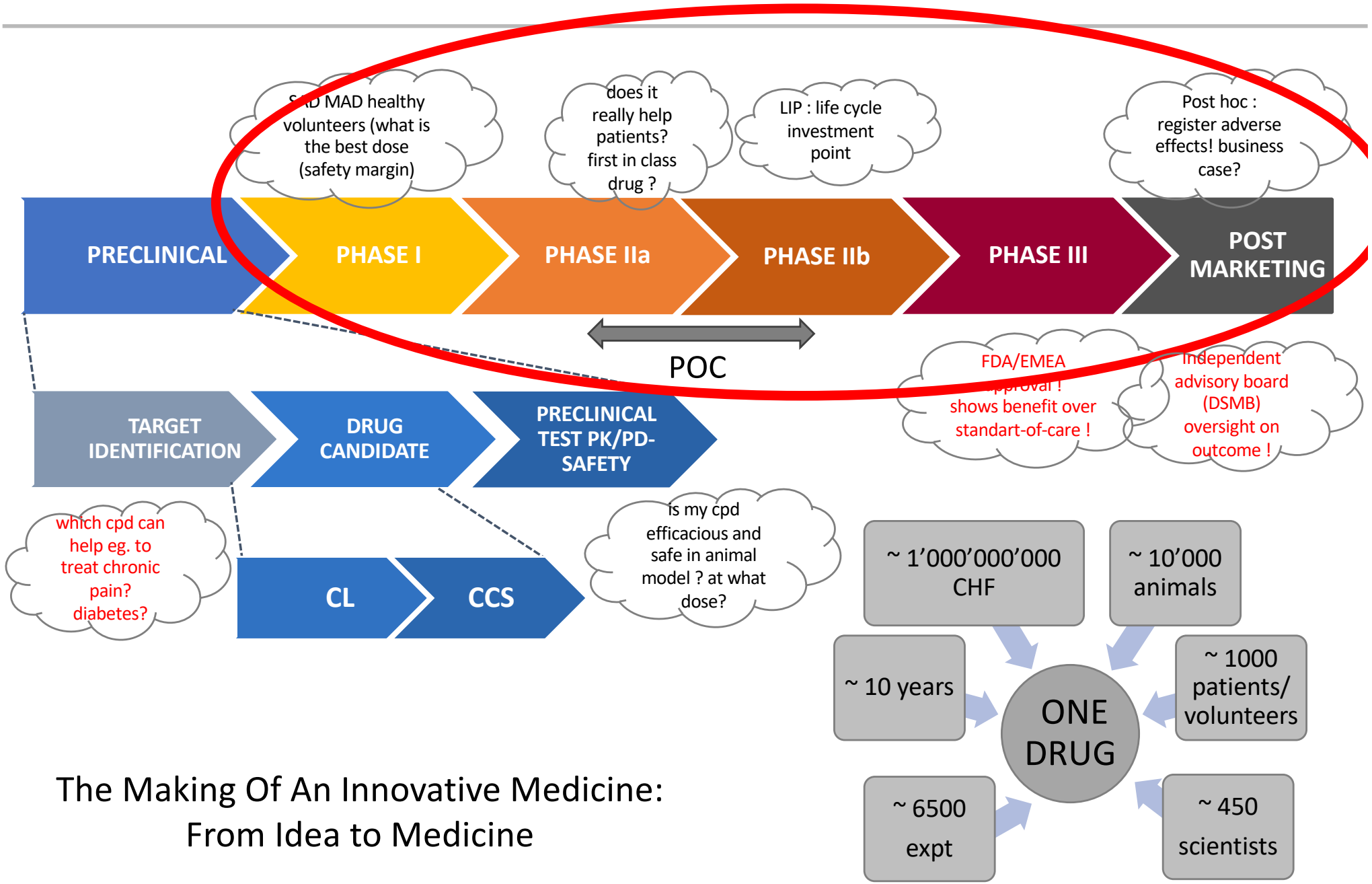


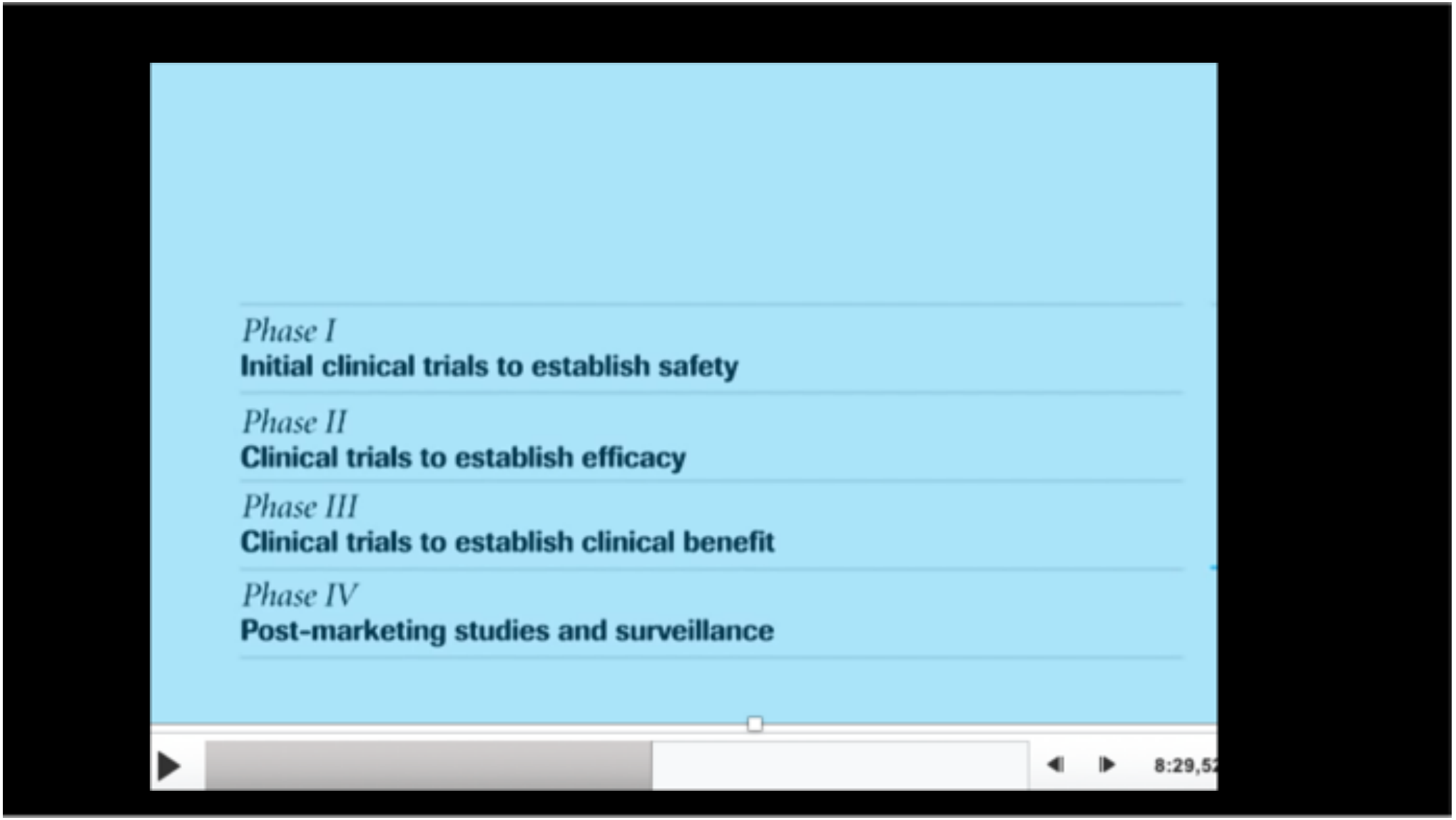
?

Drug discovery : the value chain _ clinical development

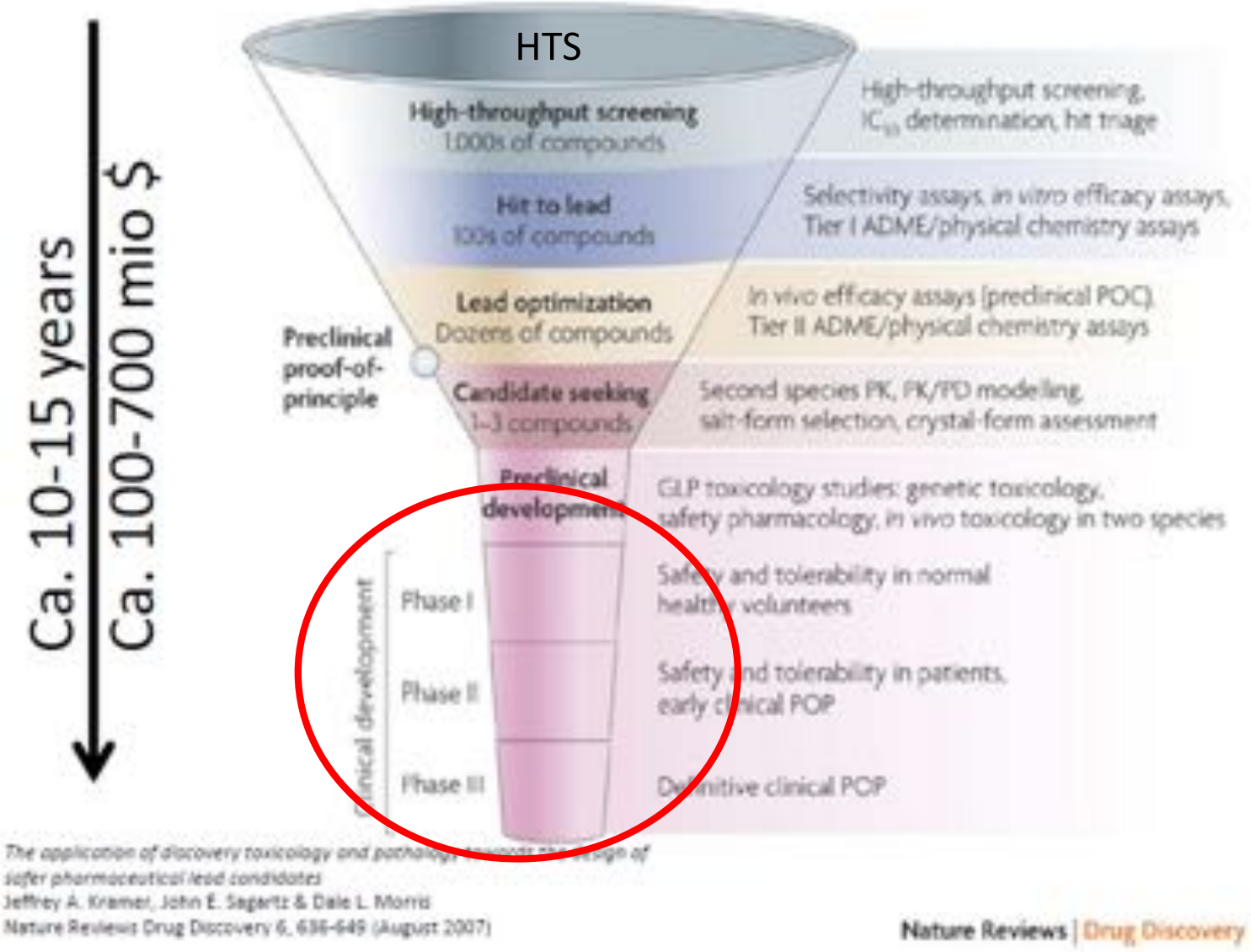


The Making Of An Innovative Medicine:
From Idea to Medicine

The Making Of An Innovative Medicine: a look at the real world



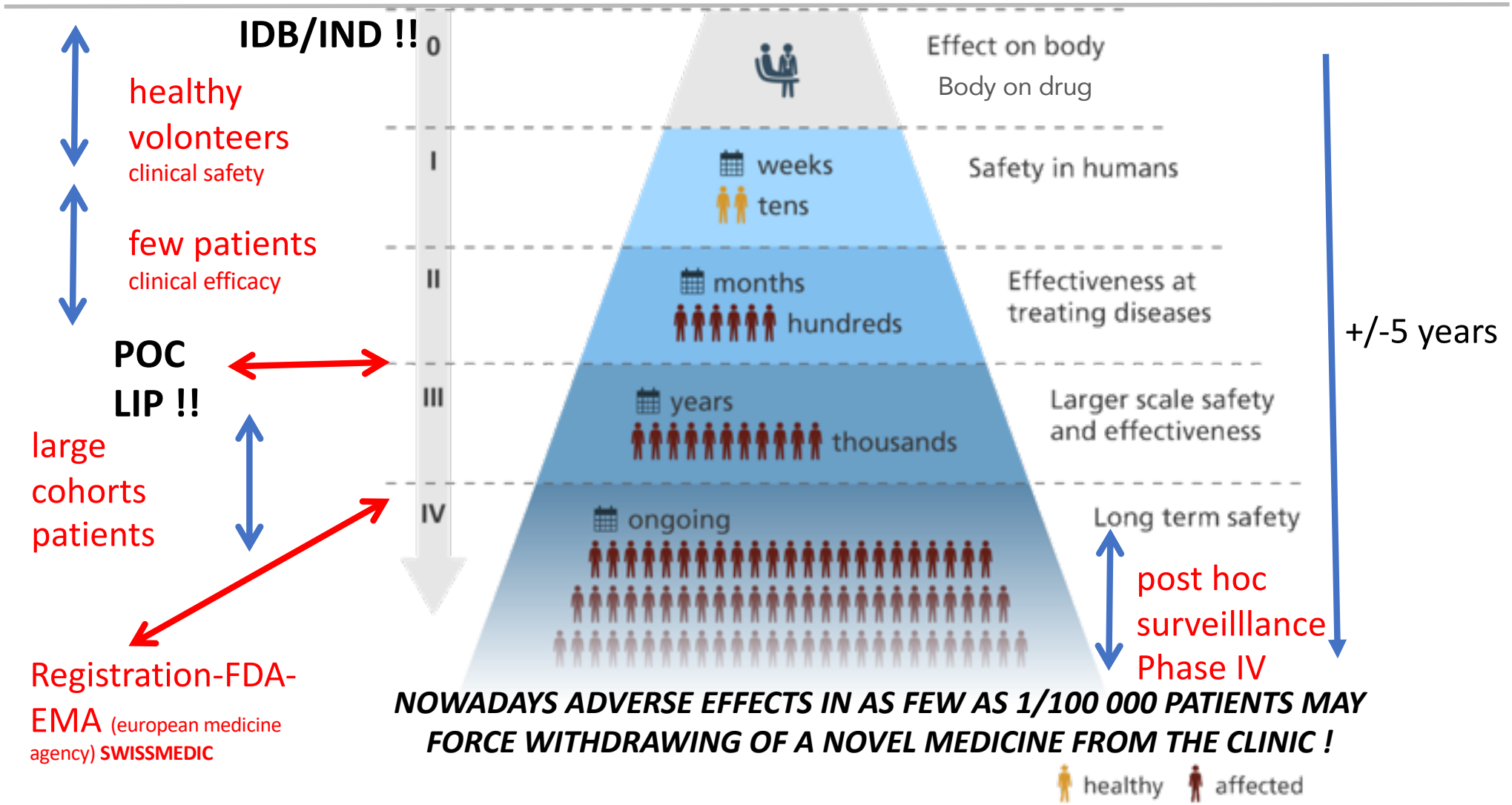
The new medicine develpment process 1:10 000 makes it !



The application of discovery toxicology and pathology towards the design of safer pharmaceutical lead candidates
Jeffrey A. Kramer, John E. Sagartz & Dale L. Morris
Nature Reviews Drug Discovery 6, 636-649 (August 2007)

Nature Reviews | Drug Discovery

Clinical development = clinical research

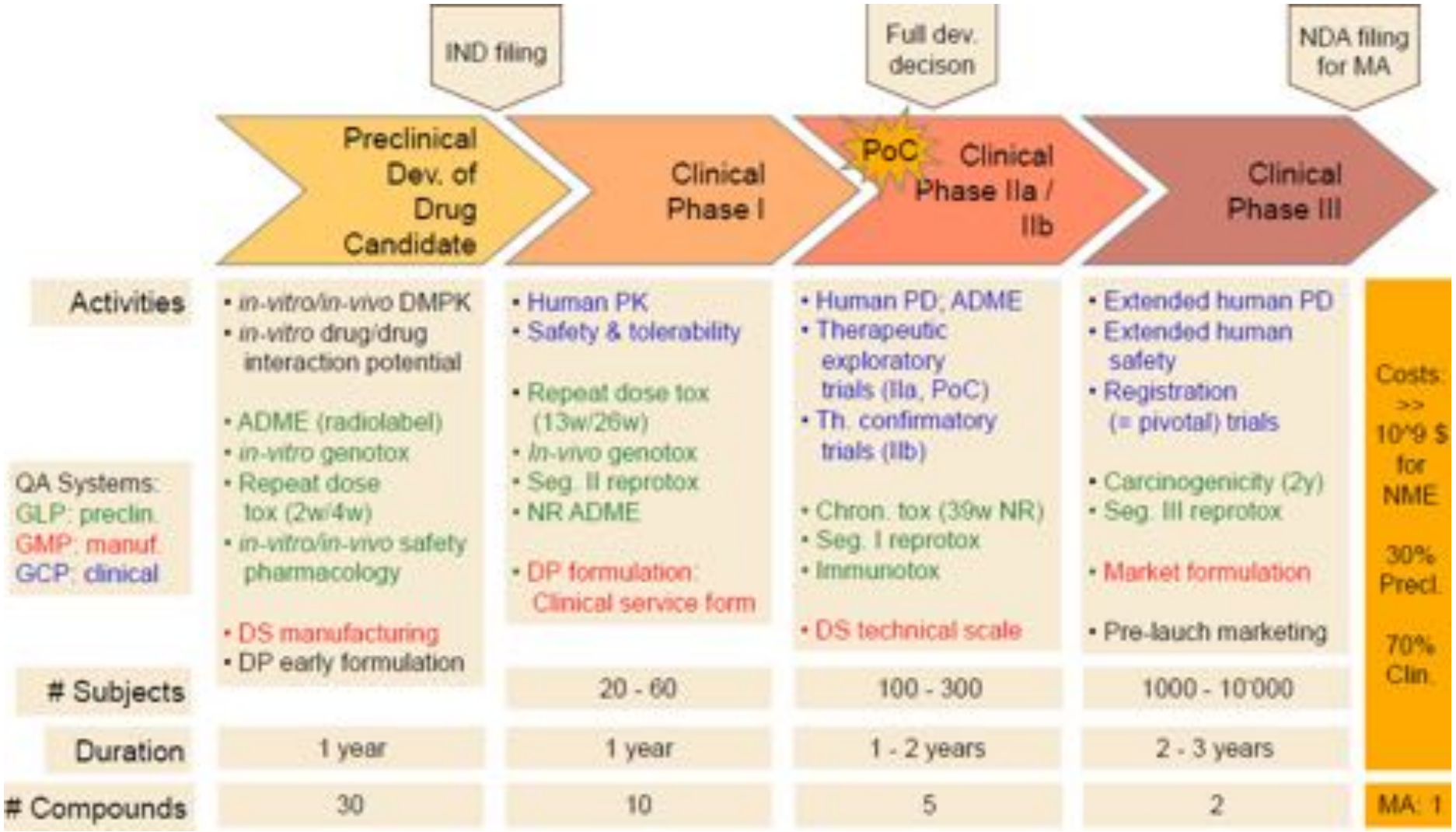


NOWADAYS ADVERSE EFFECTS IN AS FEW AS 1/100 000 PATIENTS MAY FORCE WITHDRAWING OF A NOVEL MEDICINE FROM THE CLINIC !

swissmedic

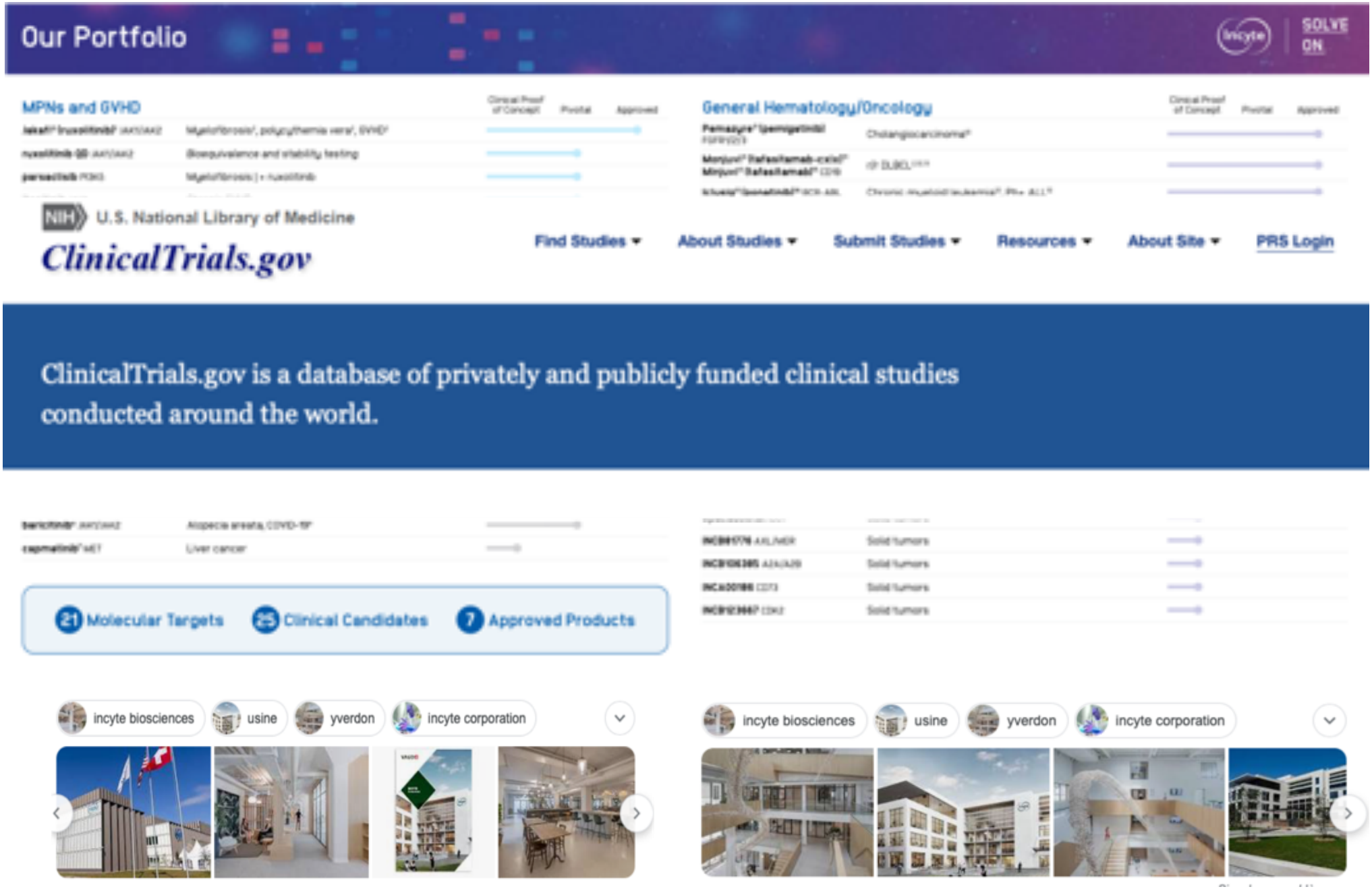
ETHICS COMITEES ARE INVOLVED IN EACH CLINICAL TRIALS PROTOCOLS - EACH CLINICAL TRIAL IS HANDLED NATIONALY (SEPARATELY FOR EACH COUNTRY)

Preclinical-clinical pharmacology : the value chain



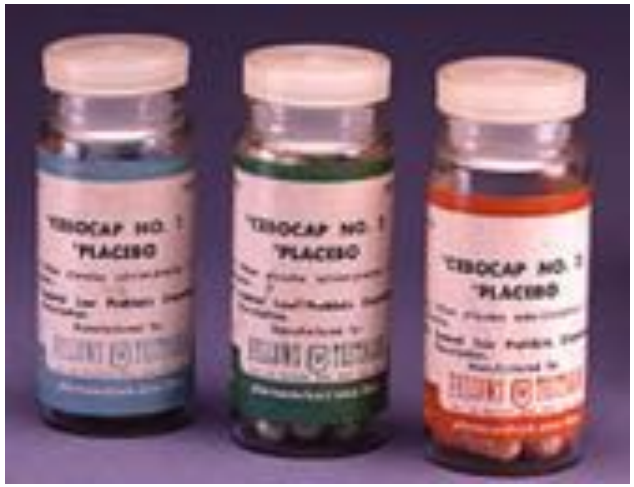
Clinical research portfolio eg Incyte Inc.

https://clinicaltrials.gov

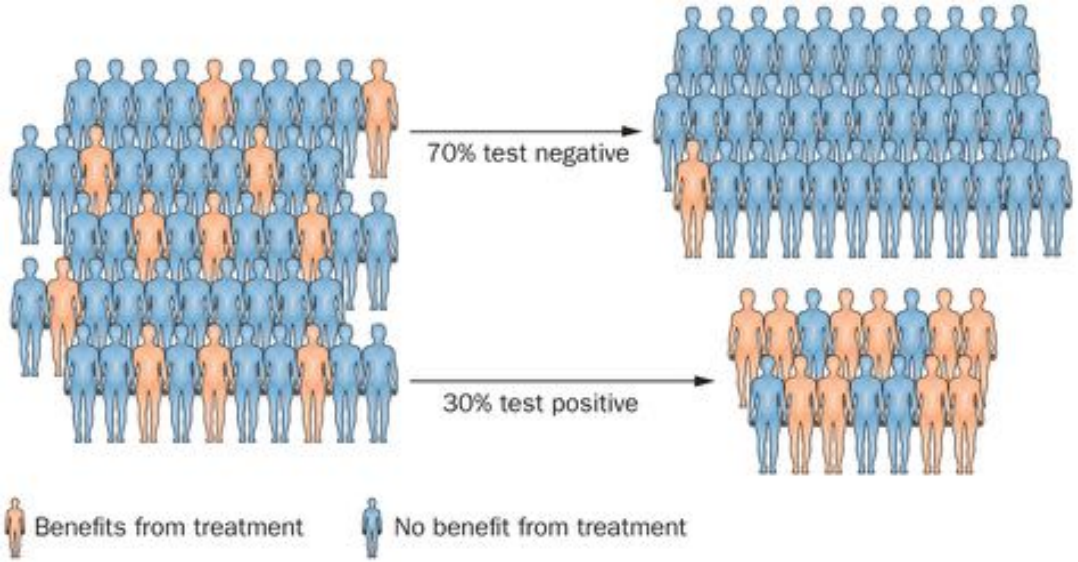


Clinical research revisited, the responders vs non responders

- **STRATIFICATION OF THE COHORTS IN GROUP OF RESPONDERS – NON RESPONDERS - PERSONALIZED HEALTHCARE !**
- **DOUBLE BLIND PLACEBO CONTROLLED TRIALS HAVE EMERGED AS STANDART APPROVED PROCEDURES FOR CLINICAL TRIALS**



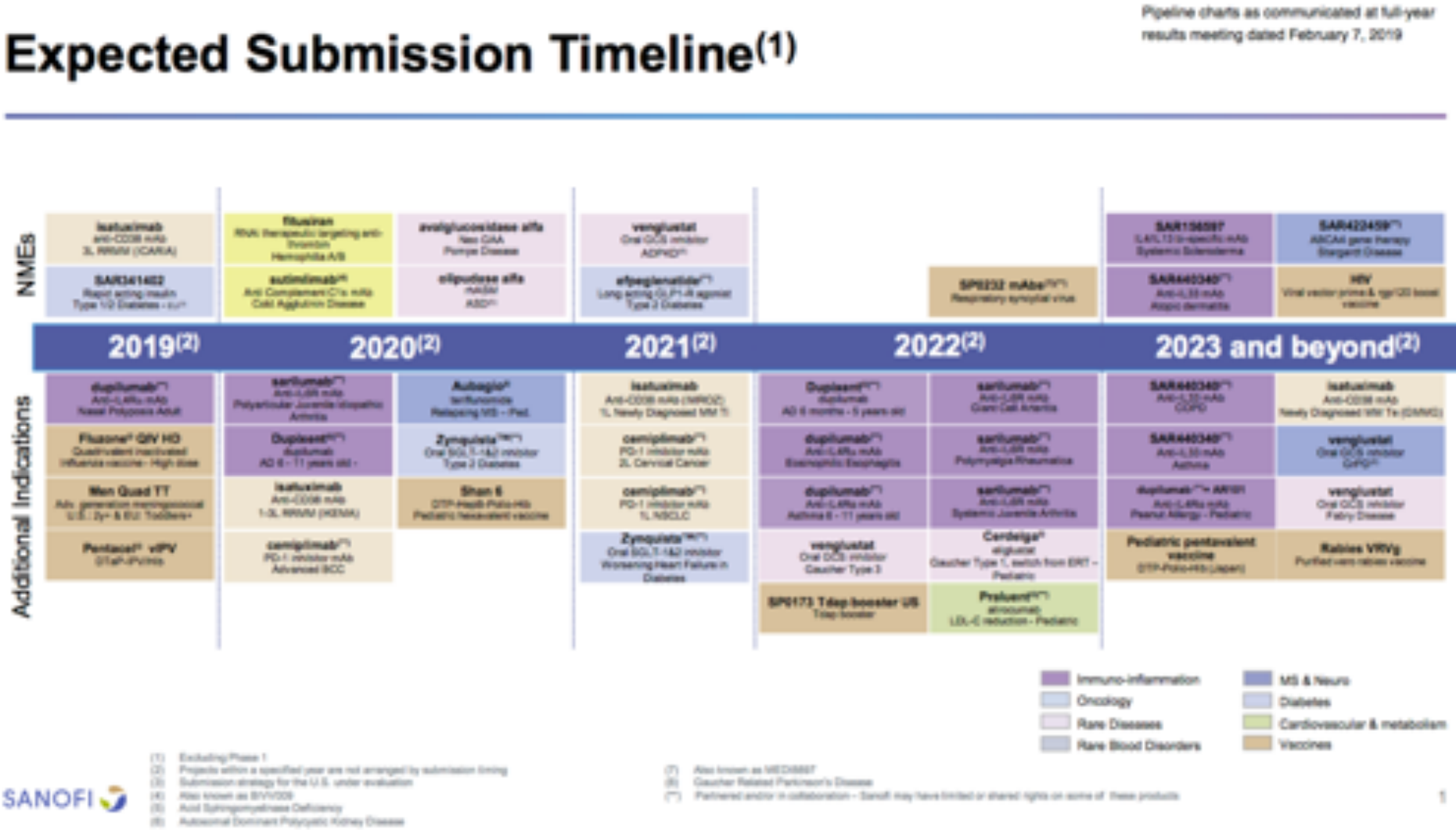
Placebo are inert tablets, sugar pills



"NEGATIVE CONFOUNDING EFFECTS" MAY BLURRED EFFICACY OF AN INNOVATIVE MEDICINE !

The "one pill fits all" concept no longer supported as each group of individuals carry a different blueprint !
An extraneous variable that wholly or partially accounts for the observed ***effect*** *on disease status*

Clinical research ends up with FDA submission and marketing



The "one pill fits all" concept no longer supported as each group of individuals carry a different blueprint !

An extraneous variable that wholly or partially accounts for the observed ***effect*** *on disease status*

Clinical research explained in 2 minutes by Harvard YOUTUBE !

Clinical research : a 360 degrees view or becoming a clinical scientist

- WHO IS DOING THIS ?
- AN EXPERIMENT WITH HUMAN SUBJECTS !
  (healthy volonteers)
- MAINLY CARRIED OUT IN CLINICAL SETTING, CLOSE TO THE EMERGENCY ROOM
- DATA SHOULD/HAVE TO BE REPORTED TO A SPONSOR INDEPENDANT MONITORING BODY (DSMB)

Phase 0-I is the most risk associated clinical phase as the medicine is going to be administrated for the first time to human

Phase II requires the technical infrastructure to test the beneficial therapeutic effect
<u>POC</u>

Phase IV the safety profile of the new medicine Pharmacovigilance !

Phase III the security efficacy profile of the new medicine should be well characterized

ETHICS COMITEES ARE INVOLVED IN EACH CLINICAL TRIALS PROTOCOLS - EACH CLINICAL TRIAL IS HANDLED NATIONALY (SEPARATELY FOR EACH COUNTRY)

Clinical research : making it more inclusive

NEWS | 02 August 2023

Alzheimer's drug trials plagued by lack of racial diversity

Under-representation of people of colour sparks concerns over the safety and efficacy of drugs in diverse populations.

Sara Reardon

A clinical-trial participant receives the experimental drug aducanumab. White people are over-represented in trials for Alzheimer's treatments. Credit: Charles Krupa/AP Photo

Black and Hispanic people are up to twice as likely as white people to develop Alzheimer's disease, but they have a much lower chance of being included in clinical trials for Alzheimer's treatments.

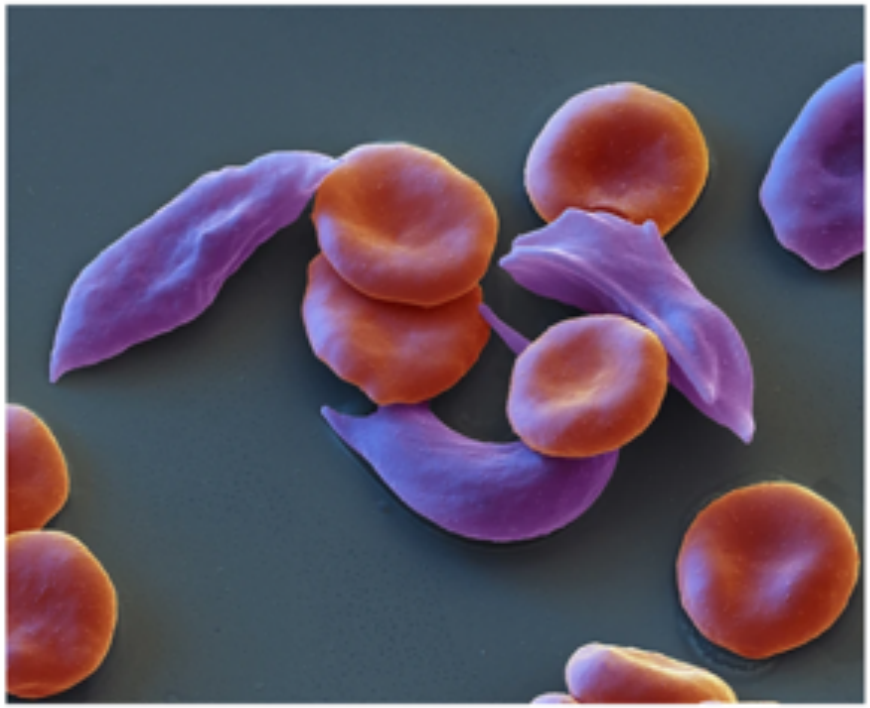
NEWS | 16 November 2023

UK first to approve CRISPR treatment for diseases: what you need to know

Breaking news November 16. 2023

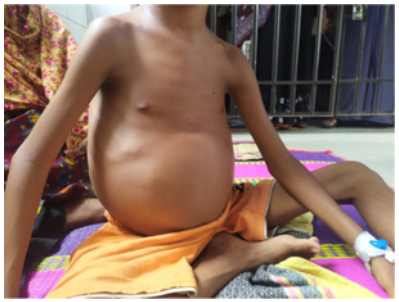
The landmark decision could transform the treatment of sickle-cell disease and β-thalassaemia – but the technology is expensive.

Carissa Wong



Sickle-cell anaemia is marked by red blood cells that are misshapen and sticky, affecting blood flow. Credit: Eye Of Science/SPL

VERTEX



In a world first, the UK medicines regulator has approved a therapy that uses the CRISPR–Cas9 gene-editing tool as a treatment. The decision marks another high point for a biotechnology that has been lauded as revolutionary in the decade since its discovery.

The therapy, called Casgevy, will treat the blood conditions sickle-cell disease and β-thalassaemia. Sickle-cell disease, also known as sickle-cell anaemia, can cause debilitating pain, and people with β-thalassaemia often require regular blood transfusions.

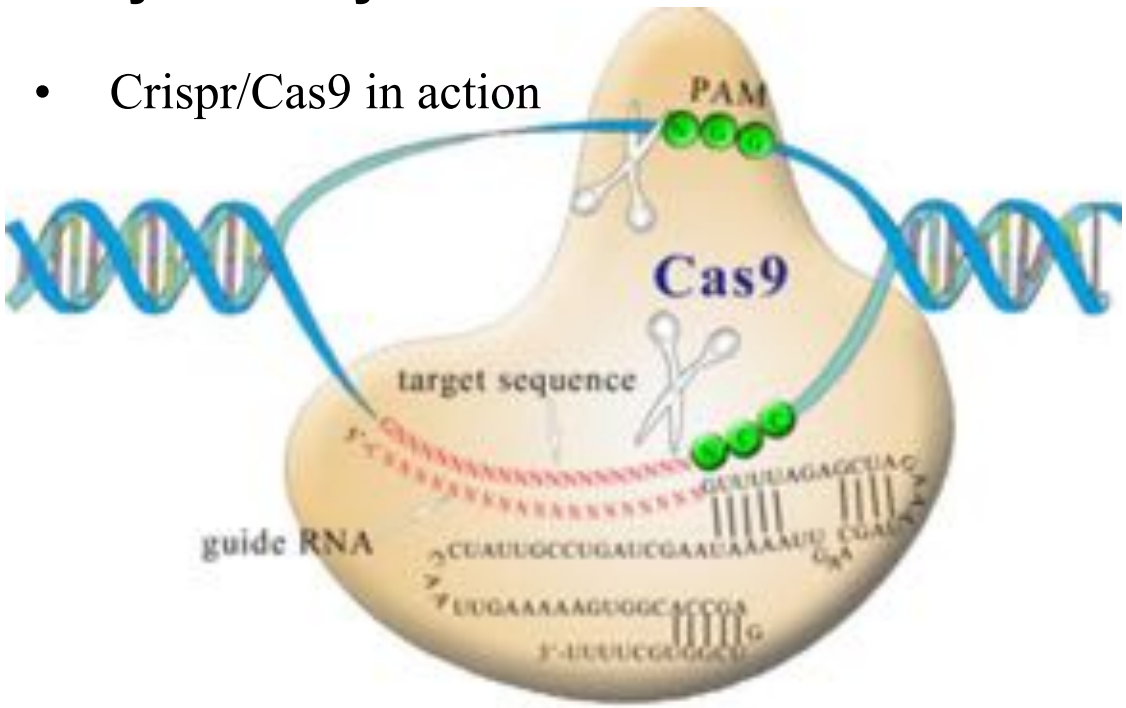
300 millions subjects with « thalassemia trait »
100’000 people have transfusion-dependent thalassemia

SOMATIC gene therapy : realistic but highly expansive medical breakthrough

SOMATIC tissue Crispr/Cas9 genome editing – realistic therapeutic av

The first technology that can basically link any disease with a genetic cause

- Crispr/Cas9 in action

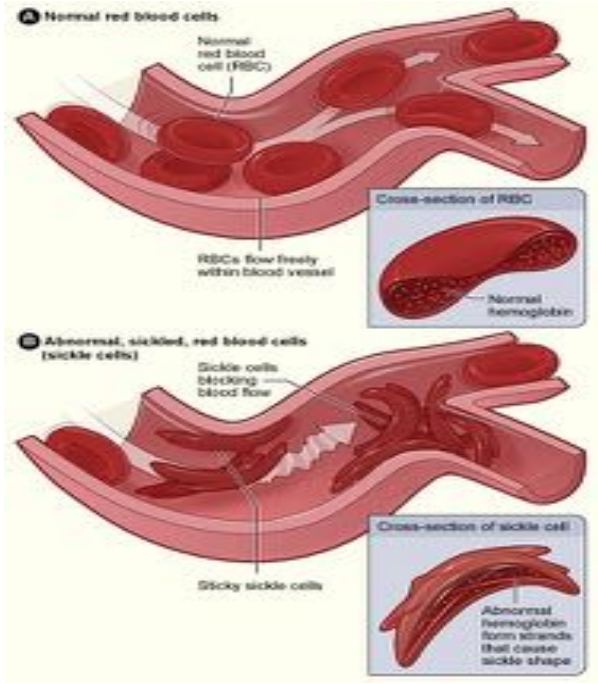


***ex vivo* somatic cell gene therapy ?**

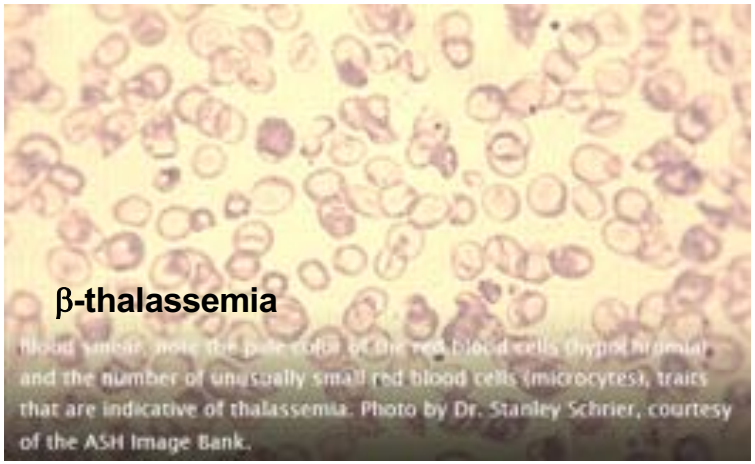
- sickle cell anemia
- beta thalassemia
- leukemia
- SCID
- CF
- …..

- **C**lustered **R**egularly **I**nterspaced **S**hort **P**alindromic **R**epeats
- breakthrough technology (a product of basic research : bacterial innate immunity)
- opportunities and challengies for potential clinical applications !
- ethical concerns ! off targets ! NGS will be key to safety !
- **CRISPR Therapeutics. EDITAS, VERTEX and more with patent pending debates**

Clinical case : sickle Cell disease and β-thalassemia: major disorder of β-globin



- The terms *sickle cell disease* (SCD) and β-thalassemia describe a group of inherited red blood cell disorders
- People with SCD have abnormal hemoglobin (*hemoglobin S) or* sickle hemoglobin, in their red blood cells, enlarged speen
- Normal red blood cells live about 90 to 120 days, but sickle cells last only 10 to 20 days*.*
- The lack of tissue oxygen can cause attacks of sudden, severe pain
- Chief predictor : increased level of fetal hemoglobin
- At the present time, hematopoietic stem cell transplantation (HSCT) is the only therapy for SCD.



Genetic, biochemical, and clinical observations suggest a salutary role for HbF in the β-globin disorders.
The sum of this evidence indicates that even modest induction of HbF may be sufficient to ameliorate SCD, thalassemia

Beta thalassaemia : large diversity of mutations with different degrees of severity of symptoms, geographically ww spread

Figures 10 and 11. The central question in the field of beta-thalassaemia is exemplified by the two children. The child on the left has beta-thalassaemia at its worst: bone marrow expansion, multiple pathological threats, and clinical deformities, if he had not been transfused he would be dead. The child on the right is homozygous for a mutation at the same locus as the other child, and yet is perfectly well.

Figure 13. The two boys have identical mutations in the beta-thalassaemia gene. Obviously, the phenotype needs to be explained by some other modifications.

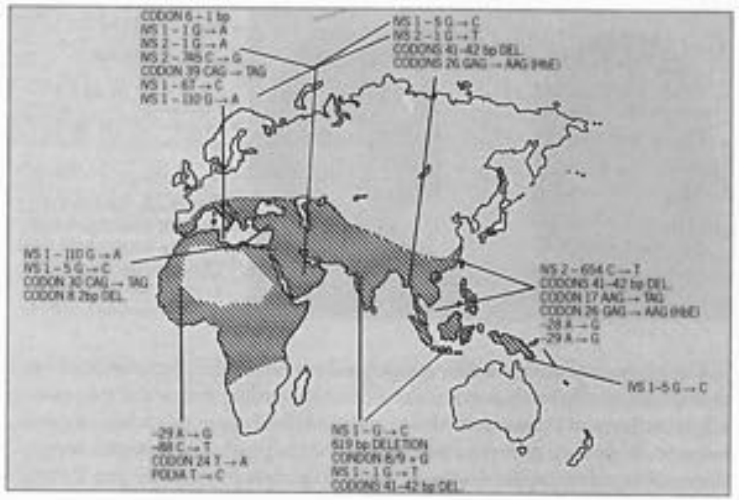
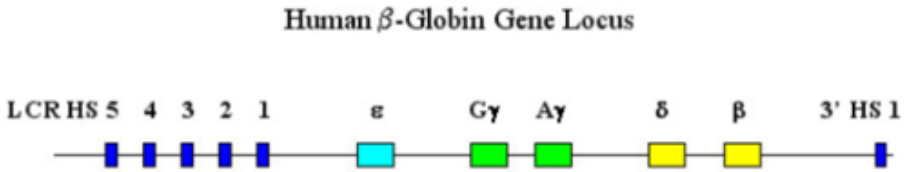
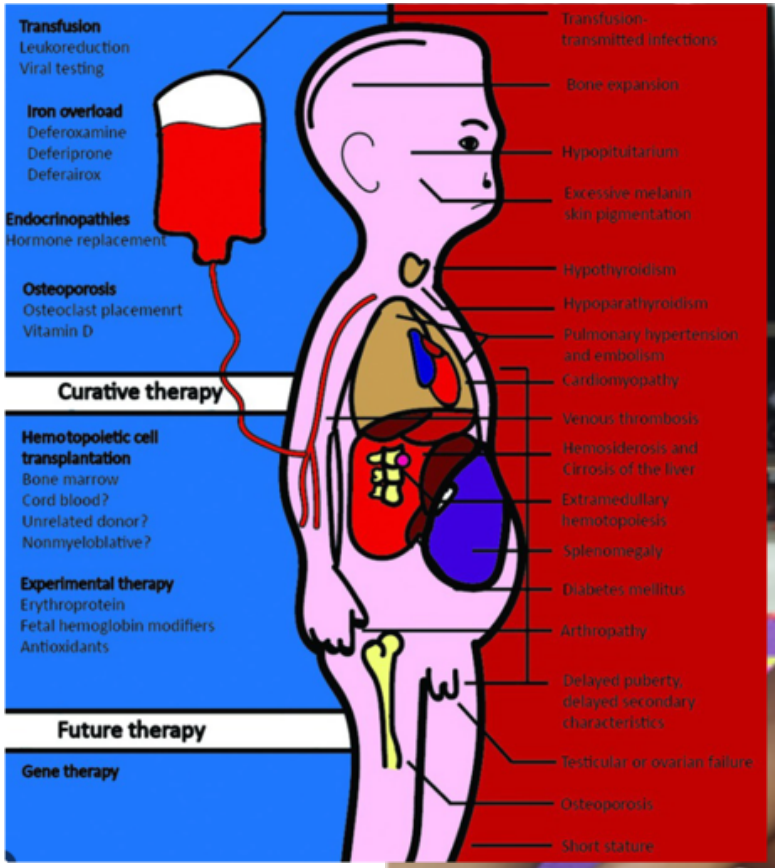


Figure 12. Each population exhibits different mutations in the beta-thalassaemia gene.



Beta thalassaemia : splenomegali degrees of severity of symptoms, geographically ww spread



Role of BCL11a in developmental regulation of globin genes

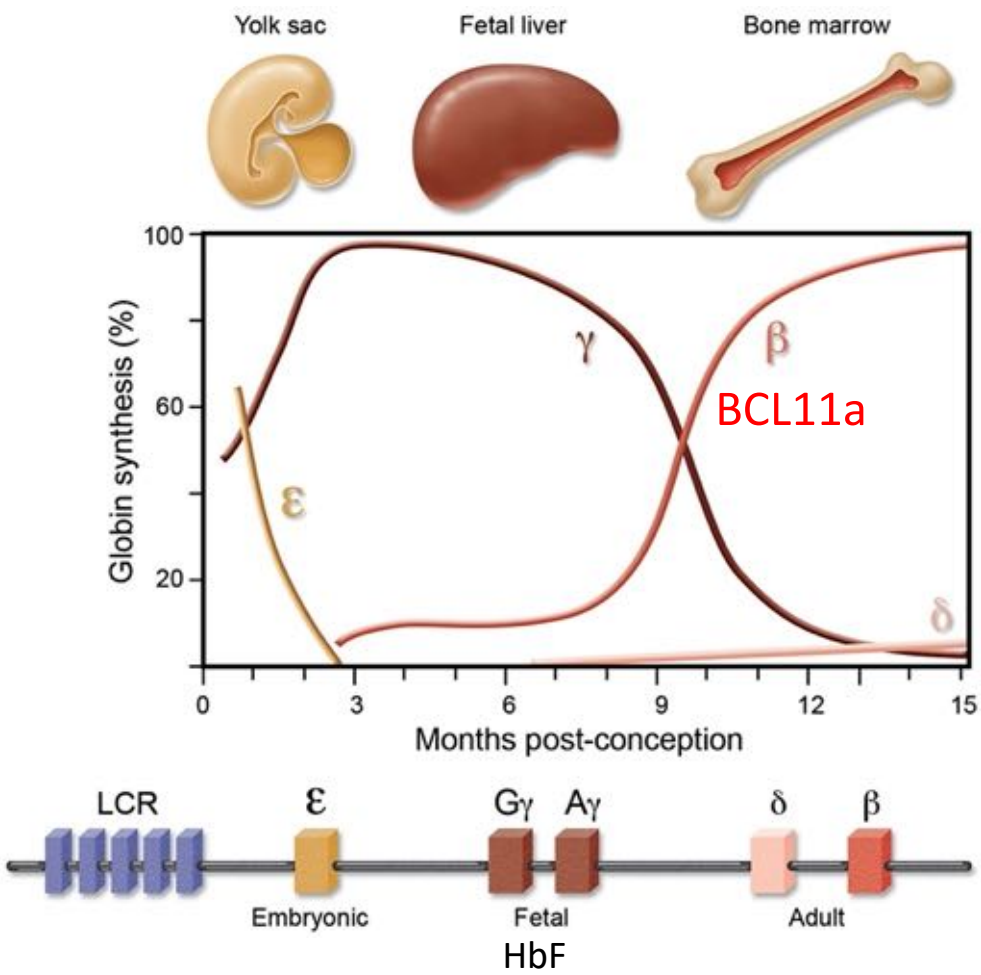


Figure 1. The β-globin genes are encoded from a single cluster and under strict developmental control. There are 2 developmental switches in expression from the cluster, from embryonic-to-fetal during the first trimester of conception, and from fetal-to-adult around the time of birth.

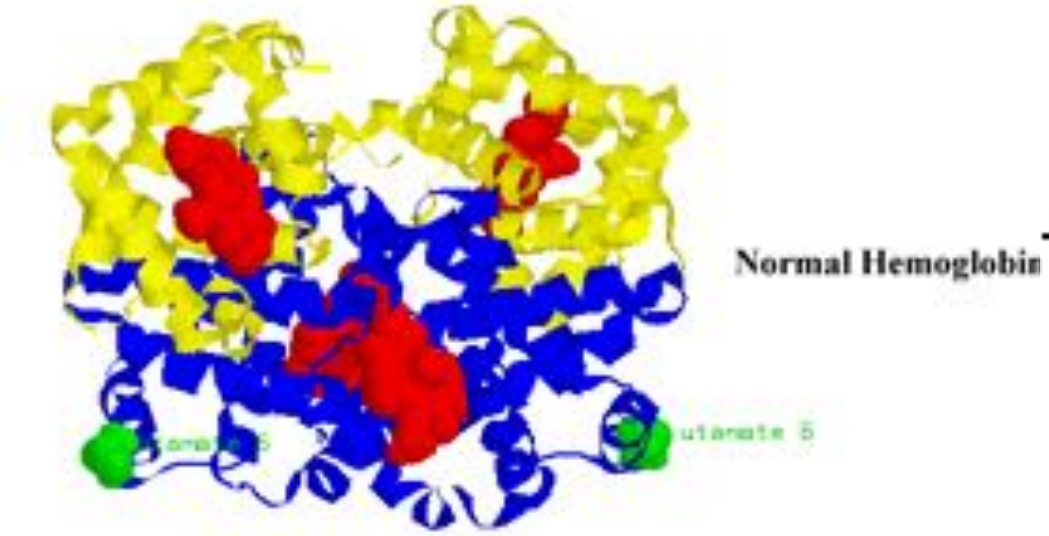
Two gene clusters encode the various globins—the alpha globin cluster on chromosome 16 contains the embryonic gene, and adult 1 and 2 genes, and the beta cluster on chromosome 11 holds the embryonic , the fetal G and A, and adult genes (Figure 1).

Adults retain low-level expression of HbF (roughly between 0.1% and 1% total hemoglobin), with only a subset of erythrocytes possessing measurable HbF

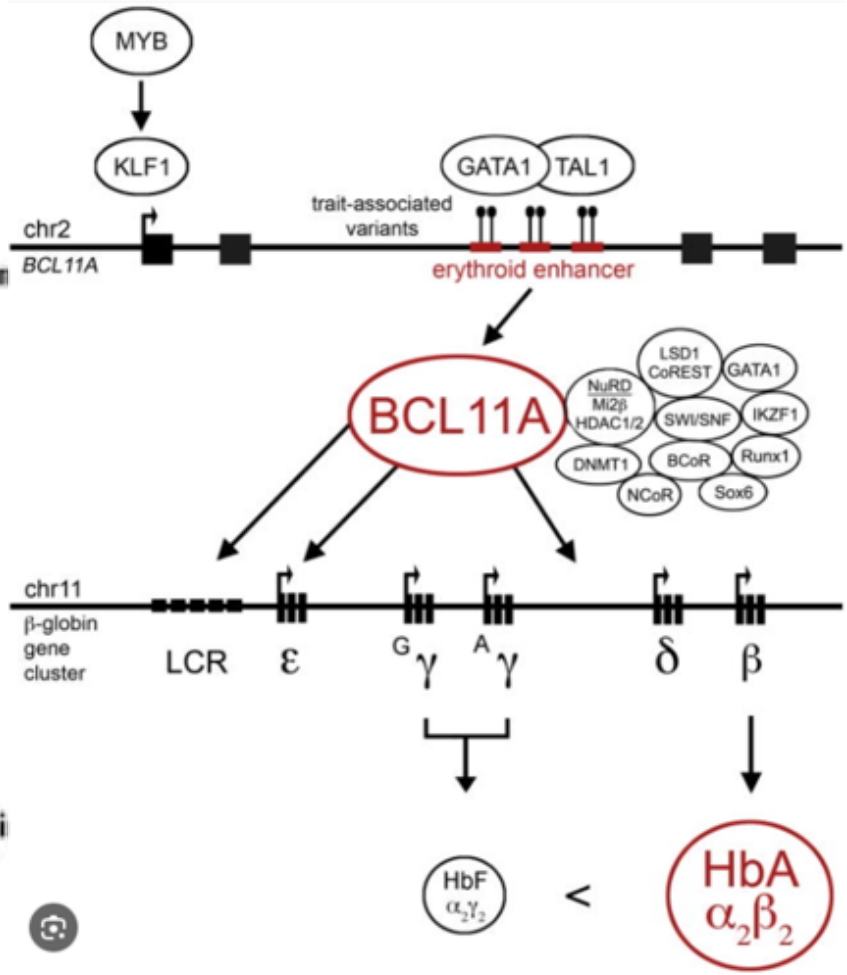
A preponderance of genetic, biochemical, and clinical observations suggest a salutary role for HbF in the βglobin disorders. The sum of this evidence indicates that even modest induction of HbF may be sufficient to ameliorate SCD

Review : Bauer et al. Blood. 2012

BCL11A : a master repressor of fetal hemoglobin expression



Note: The Sickle hemoglobin image is drawn at 50% of the size of the Normal hemoglobin



Sickle cell disease, distinguished by its unique hemoglobin structure because of the characteristic glutamate-to-valine substitution of BS, was heralded as the first “molecular disease

Role of BCL11a in developmental regulation of globin genes

An erythroid enhancer of *BCL11A* subject to genetic variation determines fetal hemoglobin level

Daniel E. Bauer[1,2,4], **Sophia C. Kamran**[4,5], **Samuel Lessard**[6], **Jian Xu**[1,4], **Yuko Fujiwara**[1], **Carrie Lin**[1], **Zhen Shao**[1], **Matthew C. Canver**[4], **Elenoe C. Smith**[1], **Luca Pinello**[3], **Peter J. Sabo**[7], **Jeff Vierstra**[7], **Richard A. Voit**[8], **Guo-Cheng Yuan**[3,9], **Matthew H. Porteus**[8], **John A. Stamatoyannopoulos**[7], **Guillaume Lettre**[6], and **Stuart H. Orkin**[1,2,4,5,*]

[1]Division of Hematology/Oncology, Boston Children's Hospital, Boston, MA, 02115

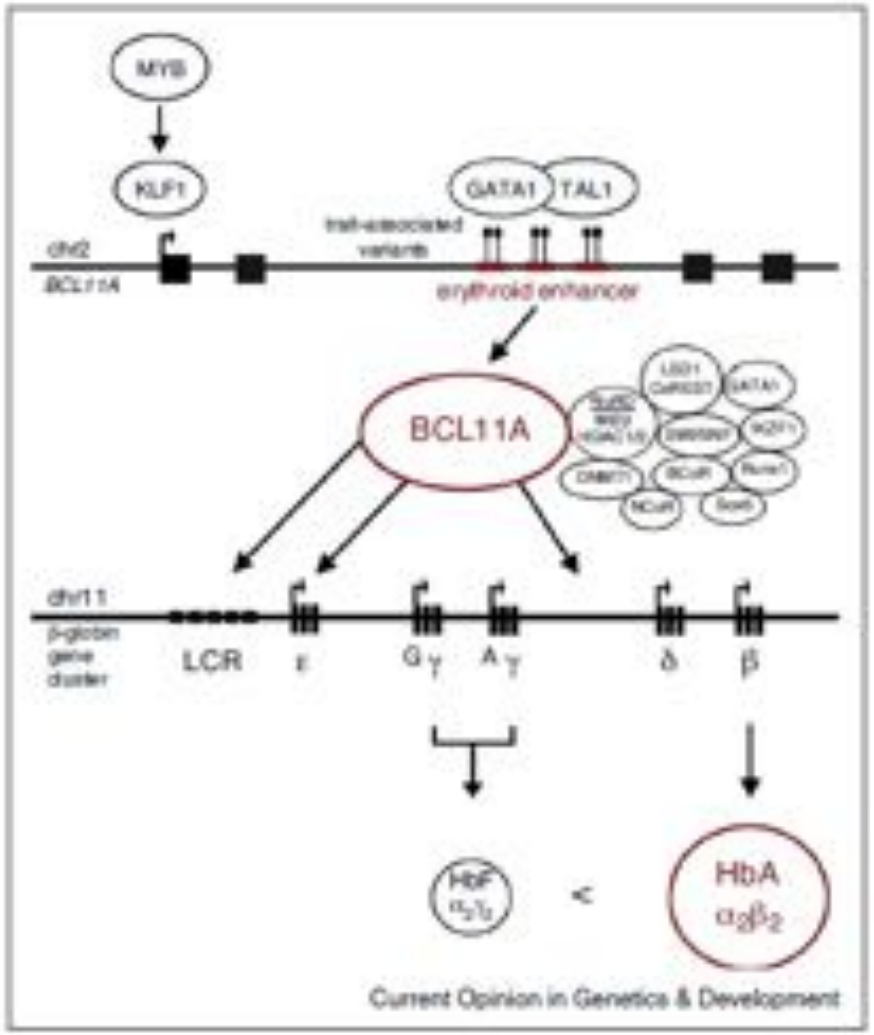
Published in final edited form as:
Science. 2013 October 11; 342(6155): 253–257. doi:10.1126/science.1242088.

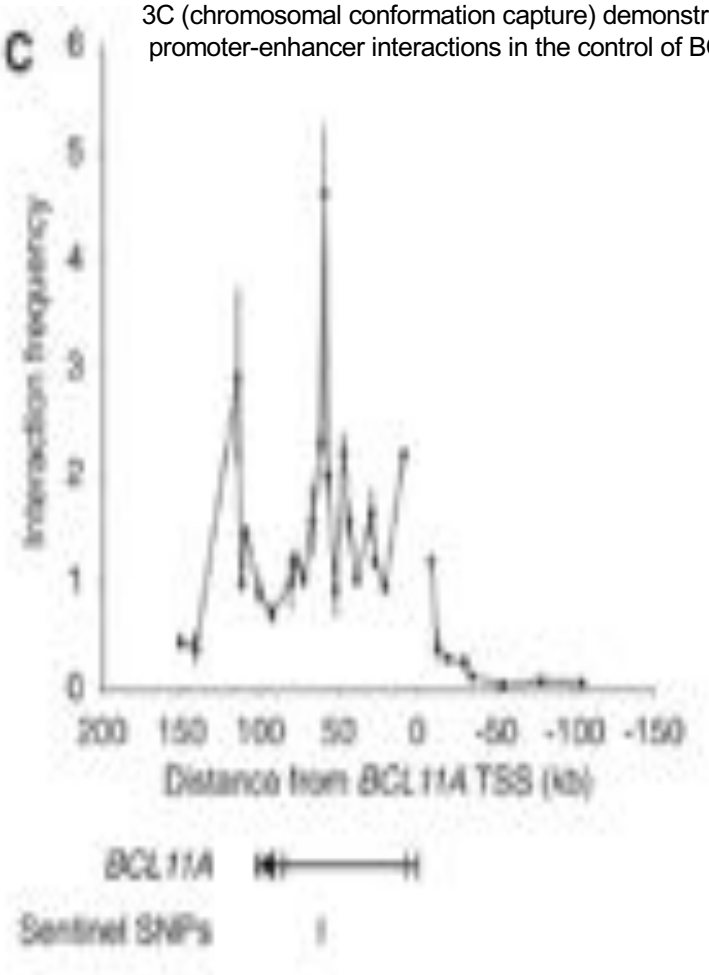
BCL11A enhancer dissection by Cas9–mediated *in situ* saturating mutagenesis

Matthew C. Canver[1*], Elenoe C. Smith[1*], Falak Sher[1*], Luca Pinello[2*], Neville E. Sanjana[3*], Ophir Shalem[3], Diane D. Chen[1], Patrick G. Schupp[1], Divya S. Vinjamur[1], Sara P. Garcia[2], Sidinh Luc[1], Ryo Kurita[4], Yukio Nakamura[4,5], Yuko Fujiwara[1,6], Takahiro Maeda[7], Guo-Cheng Yuan[2], Feng Zhang[3§], Stuart H. Orkin[1,6§] & Daniel E. Bauer[1§]

doi:10.1038/nature15521

BCL1A-HbF repression axis : erythroid enhancer – promoter





3C (chromosomal conformation capture) demonstrating promoter-enhancer interactions in the control of BCL11A

typical enhancer associated marks:
H3K4me1 and H3K27ac

Bauer D and Orkin S. Current Opinion G+D. 2015

Background

Genome-Wide Association Study (GWAS) or Common-Variant Association Study (CVAS), is an examination of common genetic variants in different individuals to see if any variant is associated with a trait. GWASs typically focus on associations between single-nucleotide polymorphisms (SNPs) and major diseases.

Genome-scale chromatin mapping studies have highlighted the enrichment of GWAS variants in regulatory DNA elements, suggesting many causal variants may affect gene regulation

GWAS of **HbF** level have identified trait-associated variants at **BCL11A** repressor

The transcriptional repressor BCL11A has been validated as a direct regulator of HbF level

Constitutive BCL11A deficiency results in embryonic lethality and impaired lymphocyte development

Erythroid-specific deficiency of BCL11A counteracts developmental silencing of embryonic and fetal globin genes and rescues the hematologic and pathologic features of sickle cell disease (SCD) in mouse models

Aim : Further understand how common genetic variation impacts BCL11A , HbF level and **β** -globin disorder severity

Comparison of the distribution of the HbF-associated SNPs at B with DNase I sensitivity sites

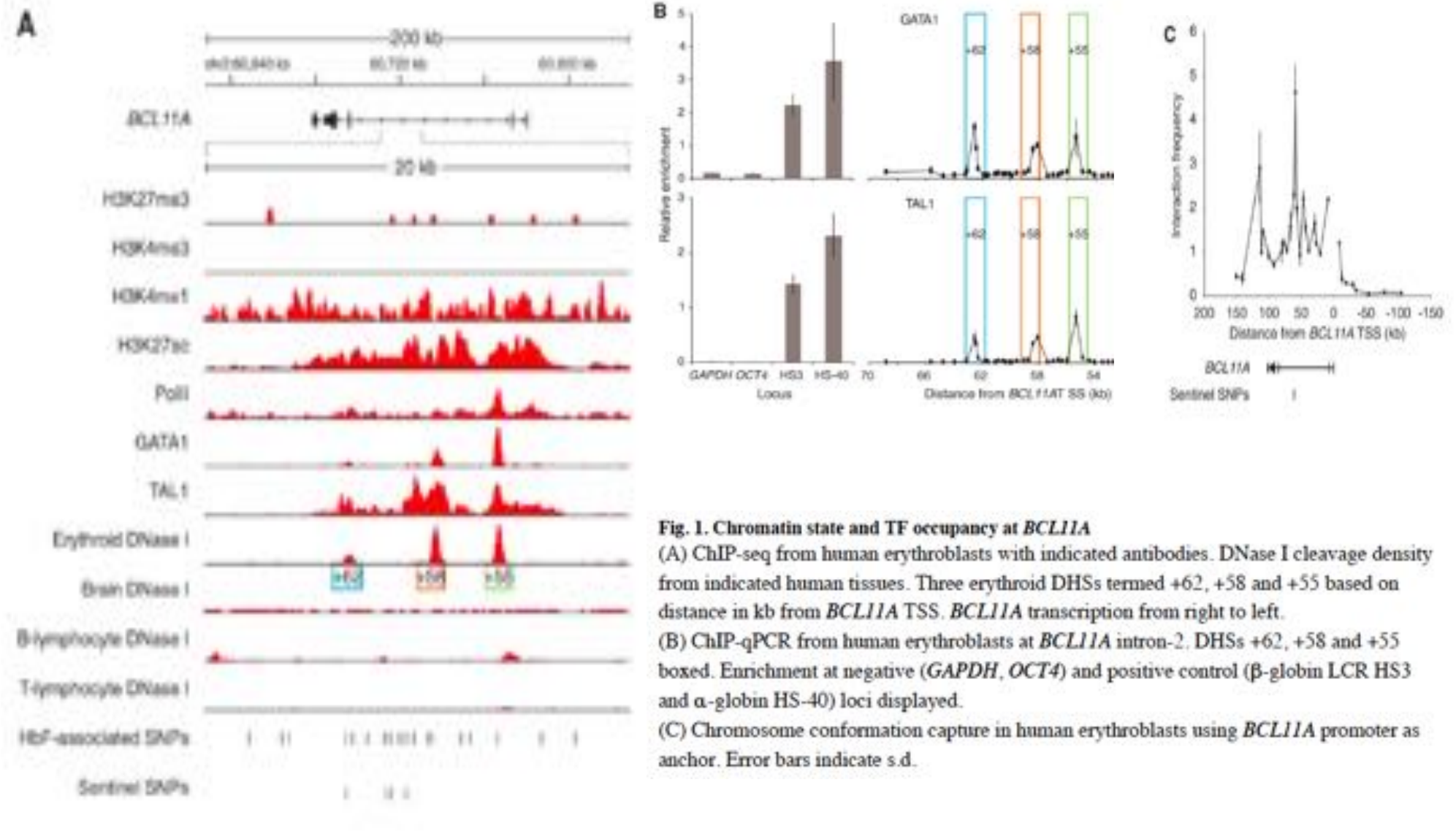


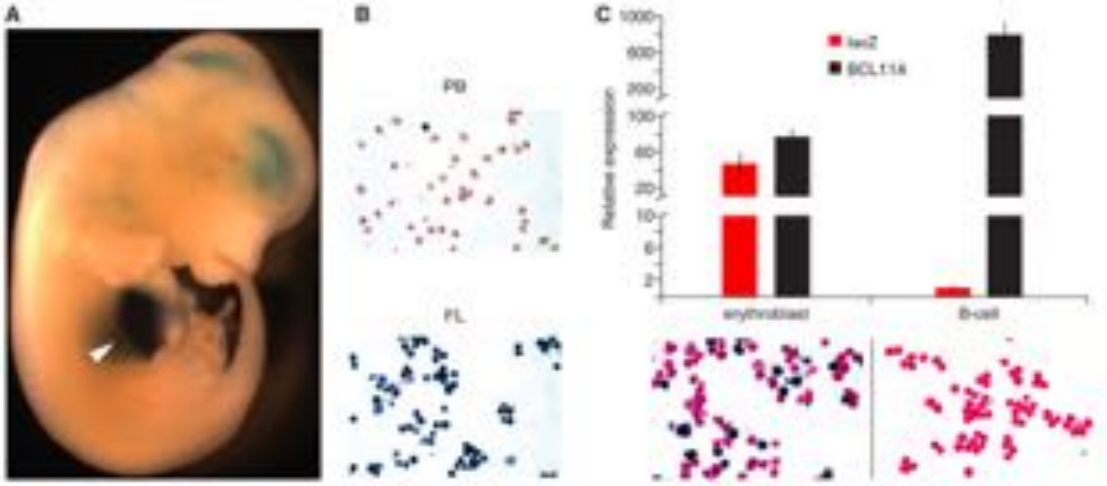
Fig. 1. Chromatin state and TF occupancy at *BCL11A*

(A) ChIP-seq from human erythroblasts with indicated antibodies. DNase I cleavage density from indicated human tissues. Three erythroid DHSs termed +62, +58 and +55 based on distance in kb from *BCL11A* TSS. *BCL11A* transcription from right to left.

(B) ChIP-qPCR from human erythroblasts at *BCL11A* intron-2. DHSs +62, +58 and +55 boxed. Enrichment at negative (*GAPDH*, *OCT4*) and positive control (β-globin LCR HS3 and α-globin HS-40) loci displayed.

(C) Chromosome conformation capture in human erythroblasts using *BCL11A* promoter as anchor. Error bars indicate s.d.

The GWAS-marked BCL11A enhancer is sufficient for adult-stage erythroid expression



In stable transgenic BCL11A +52.0–64.4 reporter lines at 12.5 dpc, circulating primitive erythrocytes failed to stain for X-gal whereas definitive erythroblasts in fetal liver robustly stained positive (Fig. 3B).

Fig. 3. The GWAS-marked *BCL11A* enhancer is sufficient for adult-stage erythroid expression

(A) A 12.4-kb fragment of *BCL11A* intron-2 (+52.0–64.4 kb from TSS) was cloned to a *lacZ* reporter construct. Transient transgenic mouse embryo from 12.5 dpc X-gal stained. Arrowhead indicates liver.

(B) Cell suspensions isolated from peripheral blood (PB) and fetal liver (FL) of stable transgenic embryos at 12.5 dpc X-gal stained.

(C) Sorted erythroblasts and B-lymphocytes from young adult stable transgenic mice subject to X-gal staining or RNA isolation followed by RT-qPCR. Gene expression normalized to GAPDH and expressed relative to T-lymphocytes. Error bars indicate s.d.

the GWAS marked enhancer in erythroid specific

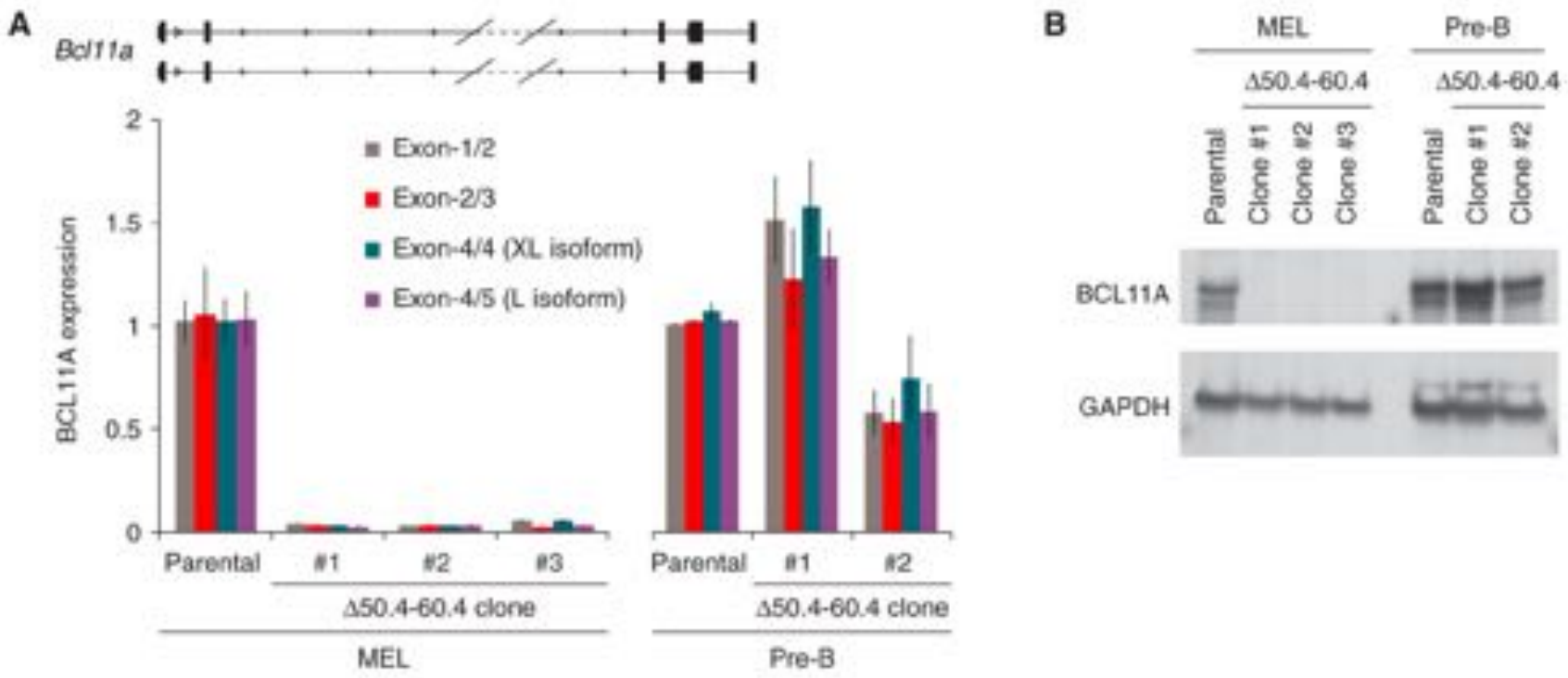


Fig. 4. The GWAS-marked *BCL11A* enhancer is necessary for erythroid but dispensable for non-erythroid expression

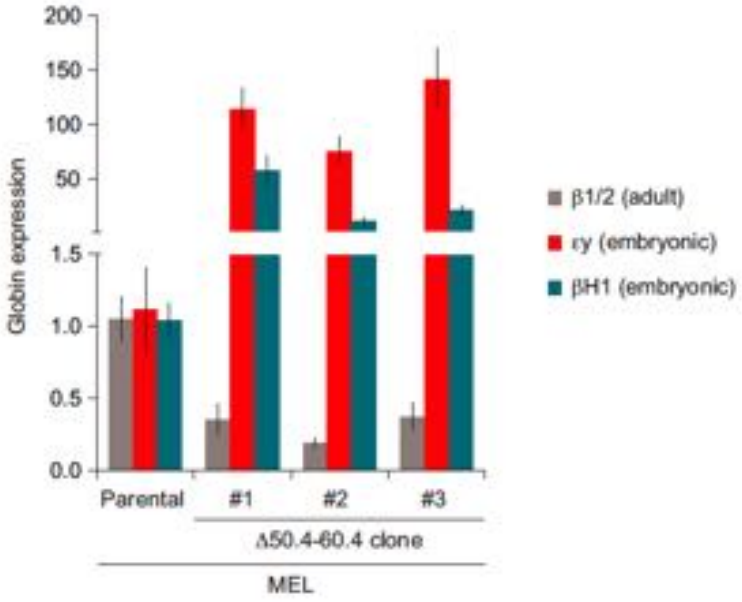
(A) Three mouse erythroleukemia (MEL) and two pre-B lymphocyte clones with biallelic deletion of the orthologous *Bcl11a* erythroid enhancer (Δ50.4–60.4) subject to RT-qPCR.

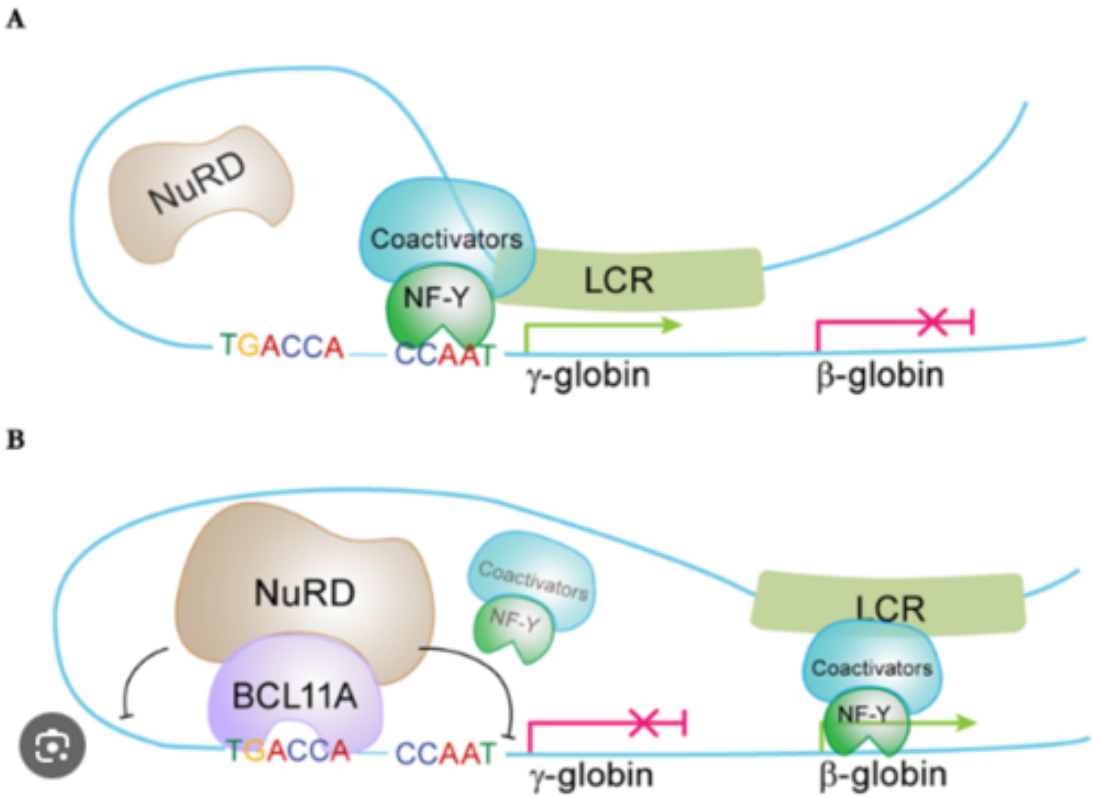
(B) Immunoblot of Δ50.4–60.4 MEL and pre-B lymphocyte clones.

the GWAS marked enhancer deletion induce HbF expression

Fig. S9
Globin Gene Expression Upon *Bcl11a* Enhancer Deletion.
Globin gene expression in Δ50.4-60.4 MEL clones by RT-qPCR. Error bars indicate s.e.m. of at least 4 experiments.

Fig. S9





Role of BCL11a in developmental regulation of globin genes

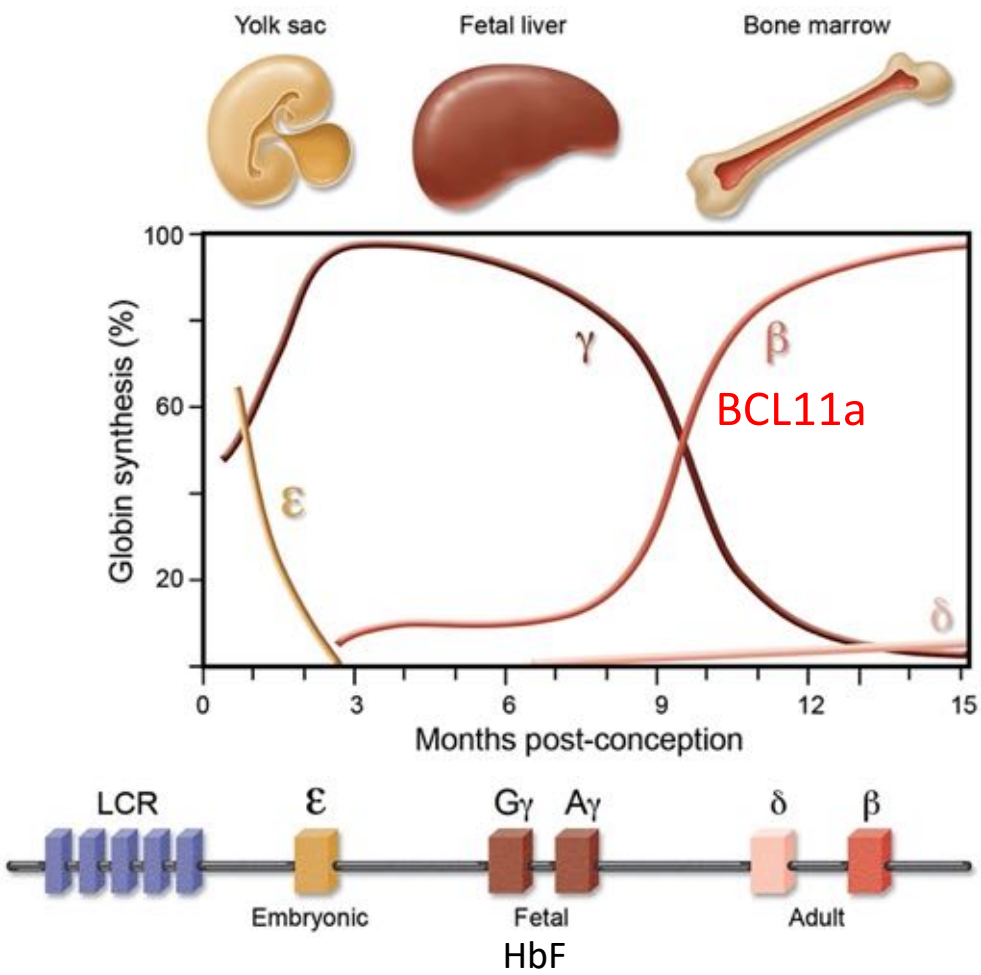


Figure 1. The β-globin genes are encoded from a single cluster and under strict developmental control. There are 2 developmental switches in expression from the cluster, from embryonic-to-fetal during the first trimester of conception, and from fetal-to-adult around the time of birth.

Two gene clusters encode the various globins—the alpha globin cluster on chromosome 16 contains the embryonic gene, and adult 1 and 2 genes, and the beta cluster on chromosome 11 holds the embryonic , the fetal G and A, and adult genes (Figure 1).

Adults retain low-level expression of HbF (roughly between 0.1% and 1% total hemoglobin), with only a subset of erythrocytes possessing measurable HbF

A preponderance of genetic, biochemical, and clinical observations suggest a salutary role for HbF in the βglobin disorders. The sum of this evidence indicates that even modest induction of HbF may be sufficient to ameliorate SCD

Review : Bauer et al. Blood. 2012

Disruption of BCL11A enhancer leads to HbF derepression

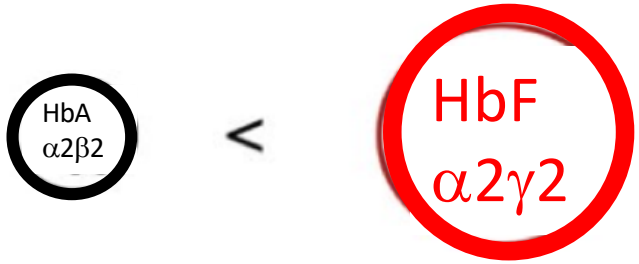
Summary :

- Identification of GWAS linked enhancers and SNPs that are erythroid specific for the regulation of BCL11a and therefore globin genes

- Disruption of this enhancer would impair BCL11A expression in erythroid precursors with resultant HbF derepression, while sparing BCL11A expression in non-erythroid lineages.

- They propose the GWAS-identified enhancer of BCL11A as a particularly promising therapeutic target for genome engineering in Globin disorders .

- The effect of SNPs variants on HbF level seems moderate / Weak
- The SNP rs…07 is located in DHS +62 that seems less important that the DHS +55 for BCL11a expression



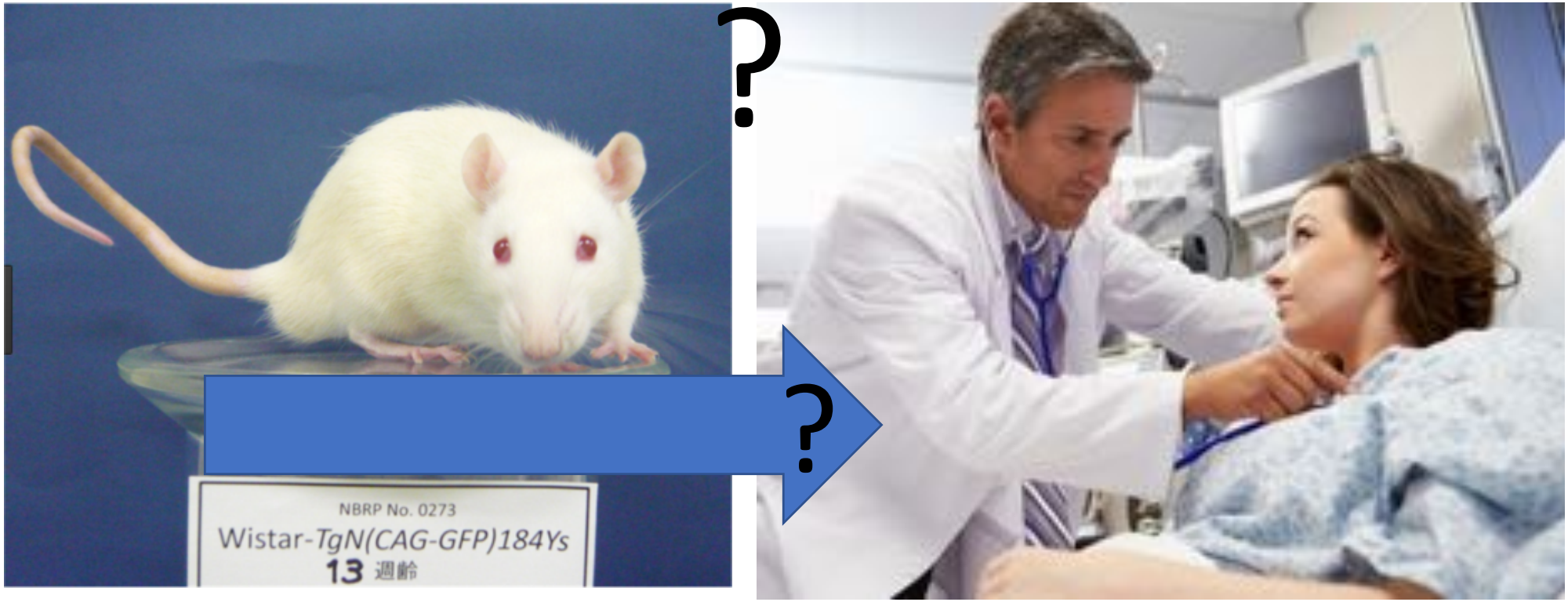
BCL11A enhancer editing *in situ* by saturation mutagenesis

- Application of CRISPR-Cas9 genome editing, saturating mutagenesis of non-coding elements in situ, to provide information about organization and function of the BCL11A erythroid enhancer
- High-resolution, high-throughput pooled tiling sgRNA screening reveals underlying enhancer sequence requirements approaching nucleotide resolution
- Apparent sequence conservation at the BCL11A enhancer masks underlying functional divergence
- Enhancer disruption by individual sgRNAs in primary erythroid precursors results in substantial HbF induction

HSC from patients → Erythrocytes-specific repression of BCL11A
→ derepression of HbF genes
→ Attenuation of Sickle disease effects
→ No effect on the other cell types ?

CRISPR for partial BCL11a enhancer deletion

- Now that it works in the rat, will it work in human ? individualized cohorts ?



Nature Magazine breaking news. Nov 16. 2023

by intravenous infusion. The therapy was developed by the pharmaceutical company Vertex Pharmaceuticals in Boston, Massachusetts, and biotechnology company CRISPR Therapeutics in Zug, Switzerland.

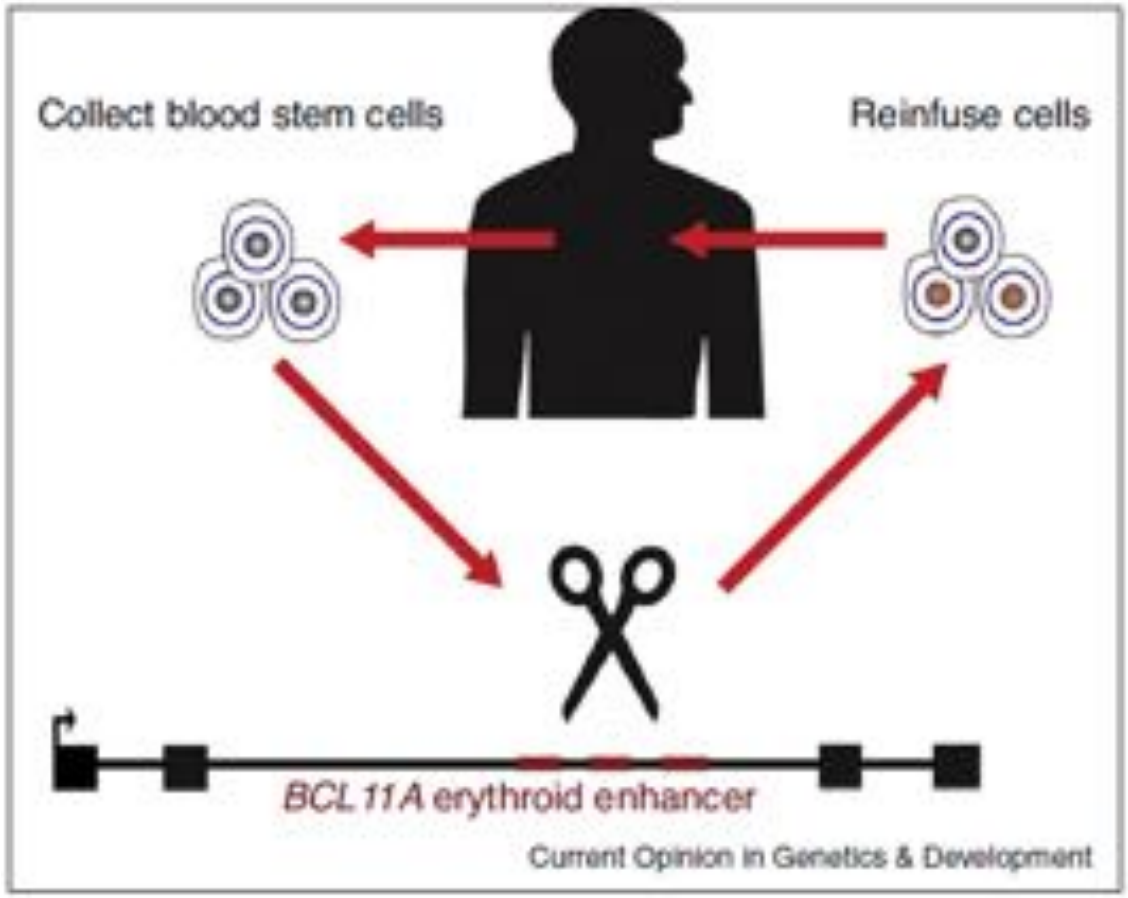
The trial for sickle-cell disease has followed 29 out of 45 participants long enough to draw interim results. Casgevy completely relieved 28 of those people of debilitating episodes of pain for at least one year after treatment.

Researchers also tested the treatment for a severe form of β-thalassaemia, which is conventionally treated with blood transfusions roughly once a month. In this trial, 54 people received Casgevy, of which 42 participated for long enough to provide interim results. Among those 42 participants, 39 did not need a red-blood-cell transfusion for at least one year. The remaining three had their need for blood transfusions reduced by more than a 70%.

VERTEX

CRISPR THERAPEUTICS

“Casgevy” uses CRISPR human genome editing tool : therapeutic genome editing of the BCL11A enhancer



HbF $\alpha_2\gamma_2$ < HbA $\alpha_2\beta_2$

UK Cost : US $ 2 millions per patient

HbA α2β2 < HbF α2γ2

- Correction of β-hemoglobin disorders allowing derepression of HbF and sparing non erythroid functions by disruption of the enhancer

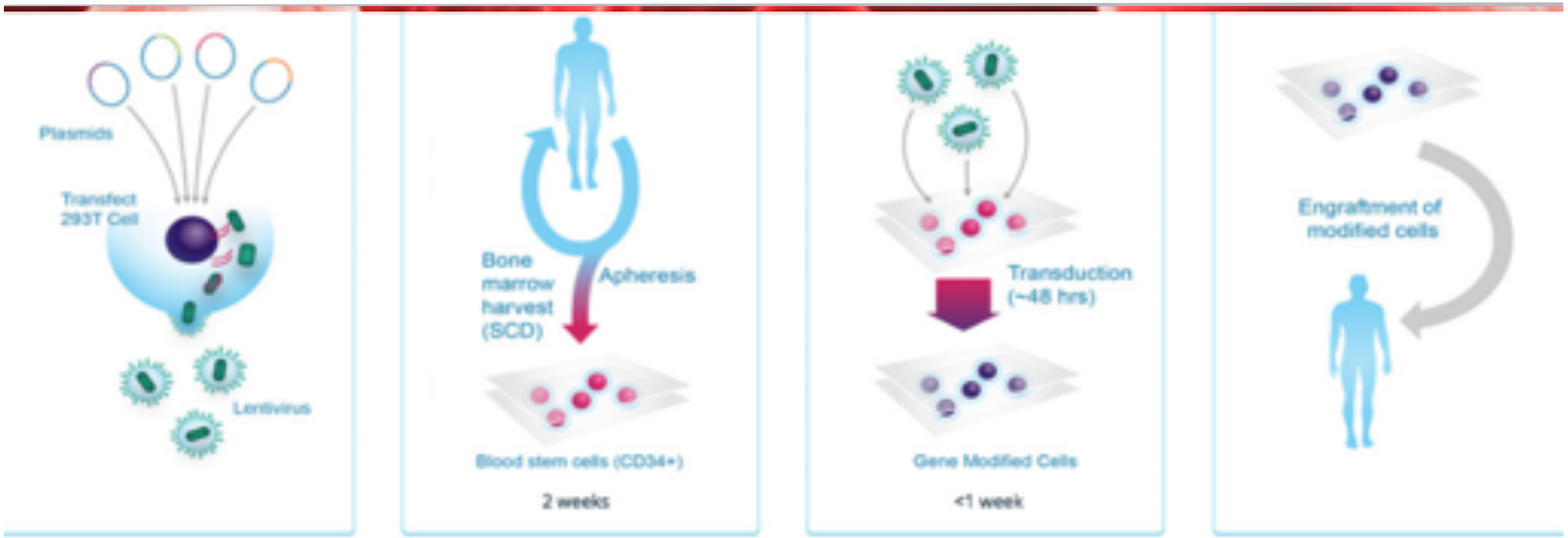
β-thalassaemia occurs when mutations lead to low haemoglobin levels in the bl low numbers of red blood cells and symptoms such as fatigue, shortness of heartbeats.

Clinicians administer Casgevy by taking blood-pro marrow of people with either disease, and using CR ing haemoglobin in those cells. The ge olecule that guides the Cas9 enzyme to the correct cuts.

Once Cas9 rea called *BCL11A*, it cuts both DNA strands. *BCL11A* a form of haemoglobin that is made only in fetuses. asgevy unleashes the production of fetal haemoglobin, which do ame abnormalities as adult haemoglobin in people with sickle-cell disease or ssaemia.

Before the gene-edited cells are infused back into the body, people must undergo a treatment that prepares the bone marrow to receive the modified cells. Once administered, the stem cells give rise to red blood cells containing fetal haemoglobin. This relieves symptoms by boosting the oxygen supply to tissues. "Patients may need to spend at least a month in a hospital facility while the treated cells take up residence in the bone marrow and start to make red blood cells with the stable form of haemoglobin," the MHRA stated in a press release.

Bluebird - Zynteglo: beta thalassemia innovative gene therapy medicine



1 **Produce virus with therapeutic payload**

Produce Lentiviral vector carrying a functional gene sequence.

2 **Isolate target cells from patient**

Mobilize, extract and isolate patient's HSCs or T cells.

3 **Transduce target cells *ex vivo***

Insert target gene sequence into the patients HSCs or T cells.

4 **Test & re-infuse gene modified cells**

Prepare patient & re-infuse patient's correct HSCs or T cells.

Gene therapy pricing plans

Zynteglo			Zolgensma			Luxturna		
Price	Payment Plan	Company	Price	Payment Plan	Company	Price	Payment Plan	Company
$1.8m	Initial payment of €315,000 followed by four equal annual payments of €315,000 only if patients continue to benefit and not need blood transfusions. Potentially 80% of the list price is at risk if the treatment fails within five years or less.	Bluebird Bio	$2.1m	Payment over time with cost of treatment spread over five years	Novartis	$850,000	Rebate programme based on Luxturna's effectiveness at 30 days, 90 days and 30 months. Payers entitled to rebate if efficacy is not shown at those points. Rebates not to exceed standard Medicaid rebate.	Spark Therapeutics

Zynteglo™ is a one-time gene replacement therapy that targets the main cause of transfusion dependent thalassemia TDT

THANK YOU.....

DO YOU HAVE ANY QUESTİONS ?

BIO 698 mid-term course evaluation FS2023

(your input is much valued thank you !)

MID TERM EVALUATION "THE MAKING OF AN INNOVATIVE MEDICINE"	HS 2022		
FOR EACH ITEM BELOW PLEASE CIRCLE ONLY A SINGLE RESPONSE	not at all	somewhat	very much
the course was sofar well organized overall			
I like the interactive part of the course (flipped classroom)			
the workshop sessions were relevant to the respective topics			
the presenters were well prepared overall			
the debates were receptive to participant's comment question			
the course enhanced my knowledge			
I realized how novel medicine development is a long complex journey			
I hope to be abe to use part of this knowledge and skills in future			
I would recommend to re/attend this course to a colleague, friends			
I am looking forward to the upccoming health hackathon			
	please tick accordingly X		
SELF ASSESSMENT LEARNING:EVALUATE KNOWLEDGE BEFORE/AFTER	before	after	
historical introduction to drug development	1 2 3	4 5 6	
therapeutic target identification _ patient need	1 2 3	4 5 6	
therapeutic modalities: SMW cpds, biologicals, RNA, DNA therapeutics	1 2 3	4 5 6	
MedChem, in silico/HTS screens/AI screen	1 2 3	4 5 6	
Personalized healthcare -precision medicine	1 2 3	4 5 6	
1= **NO** value/knowledge or skills			
3= **SOME** value/knowkedge or skills	please circle accordingly (see below)		
6= **LOT** of value/ knowledge or skills			
remarks: there are no right or wrong answers. no need to put your name (anonymous evaluation) !			
your comments :			

BIO 698 mid-term course evaluation FS2023 (your input was much valued thank you !)

MID TERM EVALUATION "THE MAKING OF AN INNOVATIVE MEDICINE"	HS 2022		
FOR EACH ITEM BELOW PLEASE CIRCLE ONLY A SINGLE RESPONSE	not at all	somewhat	very much
the course was sofar well organized overall	0%	7%	93%
I like the interactive part of the course (flipped classroom)	0%	14%	86%
the workshop sessions were relevant to the respective topics	0%	14%	86%
the presenters were well prepared overall	0%	14%	86%
the debates were receptive to participant's comment question	0%	14%	86%
the course enhanced my knowledge	0%	21%	79%
I realized how novel medicine development is a long complex journey	0%	28%	72%
I hope to be abe to use part of this knowledge and skills in future	0%	14%	86%
I would recommend to re/attend this course to a colleague, friends	0%	14%	86%
I am looking forward to the upccoming health hackathon	0%	28%	72%
	please tick accordingly X		
SELF ASSESSMENT LEARNING:EVALUATE KNOWLEDGE BEFORE/AFTER	before	after	
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Personalized healthcare -precision medicine	1 2 3	4 5 6	
1= **NO** value/knowledge or skills			
3= **SOME** value/knowkedge or skills	please circle accordingly (see below)		
6= **LOT** of value/ knowledge or skills			
remarks: there are no right or wrong answers. no need to put your name (anonymous evaluation) !			
"the course was very informative thank you for the course materials lectures"			
"thank you so much for the meanignful and intersting course"			
"may be more careful to iming for presenters or start the course with pres. so then speakers don't have to worry about time"			

09 questionnaires back from
16 IS academia participants