

R E G I S T E R N O W !

1,000,000,000 CHF investment

7,000,874 hours of work

6,587 experiments

423 researchers

1 medicine



THE MAKING OF AN INNOVATIVE MEDICINE

*Introductory workshops on translational biomedical research,
drug discovery and development*



Judge Prof Dr med Olaia Naveiras

**BIO-698 resumes Thursday September 11. 2025
4:15 PM @ CM013**



Sciences de la Vie -SV



With Justine Epiney MD PhD cand Mehdi AliGadiri MD PhD cand

Prof Roger G. Clerc

The Making Of An Innovative Medicine – class schedule

Thursday's @ 4-6 PM except 04.12/11.12.25 @2-6 PM



Session 1: Scope of the course _ general organization _ case study

11.09.25 *Embracing a career at the heart of biomedical research !?*

CM013

Session 2: Historical perspective: the modern pharmacy

18.09.25 *Advent of modern medicines - placebo controlled drug development*

CM013

Session 3: Introduction to translational research: crossing the bridge

25.09.25 *A chasm has opened wide between biomedical research and patients in need*

CM013

~~Sessions 4-5: Therapeutic target identification I & II~~

02-09.10.25 *"me too" vs a wealth of innovative targets _ small MW cpds vs biologicals*

CM013

Early front loading of biomarker identification for cohort stratification

Session 6: Structure based drug design _ medicinal chemistry_low/high throughput

16.10.25 **screening assays_ multiple parallel optimization_ML-powered screens**

CM013

Setting up screening assays, the robotics, the million cpds libraries

Session 7: Therapeutic modalities peptides and biologicals: today's -

30.10.25 **tomorrow's pharmacy NBEs**

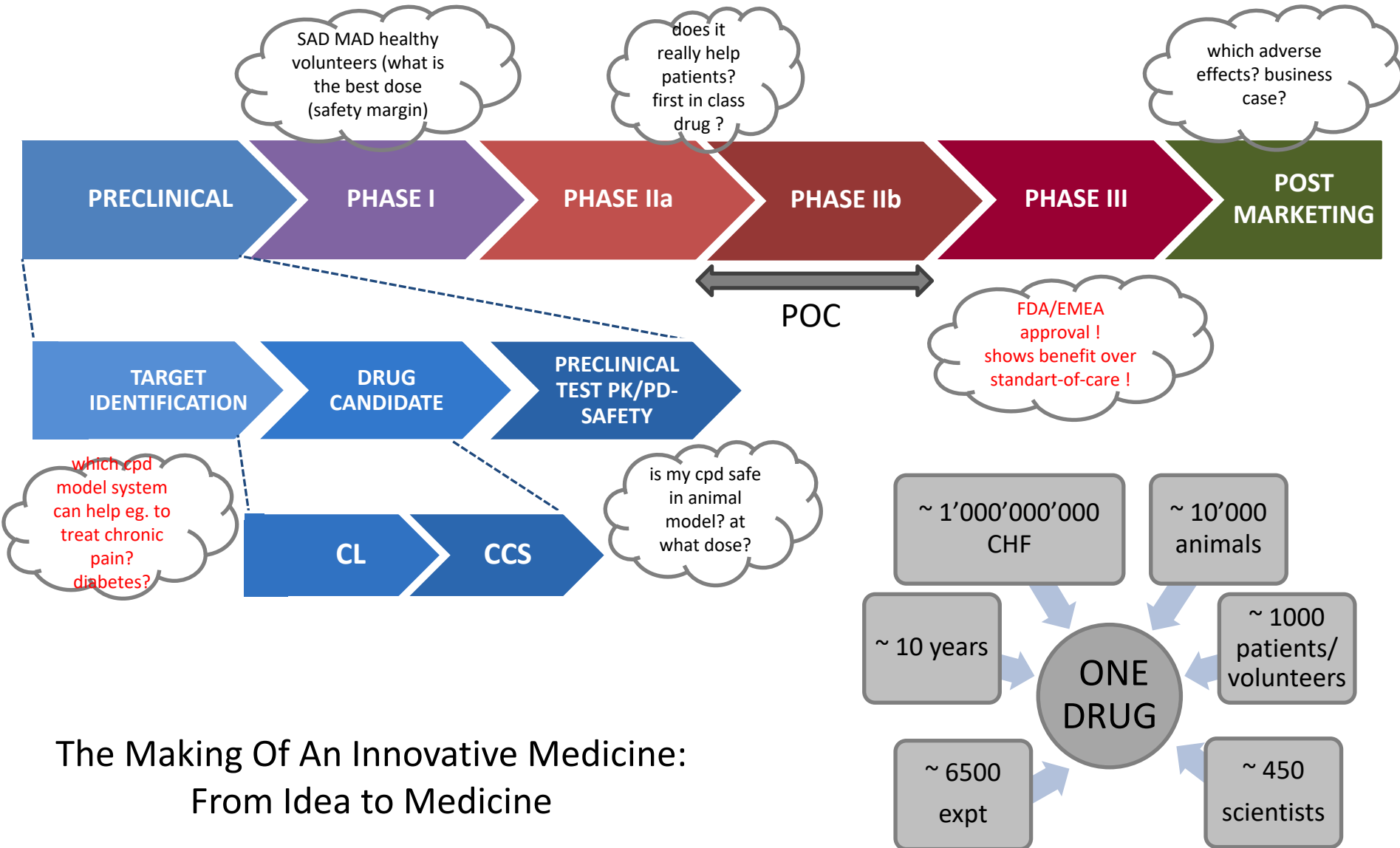
CM013

Challenges (cost of goods - healthcare payers) and opportunities

Drug Discovery : The Value Chain



«the discovery of a new medicine is a difficult and highly risky task»



The Making Of An Innovative Medicine:
From Idea to Medicine

WORKSHOP LISTING - THE MAKING OF AN INNOVATIVE MEDICINE BIO 698-HS2025 in CM013

! NON EXHAUSTIVE LISTING - SUGGESTIONS WELCOME !		
sessions	workshops	speaker/s
S02 (18-09-25)		
historical medicines	penicilin: impact, whose invention ?	
hopping on giant shoulders	prozac at the core of psychiatry	
	vaccine discovery:smallpoxJennerTodaymRNAvaccine	Eugenio
	artemisinin and malaria	
	insulin-Banting Best et al. beagle dog	
	slide51-X-ray image DNA--Rosalind Franklin	
	cyclosporin from soil sample to life saver	
S03 (25-09-25)		
translational research	expanding scope of translational therapies	
from bench to bedside and back	chronotherapy,circadian clock,sex,longevity	Solomon
	CAR-T, TCR-T cell therapies in "cold" tumors	
	Y chrom loss in immune cells drives cancer	
S04 (02-10-25)		
therapeutic target identification	rare diseases repurposing medicines	
S05 (09-10-25)		
therapeutic target identification	nocosomial inf/MRSA/phage antibacterials	
	Crispr/Cas9 gene editing huntington disease	
	AI in drug discovery / ML-powered medicine	Lou
	AIDS - Lenacapavir : end of plague ?	
S06 (16-10-25)		
structure based drug design	macrocycles and non druggable targets	
	chemoproteomics - NMEs	
	AIDS HIV from deadly virus to chronic disease	
S07 (30-10-25)		
therapeutic modalities - NBEs	therapeutic peptides/incretins et al	
	biologicals on the rise MABs medicines	
	RNA therapeutics, antisense medicines	
	Wnt pathway - PROTACs vs molecular GLUEs	
S08 (06-11-25)		
PHC personalized healthcare	BRCA1/2 preventive surgery/tumor board	
Human genomics	4P medicine - GWAS - CTCs	
	disease enabling biomarkers/micro RNAs	
	AZ-biomarker BD-tau yet still no curative drug	
	centenarian host isoallo-LCA bile acid bacteria	



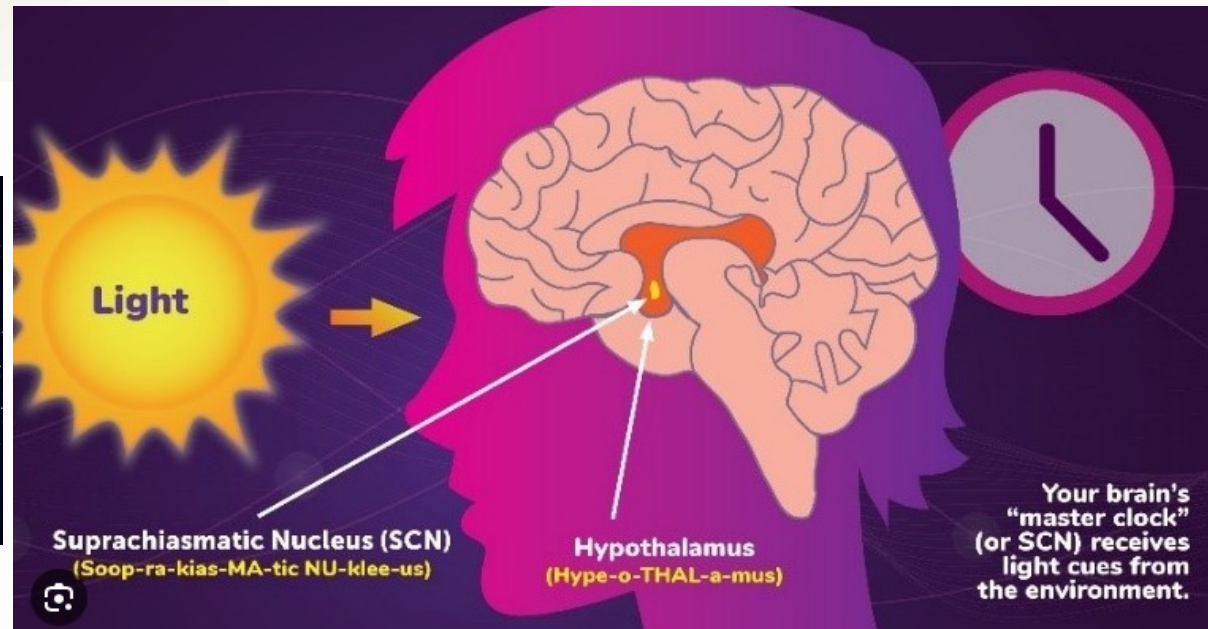
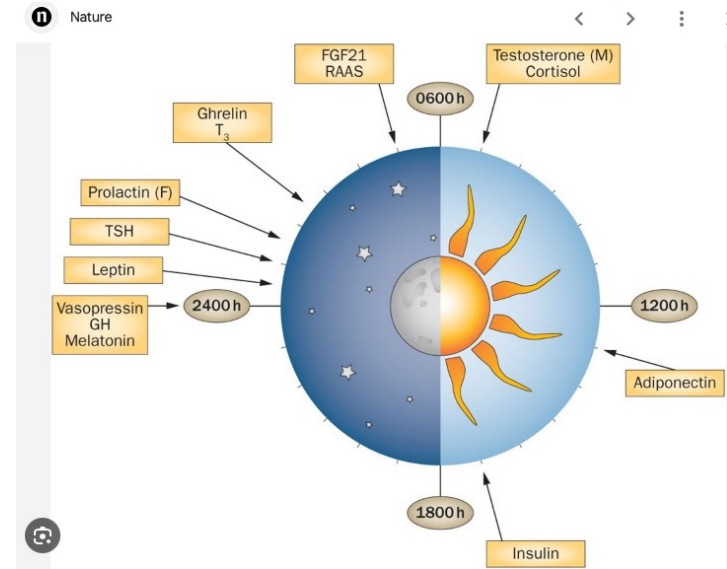
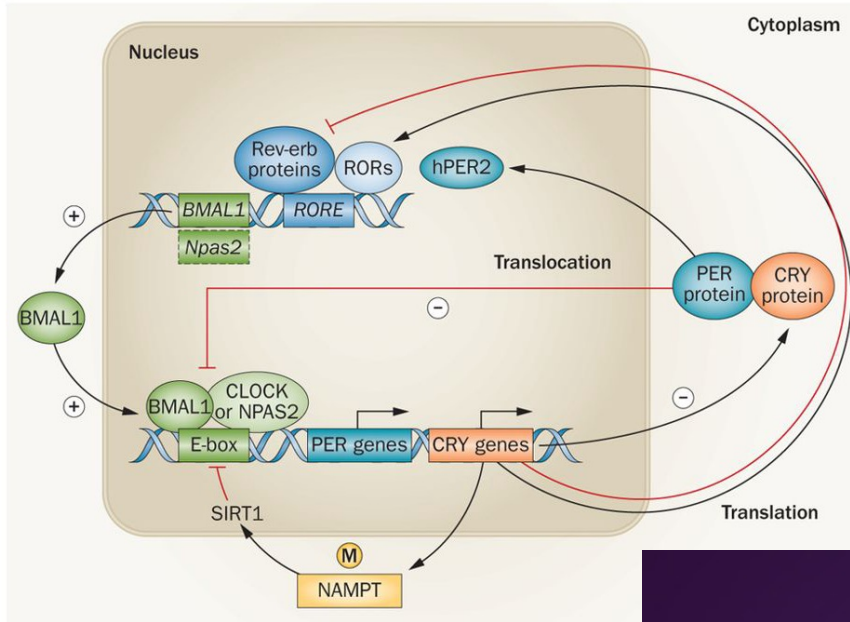
Workshops The Making Of An Innovative Medicine (today's class)



Chronobiology : feedforward/backward gene regulatory loops - the underlying molecular mechanisms



From: Clocking in: chronobiology in rheumatoid arthritis

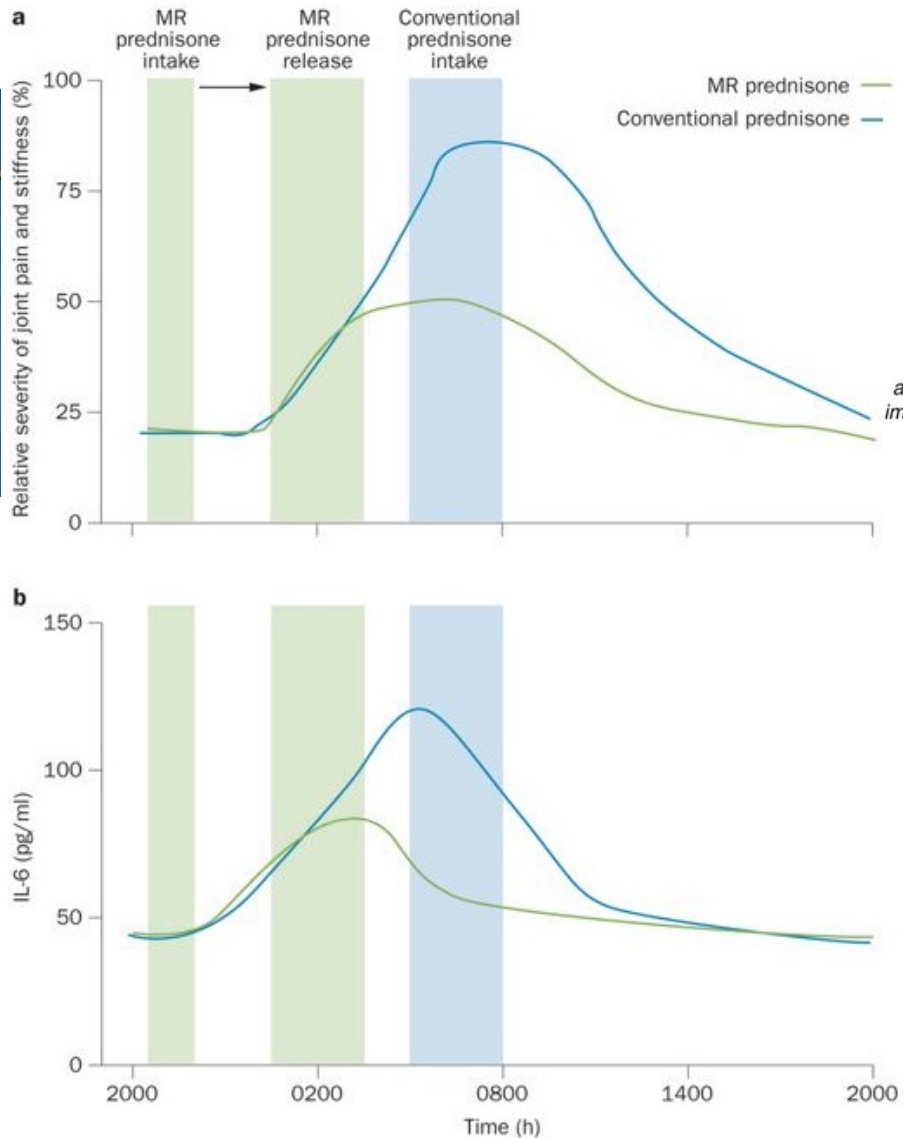


Chronotherapy workshop : relapsing RA patient mgmt

translate the 'circadian concept' in rheumatology from bench to bedside



Figure 3: Responses to conventional prednisone versus chronotherapy for RA. MR : modified release



BMJ RMD Open

7-9 Usual time for administration of exogenous prednisone (immediate-release)

6-7 Possible administration of immediate-release NSAIDs

2-3 Best time for exogenous prednisone availability (nighttime-release)

22-23 Time for administration of (nighttime-release) prednisone

20-21 Best time for administration of low dose methotrexate and nighttime-release NSAIDs

RA Chronotherapy

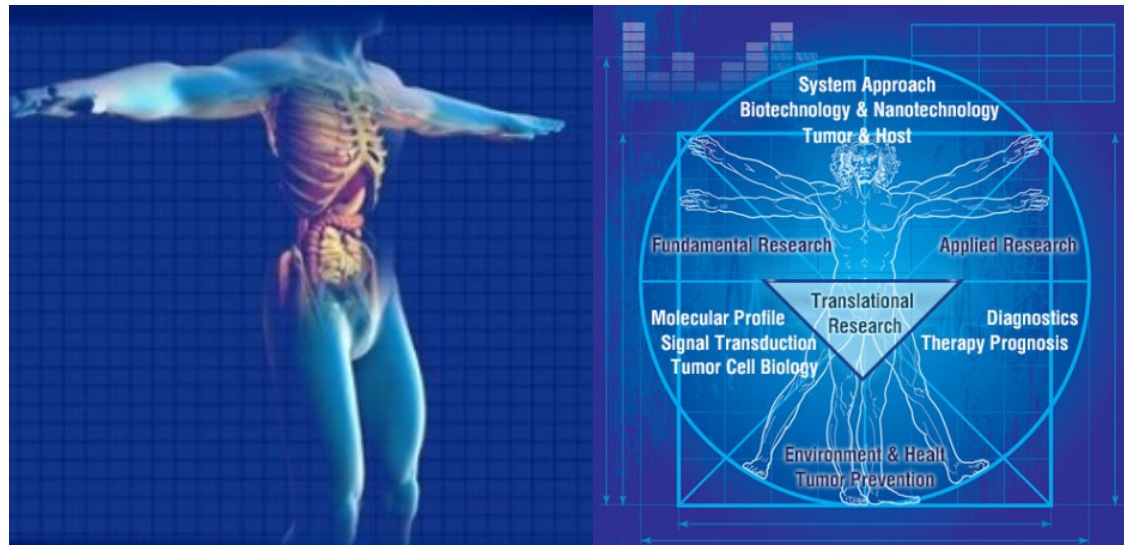
Glucocorticoids and chronotherapy in rheumatoid arthritis ...

Consulter

Buttgereit et al. 2012 Clinical and epidemiological research 72: 204-210

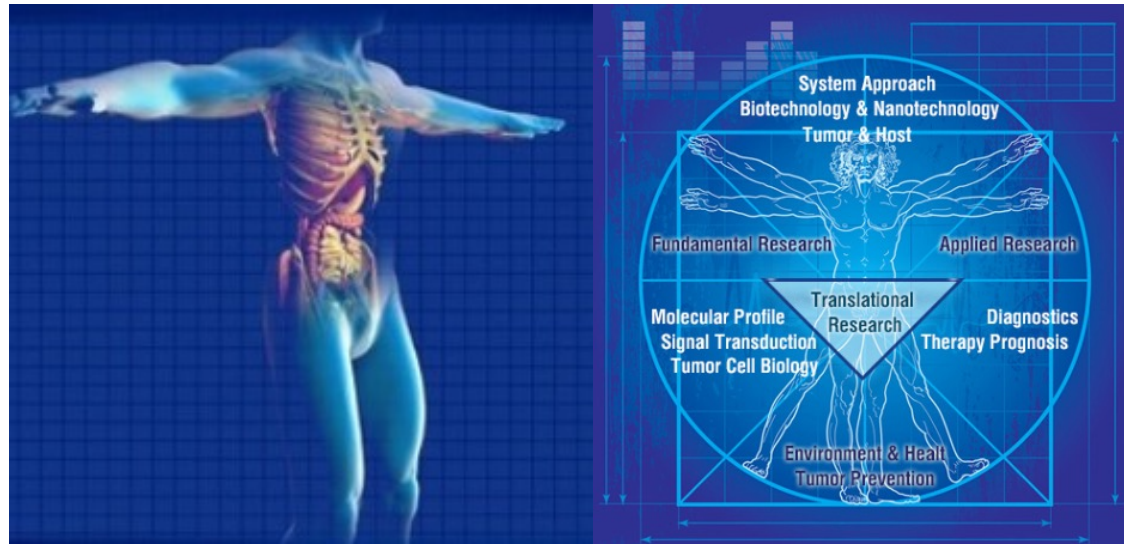


- Introduction to biomedical translational research : crossing the bridge
- What do you think is translational research all about ?





- An **emerging biomedical research concept** that brings together 2 distinct groups of researchers together towards a common goal: a quantum jump in advancing healthcare and drug discovery for patients in need





TRANSLATIONAL RESEARCH

**The Application of the
Scientific Method to
Address a Health Need**

Translational research : do what patients need next !



Before you're going to address a unmet medical need, a translational pharmacological model is needed

FROM BENCH TO BEDSIDE AND BACK !

Basic research :
the scientific
method



Clinical research :
the health need

The goal is to
learning
communicating
across disciplines to
achieve advances in
health care.



WHY ?
HOW ?

- PhDs, MD-PhDs WITH TREMENDOUS EXPERIENCE IN QUANTITATIVE MOLECULAR BIOLOGY AND MOLECULAR PATHOLOGY, UNRAVEL UNDERLYING MOA OF DISEASE

- CLINICIANS MDs NURSES WITH EXTENDED EXPERIENCE IN CLINICAL RESEARCH AND PATIENT IN NEED

Translational oncology research - cell therapies

CAR-T cells (chimeric antigen receptor T) – Kymriah®



- the development of genetically engineered cells that specifically target tumor antigens is one of the most promising recent strategies in immuno-oncology.
- harnessing the patient's own immune system to kill cancer cells (eg chimeric antigen receptor (CAR) gene modified to recognize tumor antigens)
- antigens have shown promise
- liquid tumor clinical strategies
- and tumors.

BREAKING NEWS



FDA approved for Acute lymphocytic leukemia (ALL), a fast-growing cancer of lymphocyte-forming cells called *lymphoblasts*. Cost CHF460.000.— **Tox warning:** cytokine storm Actemra tocilizumab as « antidote »

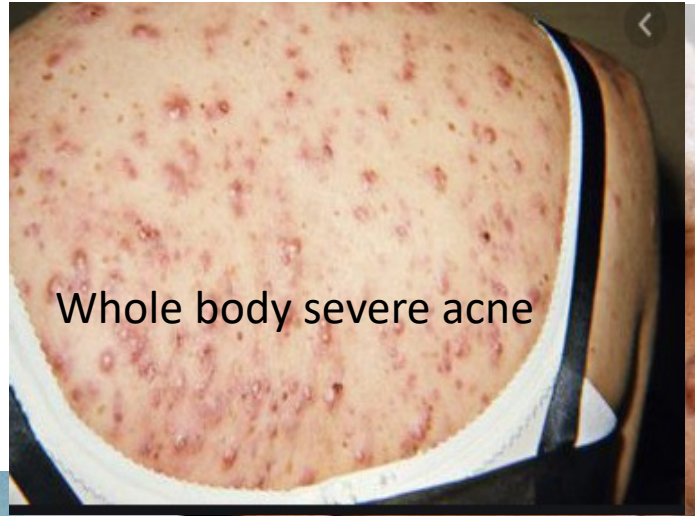
Emily Whitehead Fdn @EWhiteheadFdn · 10 mai
Today, we celebrate that Emily is 5 years cancer free!

High unmet medical needs : do now what patients need next !



**oncology patient in need
evasive resistance in cancer**

**neurodegenerative ailments
psychosomatic stress
autism alzheimer schizophrenia**



Whole body severe acne

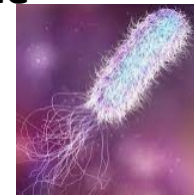


chronic migraine



rheumatoid arthritis patient

**multiresistant bacterial
infections and multiple
pathophysiological
consequences**



**WHICH MEDICINE CAN HELP
ME ? WHICH PROTEIN
PERTURBATION CAN HELP ME ?
IS THERE A SOLUTION ?**



MI CVD, T2D etc

Is your research project translational ?



**Translational Research
Differs from Scientific
Discovery Research in its
Goal and Methods**



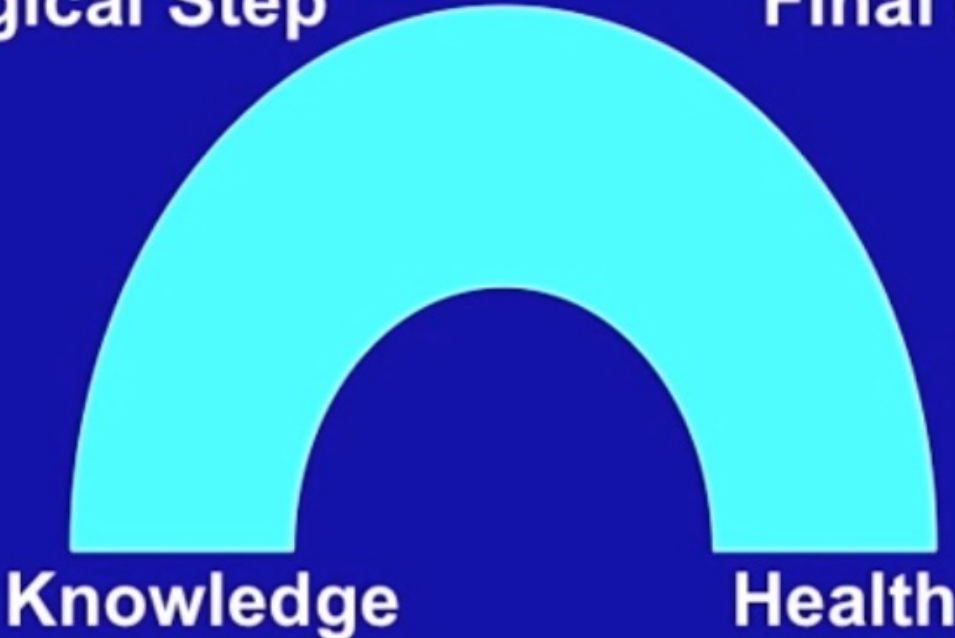
Comparison of Scientific Discovery and Translational Research

Scientific Discovery

Scientific Opportunity
Next Logical Step

Translational Research

Health Need
Final goal





The 3 Dimensions of Clinical and Translational Research

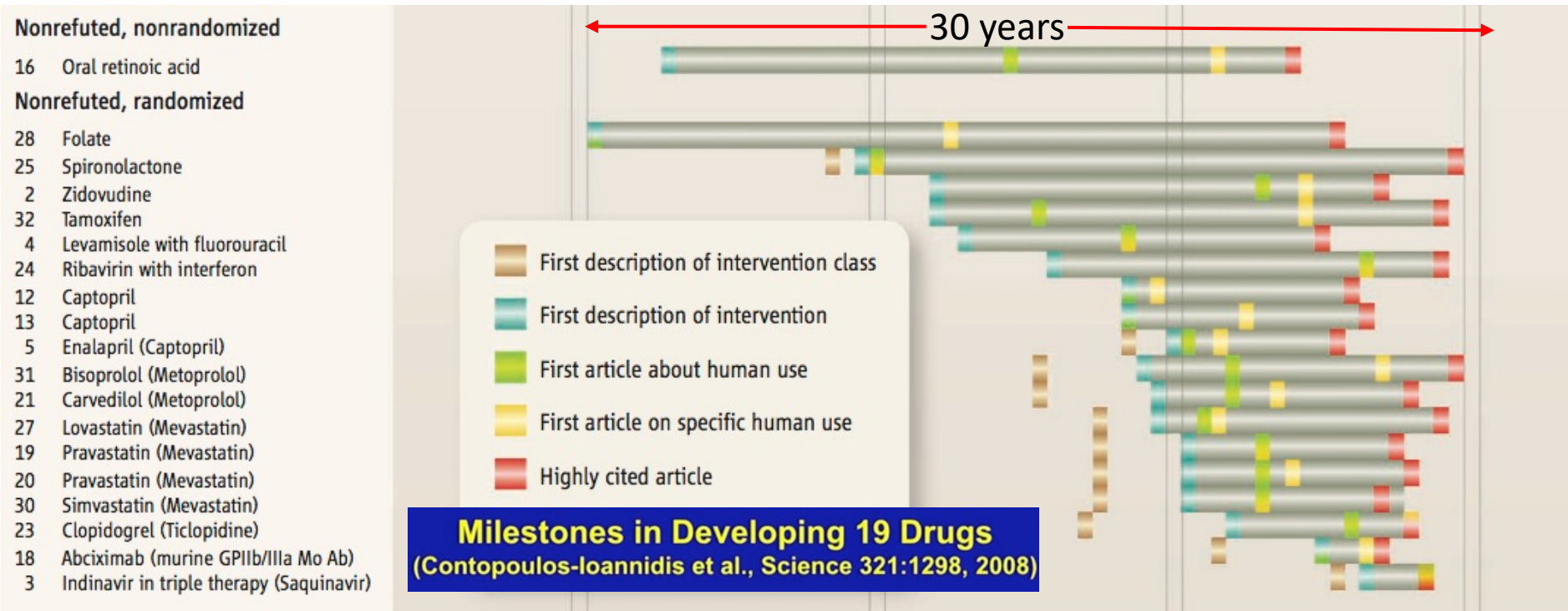
- **Multidisciplinary team building**
- **Integration across the entire T1 to T2 spectrum**
- **Integration of academic discipline with governmental agencies (granting, public health, regulatory), industry, philanthropy, and patient advocacy groups**



The Essentials Skills of the Translational Research Investigator or Team

**3. The ability to conceptually
design a Phase 3 study to assess
safety and efficacy before
embarking on the project**

Increasing time lag between DISCOVERY AND TRANSLATION: Are you going to wait for decades to get a cure to your ailment ?



- Among 18 non refuted interventions in randomized trials the translation lag was 16.5-22 years (the fastest successful translation occurred for eg. indinavir (Crixivan HIV patients) which took 4 years and Dornase (Pulmozyme CF patients) 5 years)



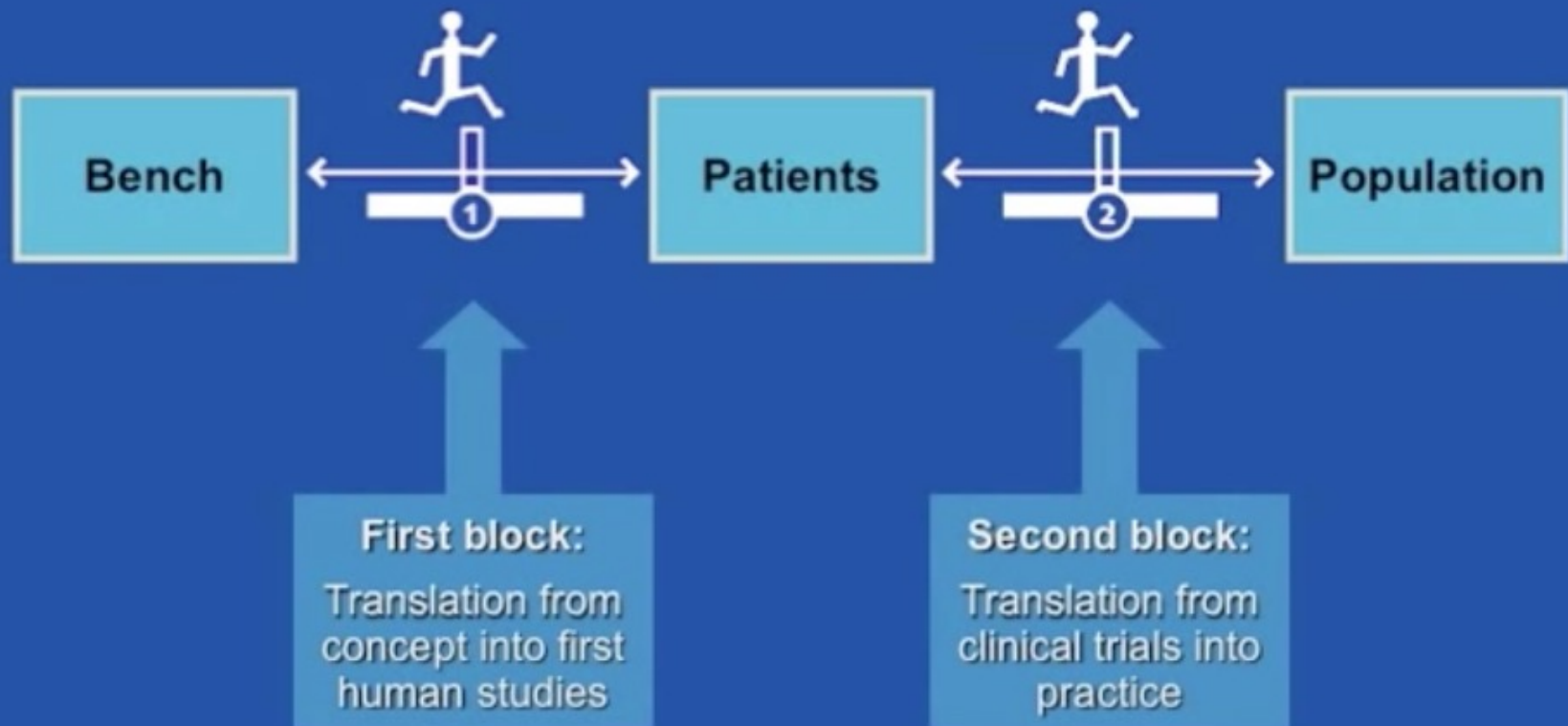


A Translational Block..... Back to 19th century medicine ?



- **Mainstream biomedical research : mutual supports between patients and research scientists : take advantage eg. of *patient derived iPSC* for the identification of novel medicines – therapeutic targets**
- **Shuttling solid/liquid biopsies and biomarkers from bench to bedside and back allow monitoring the efficacy and safety of a medicine in real time**

Translational research_ major road blocks



Healthcare research : complexity increases : crossing the valley of death ?



A chasm has recently opened up between biomedical researchers and the patients in need – the pitfalls

Basic research \longleftrightarrow Clinical research



Cartoonist Nature News and Views 2018

- costs of developing a new medicine mounts today at >1000.000.000 US \$!
 - attrition rate !
 - healthcare providers closed to bankruptcy (failure rate 99% : who wants to invest in this ?)

and healthcare costs exploding : people are tired of paying insurances

- life expectancy scaling up or down ?

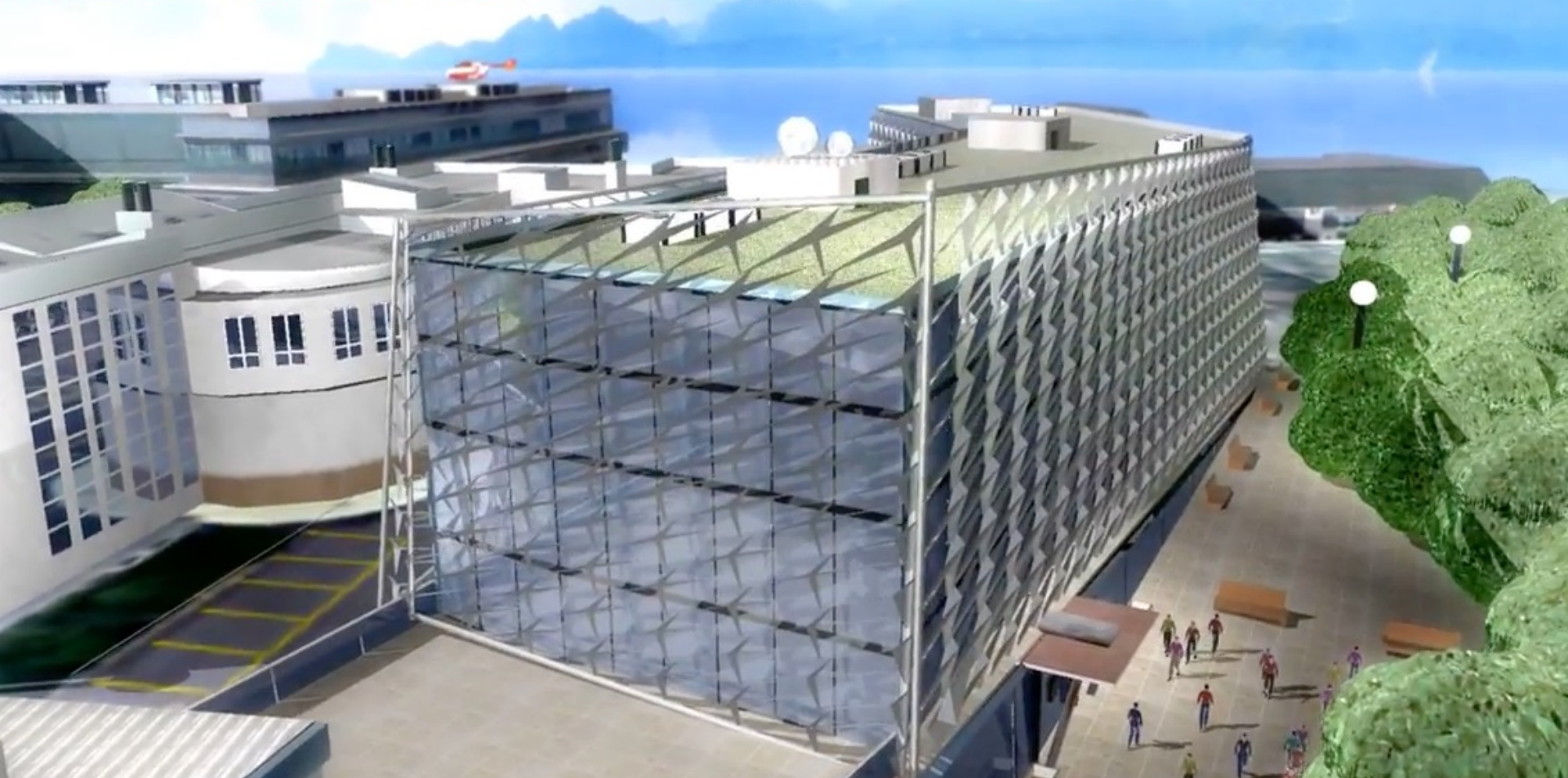
**“CROSSING THE VALLEY OF DEATH” ?...
DO NOW WHAT PATIENTS NEED NEXT !**

- eg. pharmacogenomics allows the stratification of cohorts (eg. deCODE Inc) : who owns your DNA ?
- personalized medicine/precision medicine : solution or next problem?

Lausanne - Switzerland – 2018 - a new center for translational biomedical research in ONCO IMMUNOLOGY : AGORA is born !



Agora Translational Oncology Research Building



KEY CONCEPT : BRINGING TOGETHER BIOMEDICAL SCIENTISTS AND CLINICIANS WHO DO NOT NORMALLY INTERACT WITH ! WIDE OPEN DOORS TO « PERSONALIZED HEALTHCARE » !

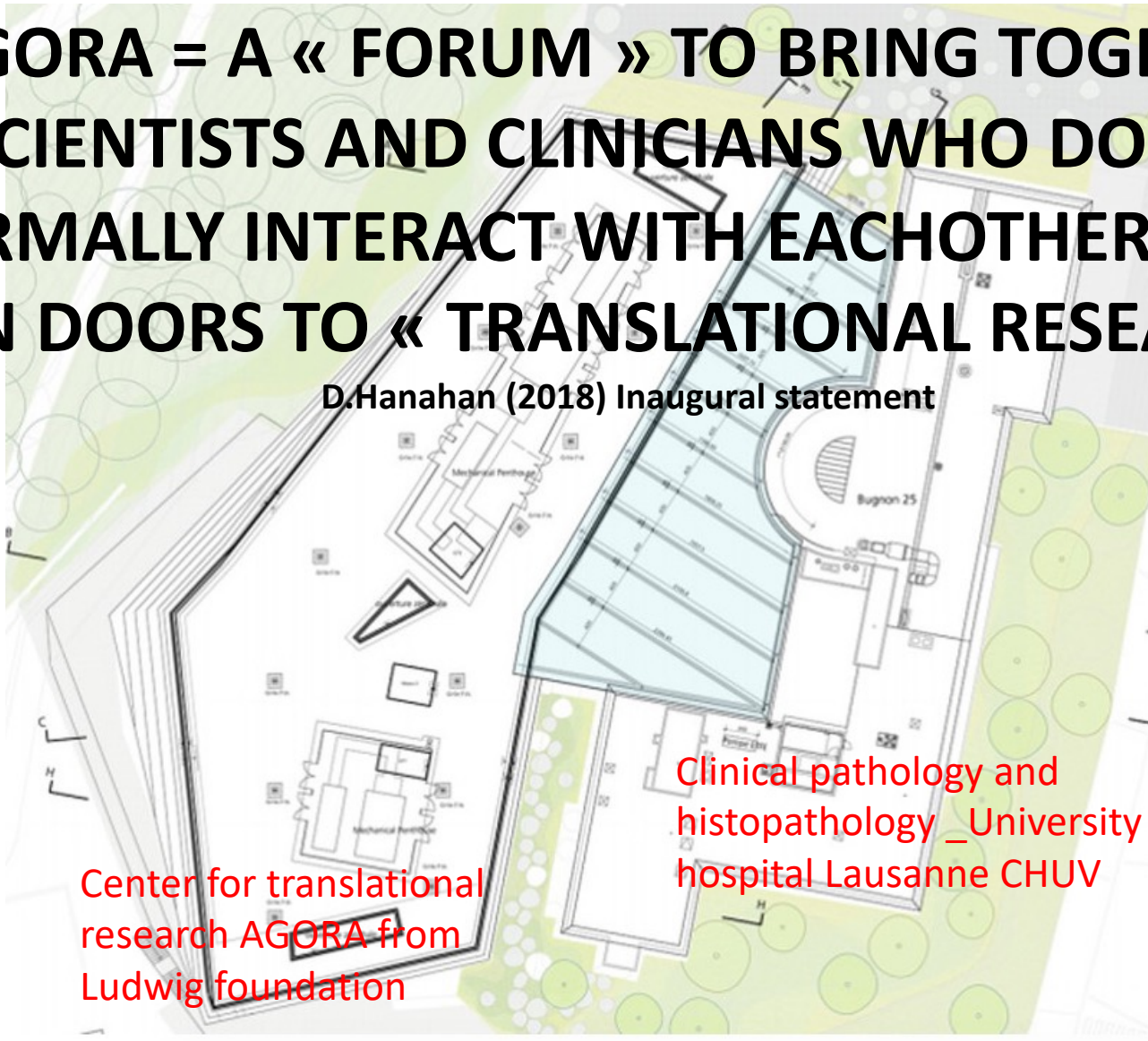


**AGORA = A « FORUM » TO BRING TOGETHER
SCIENTISTS AND CLINICIANS WHO DO NOT
NORMALLY INTERACT WITH EACH OTHER ! WIDE
OPEN DOORS TO « TRANSLATIONAL RESEARCH » !**

D.Hanahan (2018) Inaugural statement

Center for translational
research AGORA from
Ludwig foundation

Clinical pathology and
histopathology _ University
hospital Lausanne CHUV



Pioneering Translational Research : a Basel forum for clinical and exploratory research scientists to meet and discuss

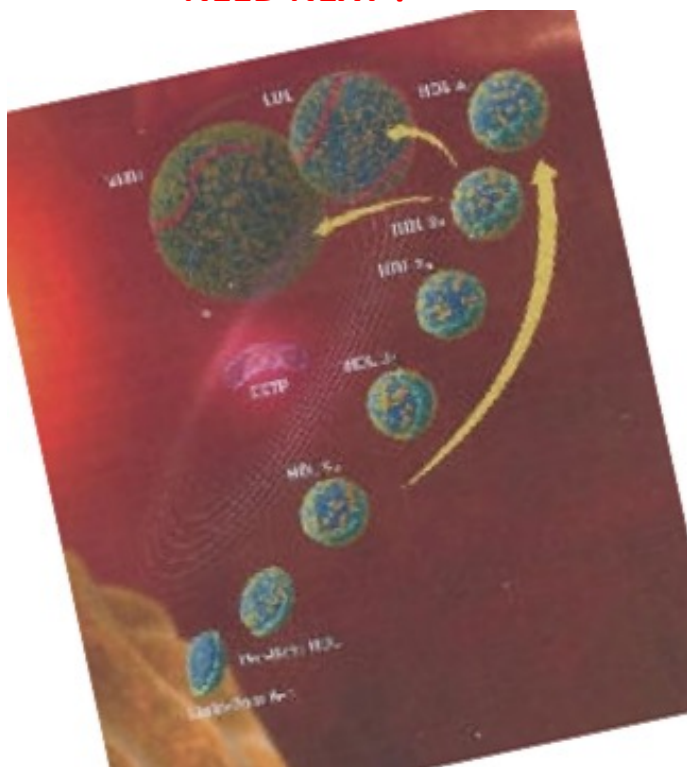


Basic
research



Clinical
research

**DO NOW WHAT PATIENTS
NEED NEXT !**



UNIVERSITÄT BASEL

PharmaCenter



Basel Translational Medicine Seminar

A Forum for Clinical and Basic Scientists to Meet and Discuss

High Density Lipoproteins, Dyslipidemia and Coronary Heart Disease

Welcome, Introduction and Moderation

Prof. Dr. Roger G. Clerc, Hoffmann-LaRoche, Basel, Switzerland

Shaping HDL Functionality with CETP: a new look at the HDL/CETP controversy

Dr. Eric J. Niesor, Hoffmann-LaRoche, Basel, Switzerland

CETP Inhibition and Cardiovascular Prevention

Prof. Dr. Thomas F. Lüscher, Chairman of Cardiology, Cardiovascular Center, University Hospital Zürich, Switzerland

Round Table Discussion with expert panelists

Thursday, Sept 22, 2011, 18:00-19:30, Pharmazentrum Lecture Hall 1

Pioneering Translational Research : a Basel forum for clinical and exploratory research scientists to meet and discuss



Basic research



Clinical research

UNIVERSITÄT BASEL

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Translational
Seminar



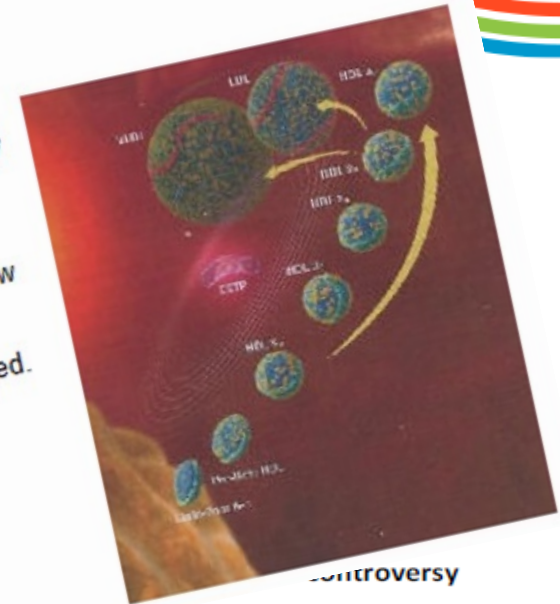
Have you already discovered the Basel Translational Medicine Seminars?

Jul 22, 2011 - pRED Basel

This forum for clinical and basic scientists offers a unique opportunity in the larger Basel area to meet and discuss informally. Organized by the Center of Excellence in Pharma Sciences from the University of Basel it covers the bi-directional efforts (from bench to bedside and vice versa) required to be successful in drug development. Usually there are two speakers:

- A pre-clinical, summarizing the pre-clinical data of a drug discovery program and emphasizing how clinical aspects/observations already impact the program at early and later stages and
- a clinical scientist presenting how a proof-of-concept study in humans is designed and conducted.

A large part of the the forum is dedicated to informal exchanges with expert panelists.
Taking place every third Thursday a month, please join us from 6:00 to 7:30 pm at the PharmaCenter, Klingelbergstr. 50-70 in Basel.



Basel, Switzerland

CETP Inhibition and Cardiovascular Prevention

Prof. Dr. Thomas F. Lüscher, Chairman of Cardiology, Cardiovascular Center, University Hospital Zürich, Switzerland

Round Table Discussion with expert panelists

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- **Criticism to translational research : many medicines arose as a move of serendipity, fortuitously : well known examples are natural products, macrolides, antibiotics such as penicilin, cyclosporin, diazepam, vitamins etc. for which no specific therapeutic potential/target were initially allocated**
- **Counter argument : an emerging new discipline with demonstrated potential to getting benefits for the patients by getting rid of silos between preclinical and clinical science**

Translational research – yesterday and today



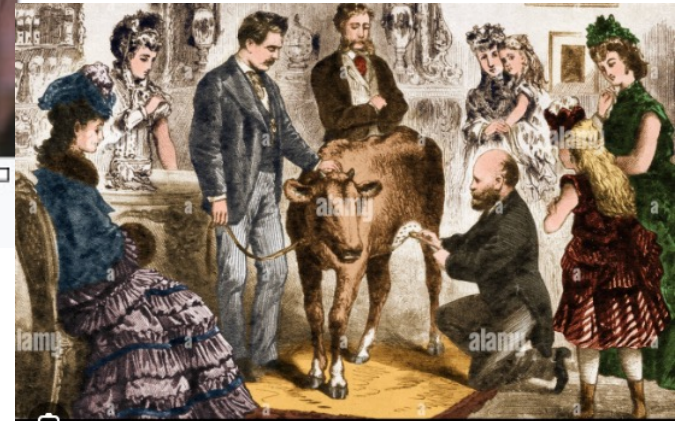
DEBATE : would you consider E.Jenner, L.Pasteur as precursors of translational medicine ?



**WHO : highly contagious
SMALLPOX was almost
eradicated in october 1977**



Jeune fille du Bangladesh atteinte de variole en 1973



**Edward Jenner
1749-1823**



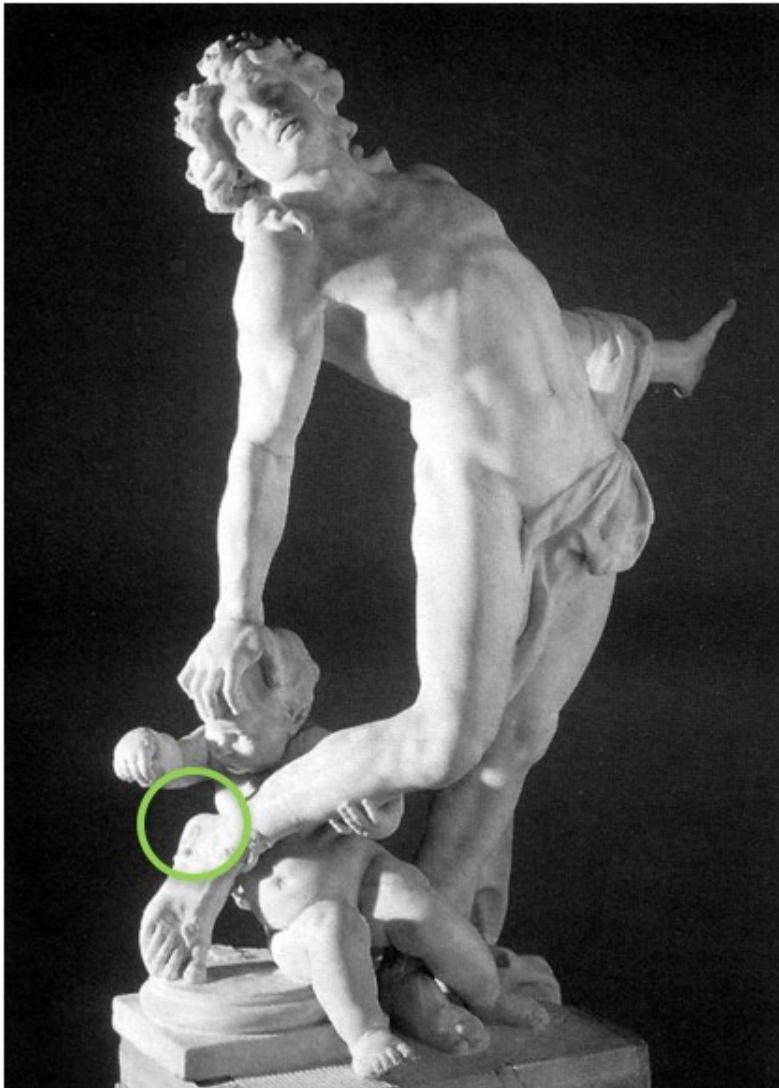


Failed example of translational research in recent biomedical research programs are several among which eg. the **monoclonal antibodies to amyloid-a beta particles**, accumulating in Alzheimer patients dramatically failing after >20 years preclinical and clinical research activities

Nevertheless biomedical exploratory research proposals as of today are expected to include a clinical relevance, a close relationship with patient in need, hence a true **translational research program**



Cancer → > 250 devastating diseases

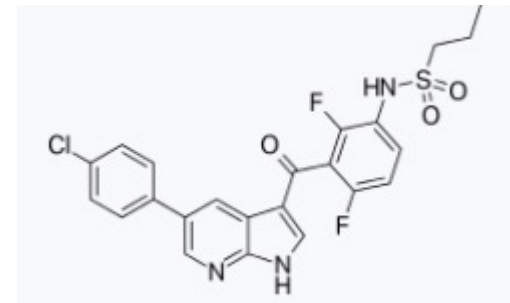


We dream of

- **Achilles' heels**
« THE vulnerable spot »
- **Magic bullets**
« THE innovative target »
- **Miracle Drugs**
« THE precision medicine »

Translational research : evasive cancer drug resistance to targeted therapies : a recurrent theme

Clinical efficacy of Vemurafenib



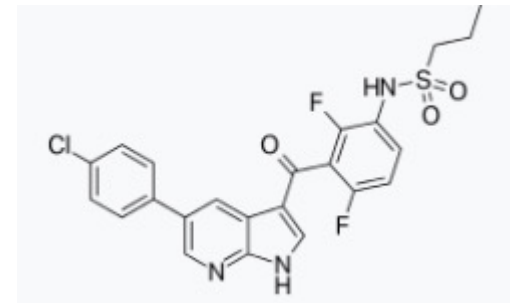
B-RAF kinase inhibitor Vemurafenib

- Vemurafenib interrupts the B-Raf/MEK step in Erk pathway if B-RAF has V600E mutations (BRAF inhibitor)
- Target the BRAF V600E mutation (FDA approved in 2011)
- Metastatic melanoma (most common mutation V600E)
- Aggressive form of skin cancer
- Programmed cell death in melanoma cell lines
- **EVASIVE CANCER DRUG RESISTANCE !**



Translational research : evasive cancer drug resistance to targeted therapies : a recurrent theme

Clinical efficacy of Vemurafenib



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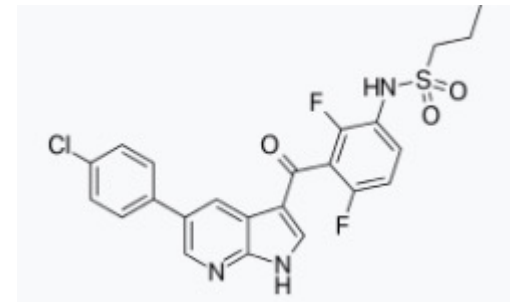
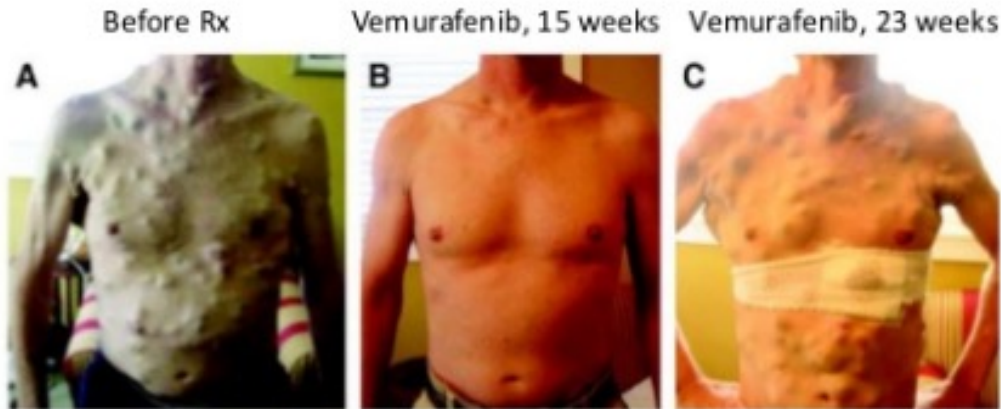
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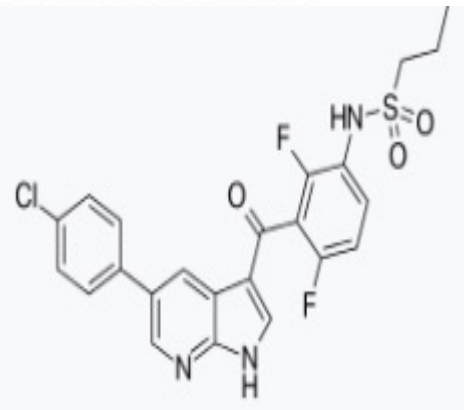
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“CROSSING THE VALLEY OF DEATH” ?...

Clinical efficacy of Vemurafenib



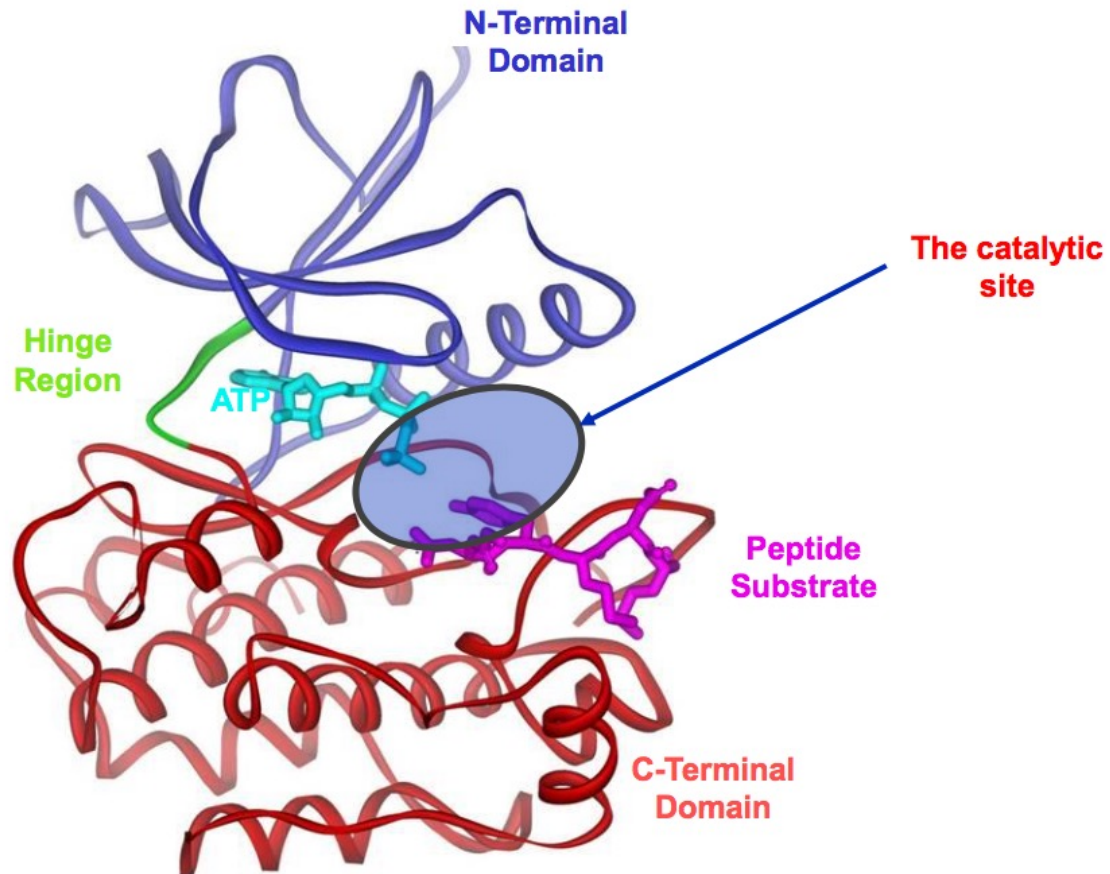
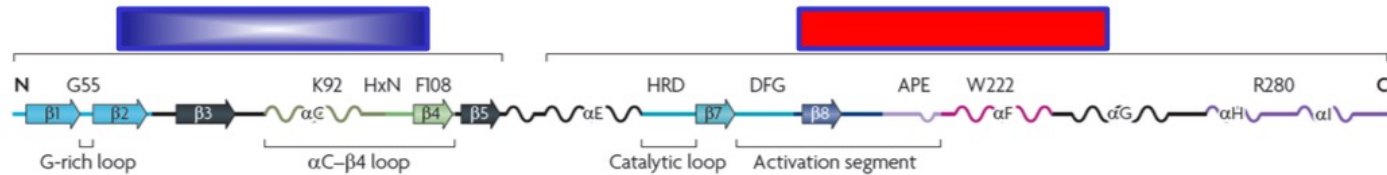
B-RAF kinase inhibitor Vemurafenib

- Vemurafenib interrupts the B-Raf/MEK step in Erk pathway if B-RAF serine threonine kinase receptor has V600E mutations
- TARGET THE BRAF V600E MUTATION (FDA APPROVED IN 2011)
- Metastatic melanoma (mean overall survival 2-3-months)
- Aggressive form of skin cancer
- Programmed cell death in melanoma cell lines
- Evasive cancer drug resistance !

Most cancer medicines are targeting protein kinases a prototype of a druggable therapeutic target



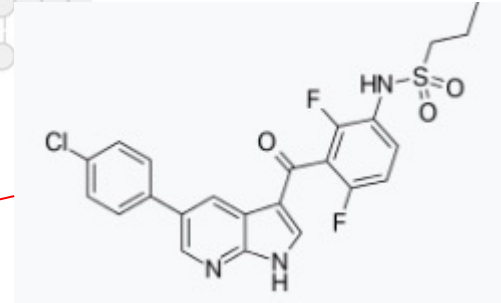
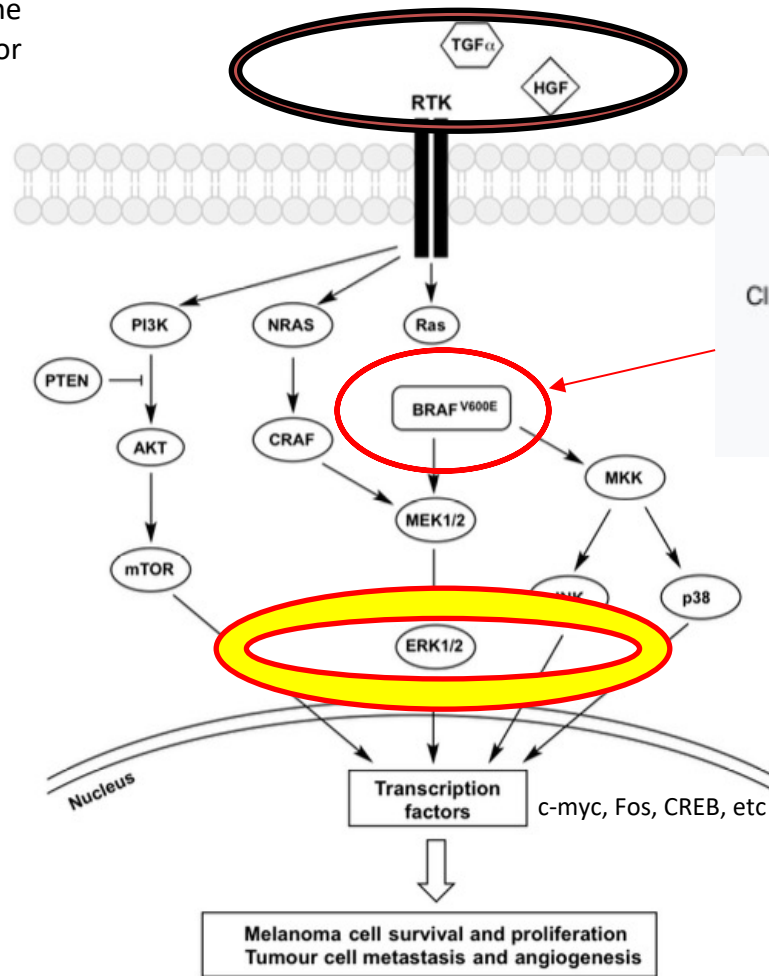
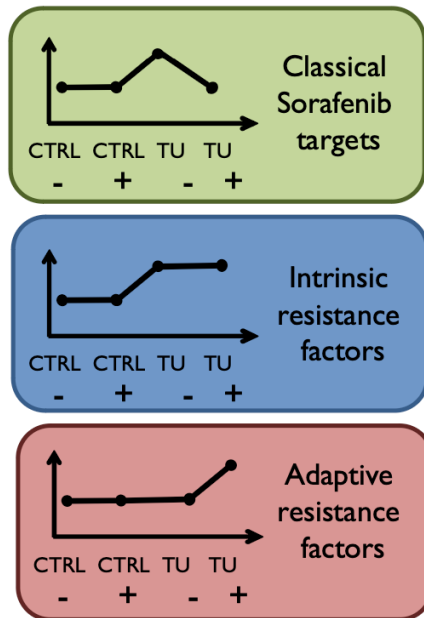
Kinase Domain = Catalytic Site



Translational Research: evasive cancer drug resistance : a recurrent theme with melanoma patients



TGF-alpha plays a role in the processes involved with tumor initiation and tumor growth.



BRAF mutations have been described affecting BRAF gene: gene copy number gain or amplification of BRAF, and alternative splicing of BRAF resulting in overexpression and leading to reactivation of ERK independently of RAS

Figure 1. Mechanisms of BRAFi resistance converge on constitutive ERK signalling. Regardless of its upstream activator RAS, BRAF^{V600E} is constantly activated, and vemurafenib treatment was shown to inhibit the kinase. However, the increased secretion of growth factors (HGF and TGF-α) coupled with the overexpression of receptors (PDGFRβ, IGFR1, EGFR and c-Met) trigger the activation of signalling

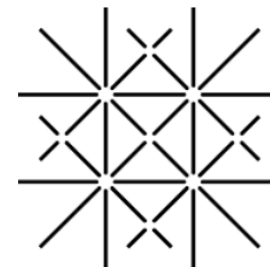
TRANSLATIONAL RESEARCH IN ACTION: quantitative phosphoproteomics allows to trace evasive cancer drug resistance



Prof M. Hall
Yeast geneticist
Lasker 2017

Prof M Heim
clinician
hepato oncologist

FROM BENCH TO BEDSIDE AND BACK



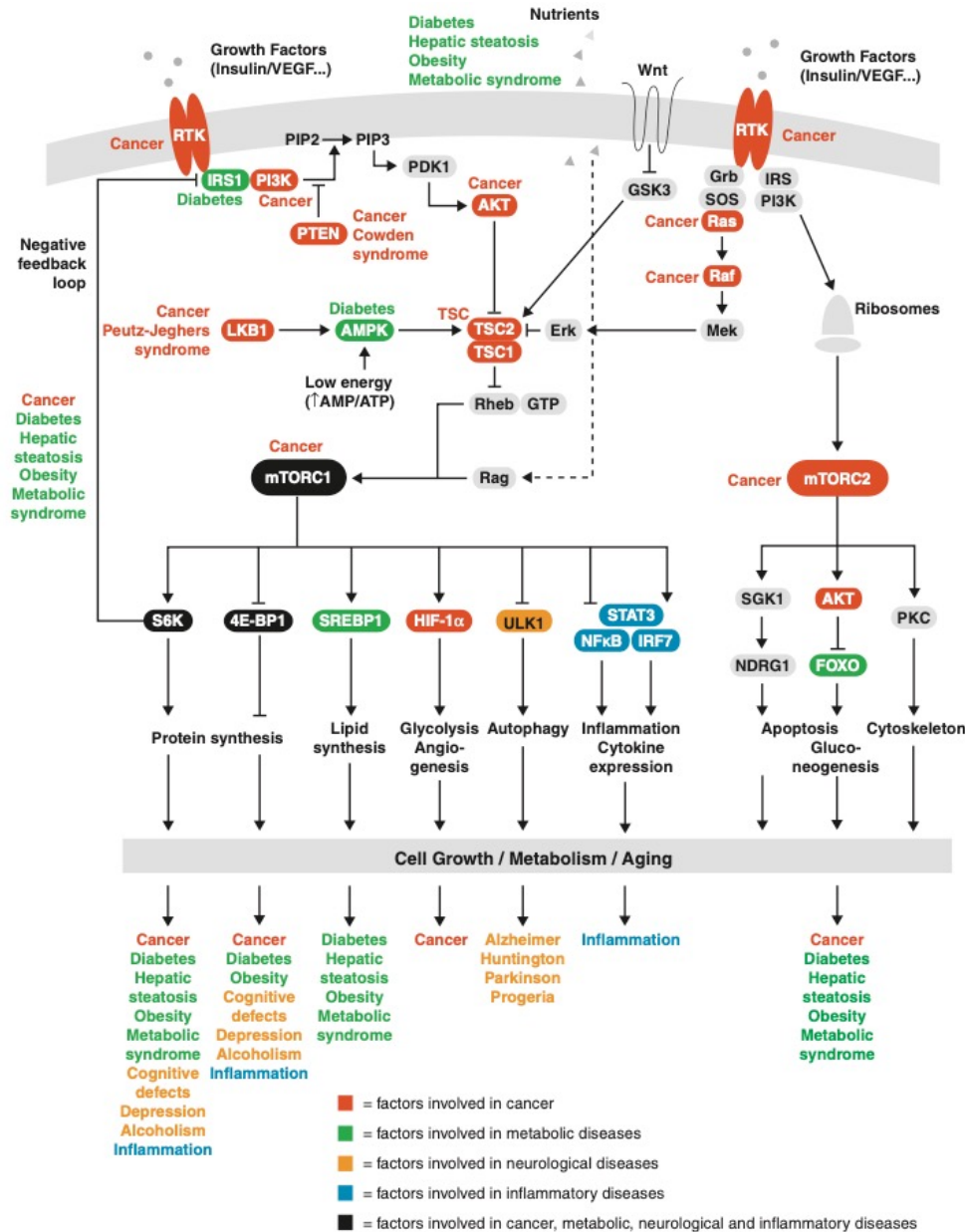
UNI
BASEL

BIOZENTRUM

Universität Basel
The Center for
Molecular Life Sciences



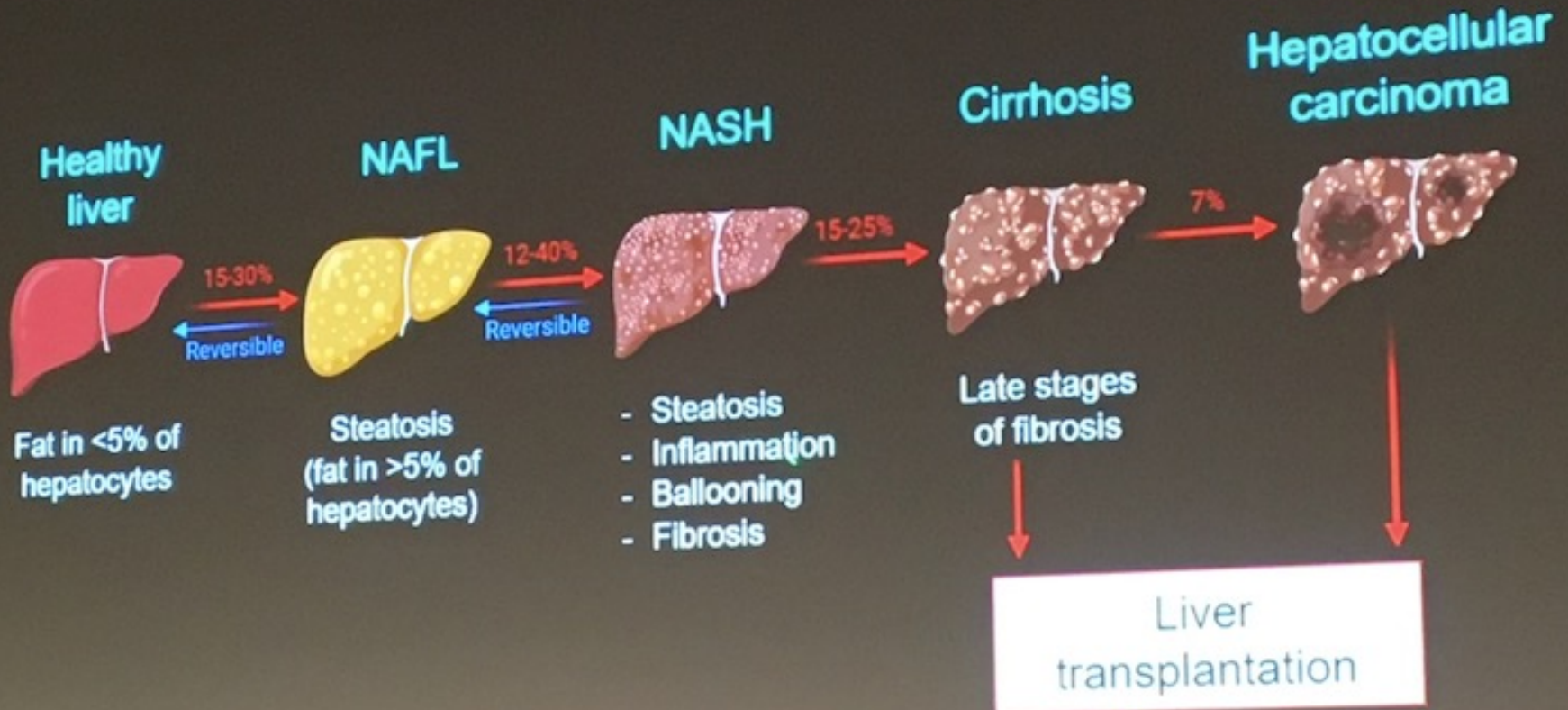
Translational Research: mTOR pathway and cancer resistance



Red box = factors involved in cancer



Liver pathophysiology of non-alcoholic fatty liver disease (NAFLD)



Translational Research: longitudinal studies allows to trace in patients evasive cancer drug resistance



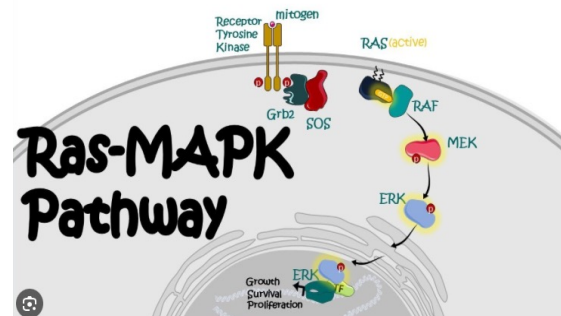
1. HOW DOES THE ACTIVITY OF CANCER SIGNALING PATHWAY CHANGE DURING THERAPY ?

Quantitative proteomics and phosphoproteomics on serial tumor biopsies from a sorafenib-treated HCC patient

Eva Dazert^a, Marco Colombi^a, Tujana Boldanova^b, Suzette Moes^a, David Adametz^c, Luca Quagliata^d, Volker Roth^c, Luigi Terracciano^d, Markus H. Heim^b, Paul Jenoe^a, and Michael N. Hall^{a,1}

^aBiozentrum, University of Basel, 4056 Basel, Switzerland; ^bDepartment of Biomedicine, University Hospital Basel, 4031 Basel, Switzerland; ^cMathematics and Computer Science, University of Basel, 4051 Basel, Switzerland; and ^dMolecular Pathology, University Hospital Basel, 4056 Basel, Switzerland

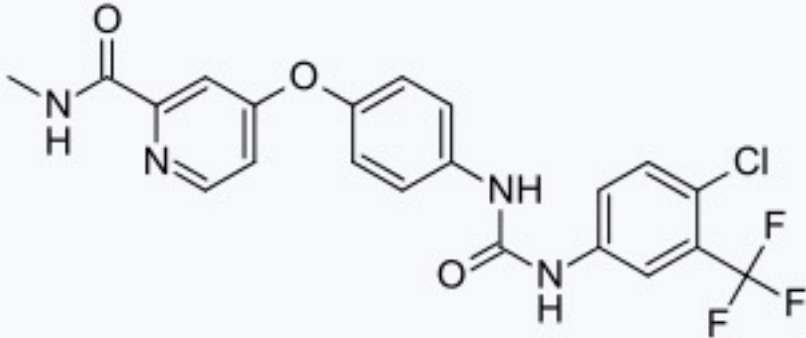
2. CAN CHANGES IN PROTEINS p-SITES BE LINKED TO TUMOR PROGRESSION OR RESISTANCE ?



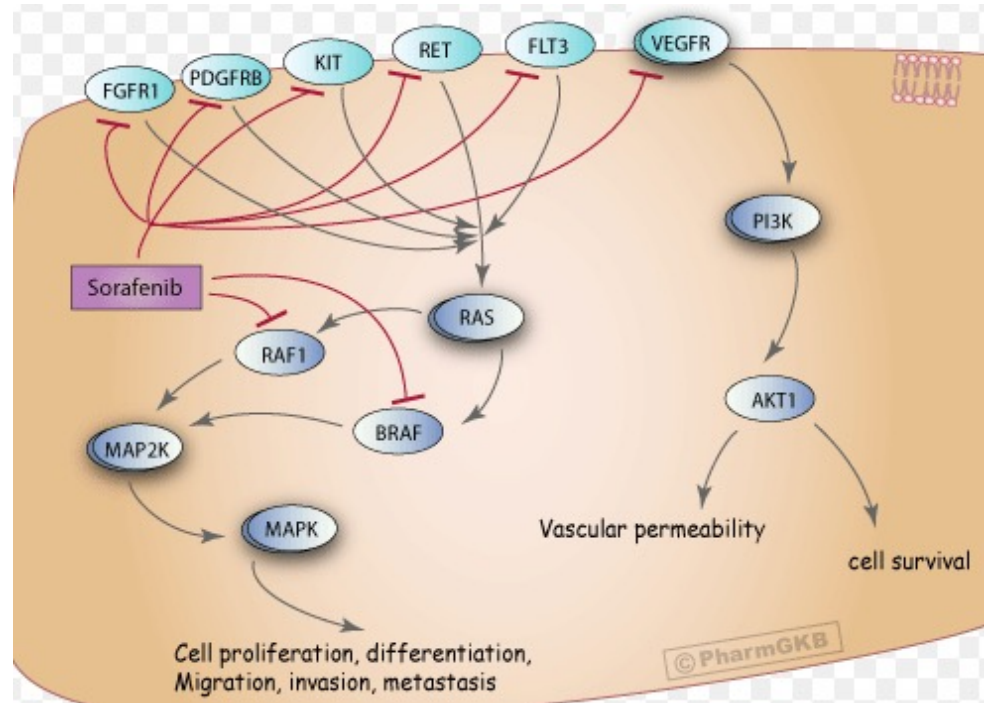
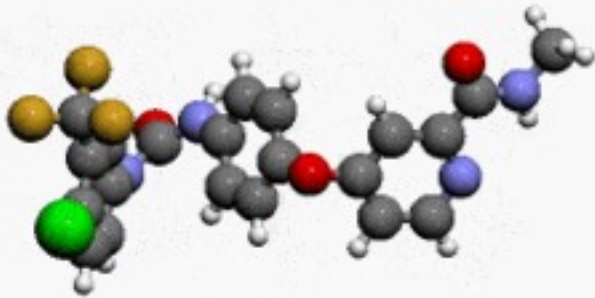
Multikinase inhibitor sorafenib as exemplary pioneer experiment



HEPATOCELLULAR CARCINOMA HCC RESISTANCE TO MULTI KINASE INHIBITOR



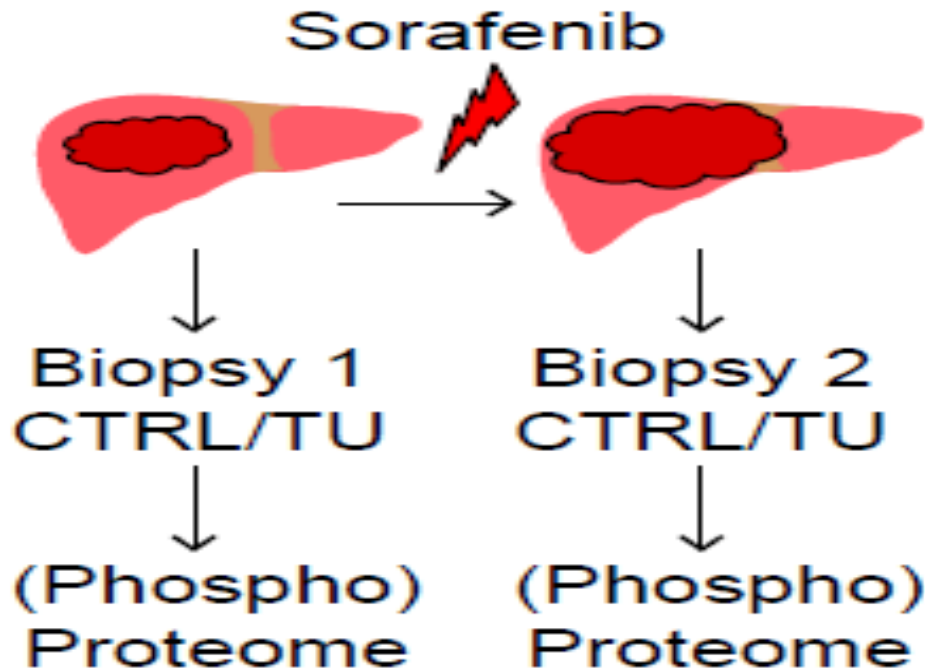
750,000 HCC new cases per year



Poor prognosis for patients : 1y survival (liver transplants excl)
Sorafenib median patient survival by 3 months

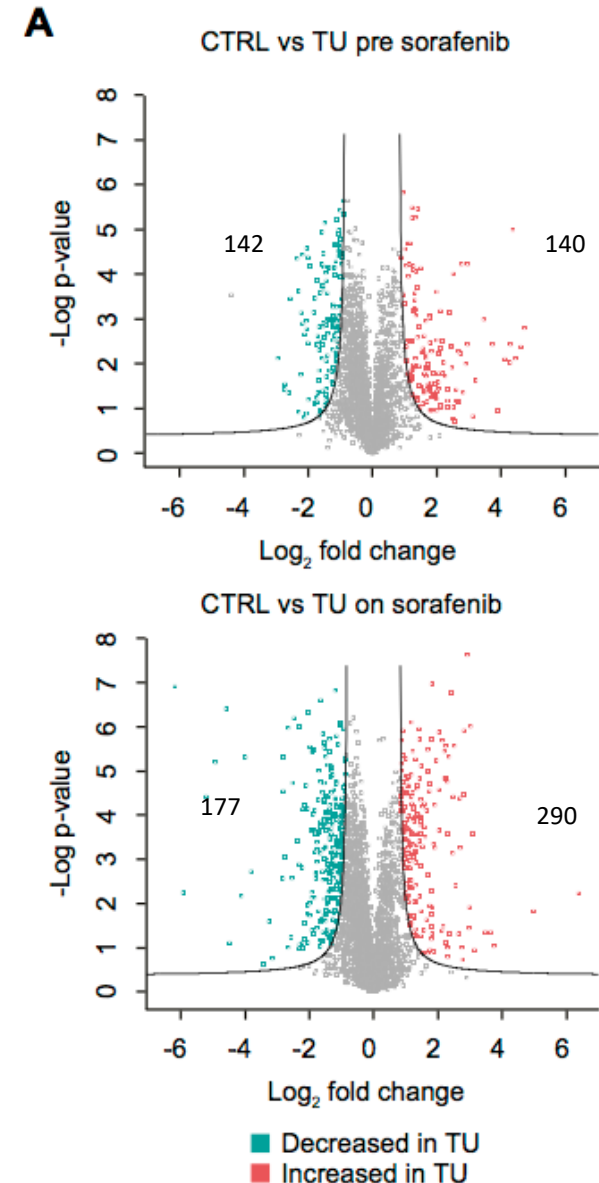


Translational Research: quantitative phosphoproteomics allows to trace evasive cancer drug resistance

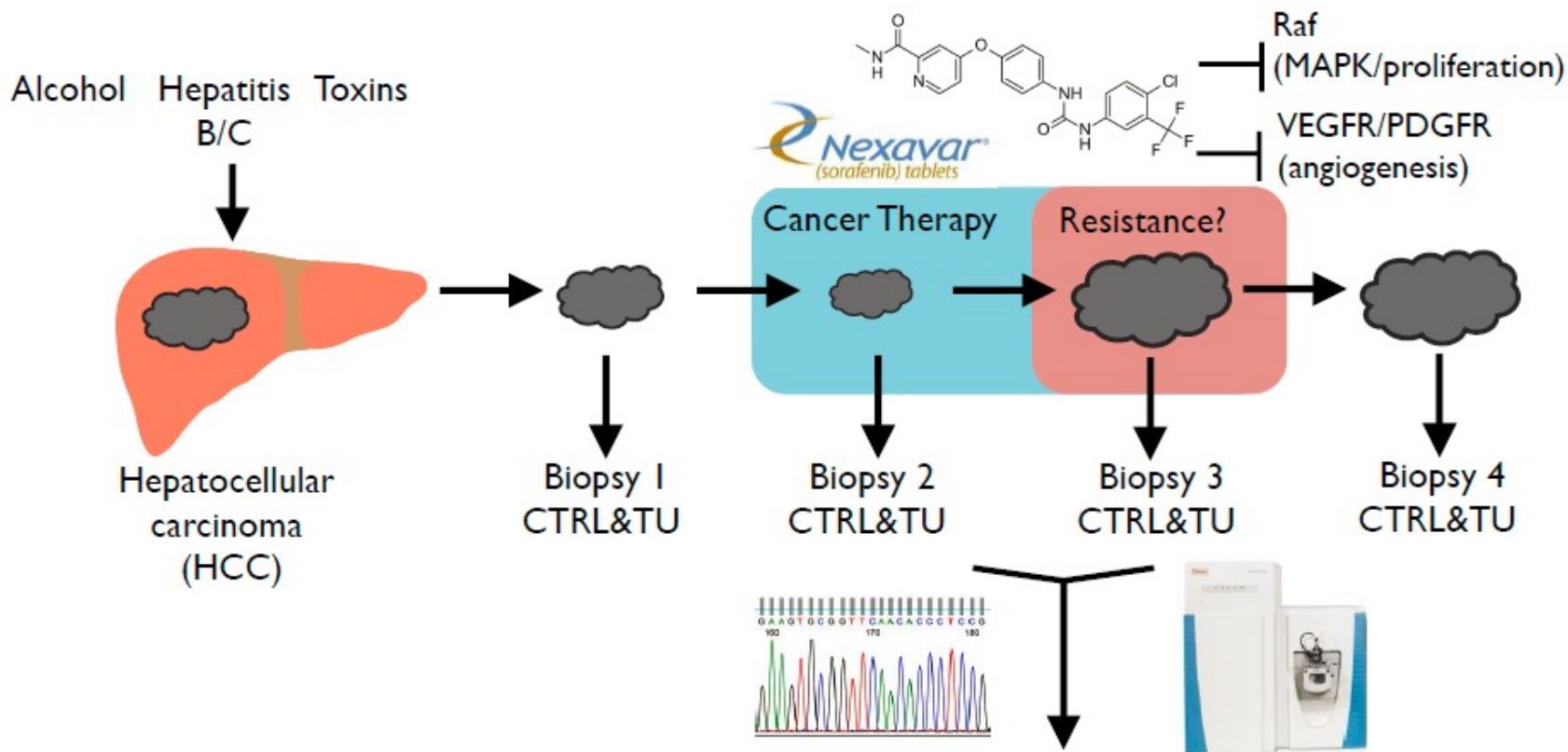


liver cancer tumor vs healthy part of the patient liver

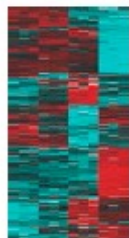
Drug cocktail can be translated to the clinic for precision therapy upon quantitative phosphoproteomics of patient needle biopsies (not resected tumors)



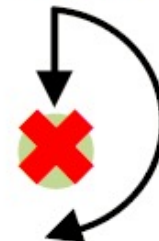
«Hall – Heim» Basel translational research: longitudinal studies allows to trace in patients evasive cancer drug resistance



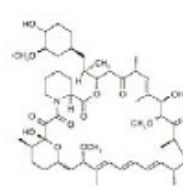
Biomarker



Resistance factors



Drug targets



Precision medicine



1. How does the activity of cancer signaling pathways change during therapy?

2. Can changes in proteins/p-sites be linked to tumor progression or resistance?

Translational Research: quantitative phosphoproteomics allows to trace evasive cancer drug resistance

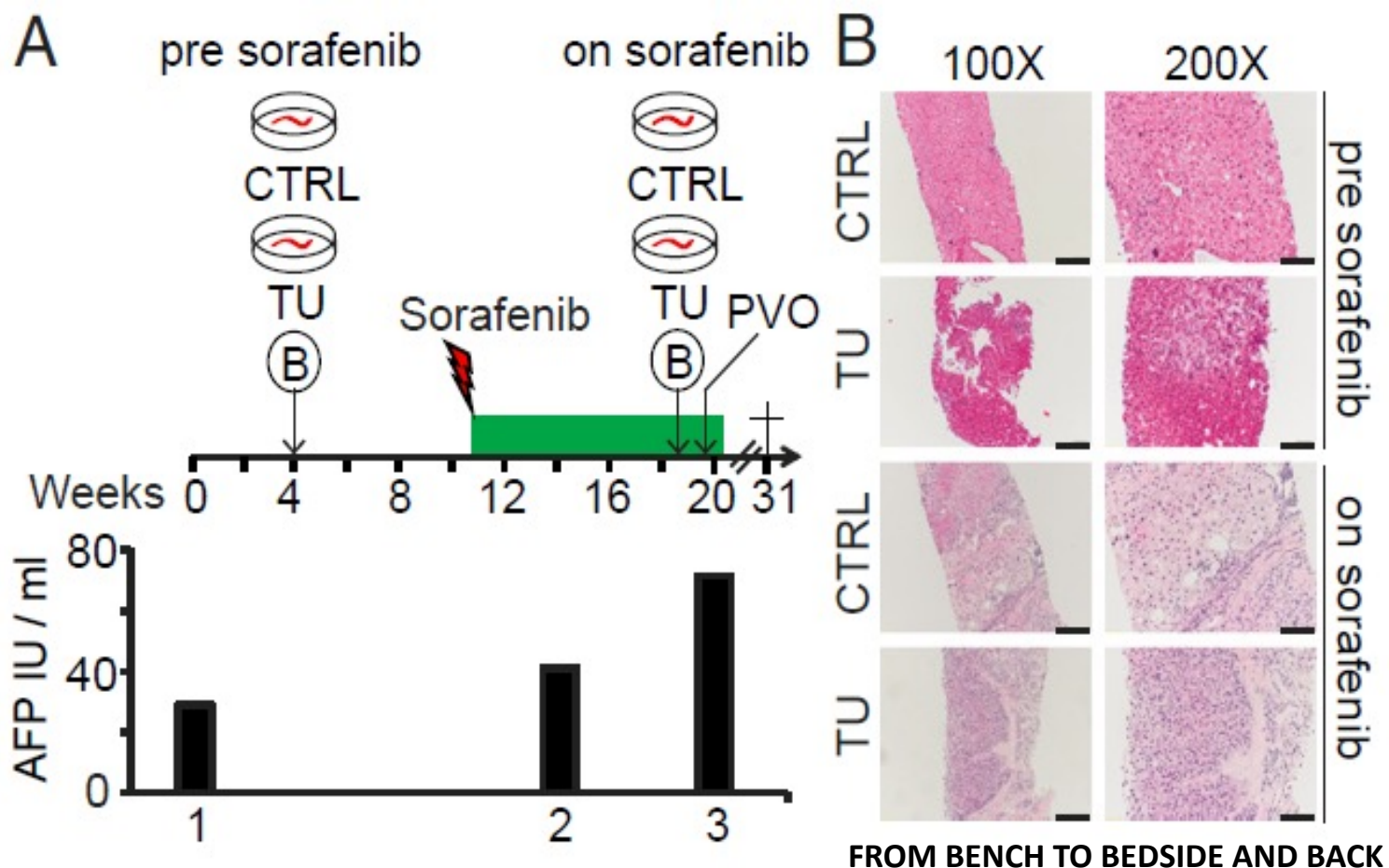


Fig. 2. Clinical data of the sorafenib-treated HCC patient. (A) Clinical history of the sorafenib-treated HCC patient. The green bar indicates sorafenib treatment. PVO, portal vein occlusion. (B) H&E staining of HCC patient biopsies. (Scale bars: 100× magnification, 200 μ m; 200× magnification, 100 μ m.)

Translational Biomedical Research: a challenge at the wake of tracing evasive cancer drug resistance from patient tumours



**CANCER PATIENT PERSONALIZED
INNOVATIVE MEDICINE WILL BE
SOLVED BY BIOPSY (MOLECULAR
PATHOLOGY SCREENS) AND NOT
MERELY BY DNA/RNA SEQ !**

(my personal opinion)

Future : suitable medicines (drug cocktails) can be translated to the clinic for precision therapy upon quantitative phosphoproteomics of patient biopsies

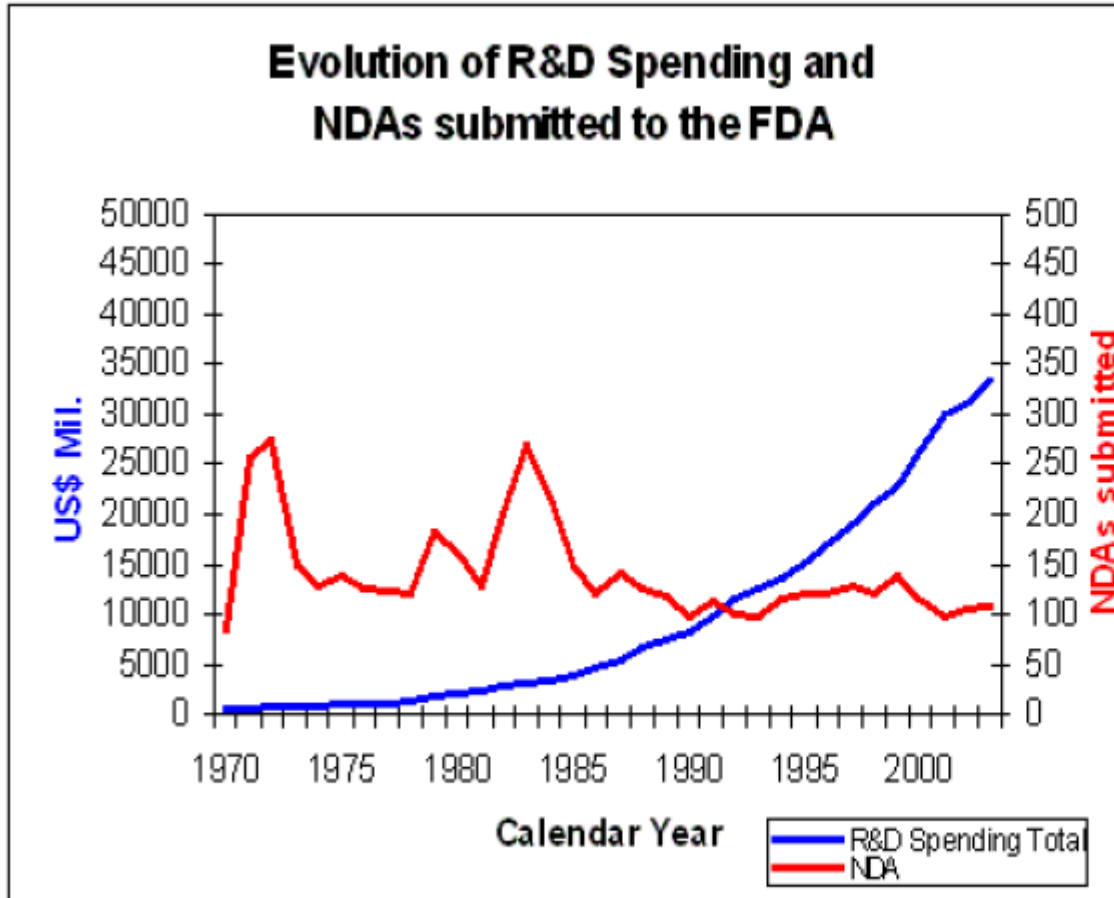
**SOLID TUMOR CANCER METASTASES MAY NEVER BEEN CURED FULLY ERADICATED,
HOWEVER HOPEFULLY REDUCED TO A CHRONIC DISEASE !**



- Translational research is meant to convert the valley of death into the Garden of Eden ? More efficient healthcare ?



Complexity increases_ crossing the valley of death ?



- Investment of Pharma has been continuously increasing
- This did not translate into a parallel increase of new drug applications (NDA) to regulatory authorities (FDA)

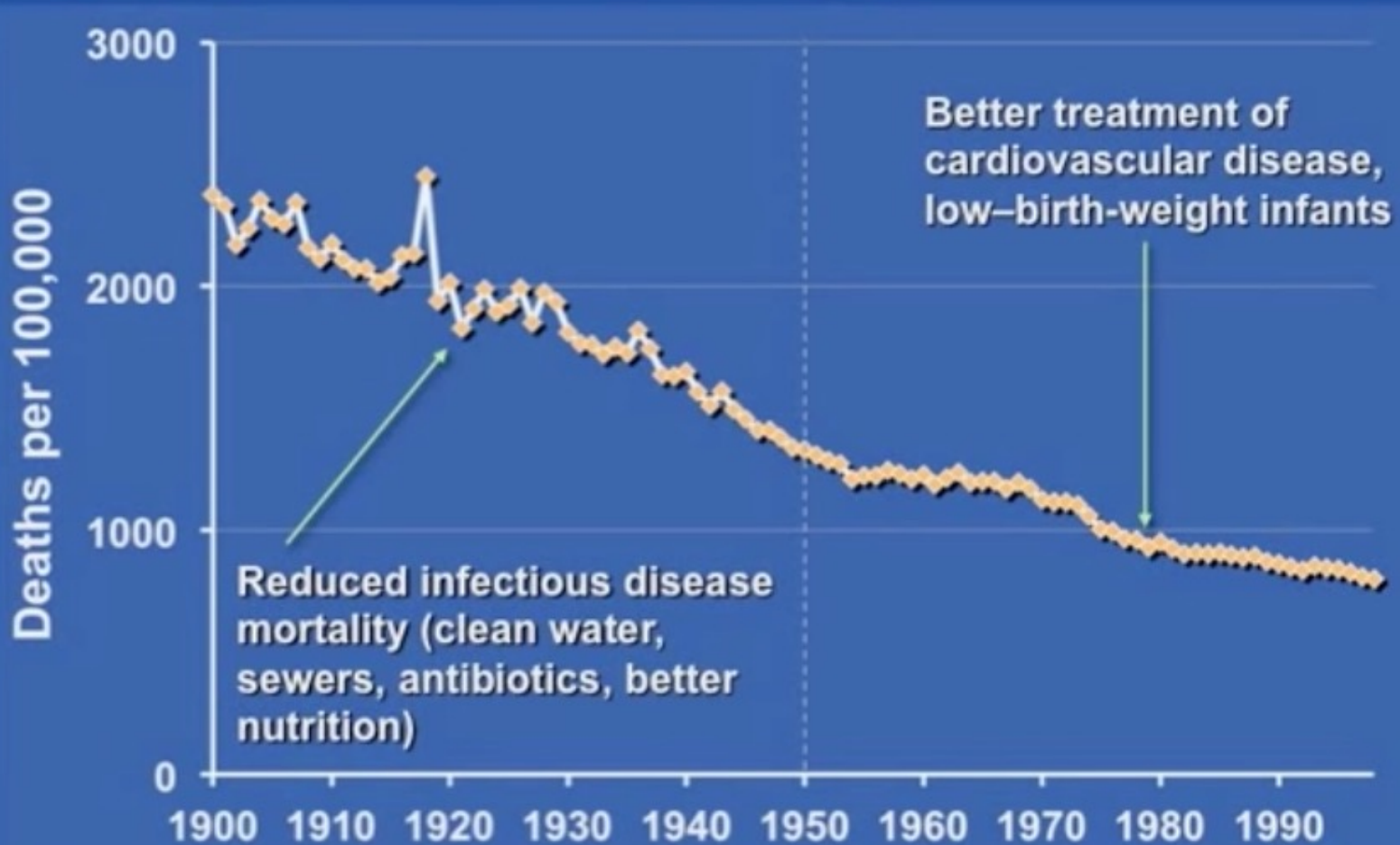
<http://www.vanosta.be/hcphrm.htm>

20th century healthcare remit _ the good news

How is your 21st century research going to keep up with this trend ?



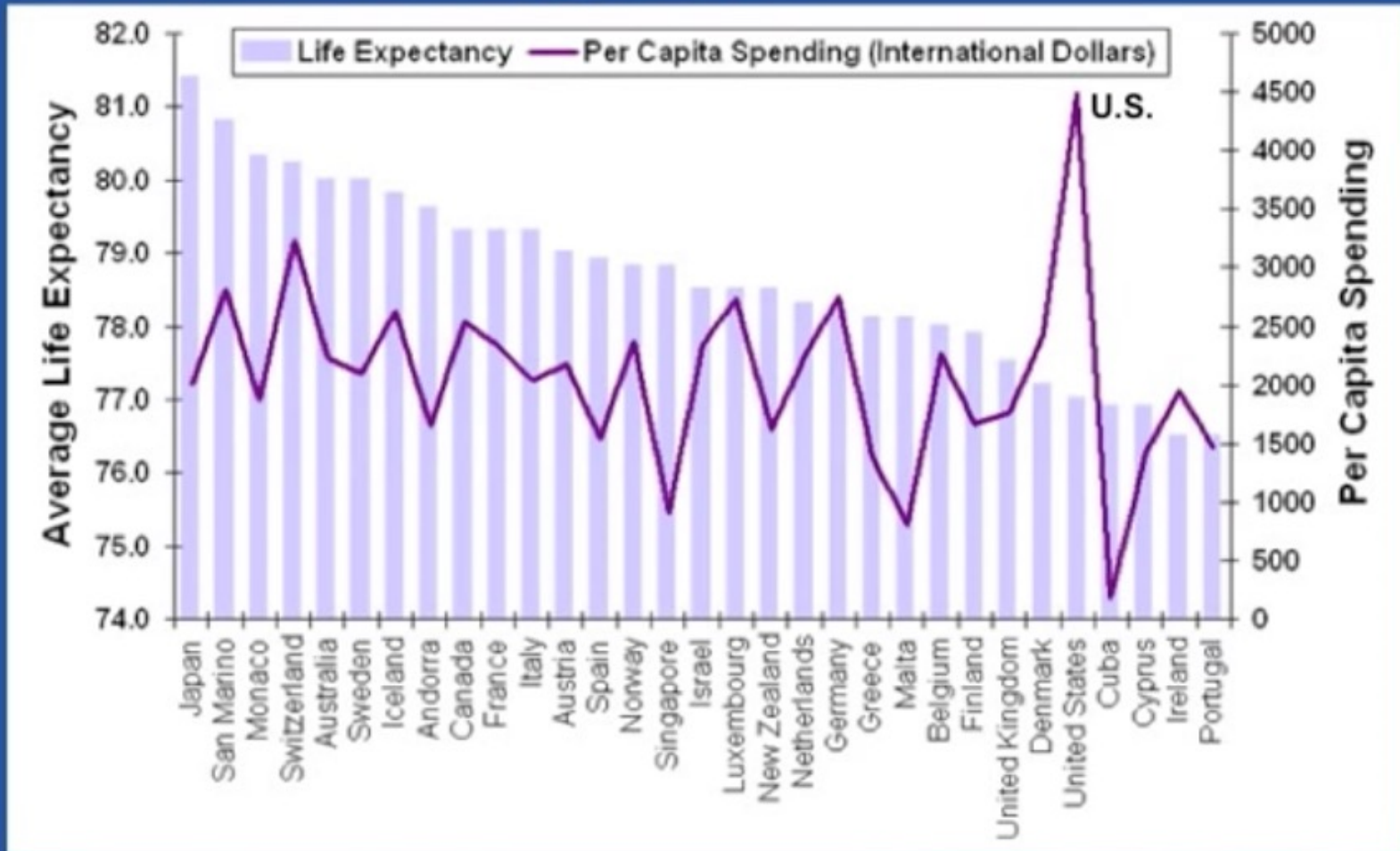
Mortality in the 20th Century



At what costs : healthcare costs are exploding _ the bad news



The Cost of a Long Life



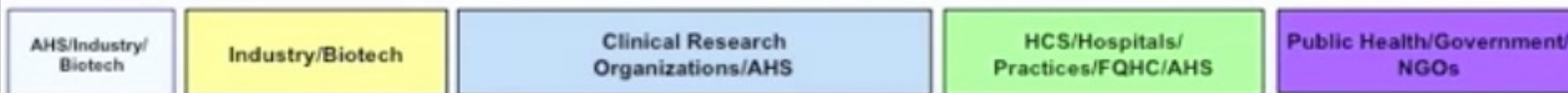
Traditional healthcare research _ ancient research programs a silo fighting recipe !



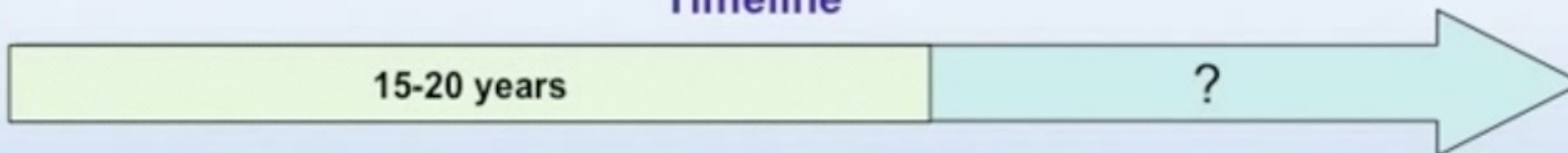
A Fragmented System with Silos and Barriers



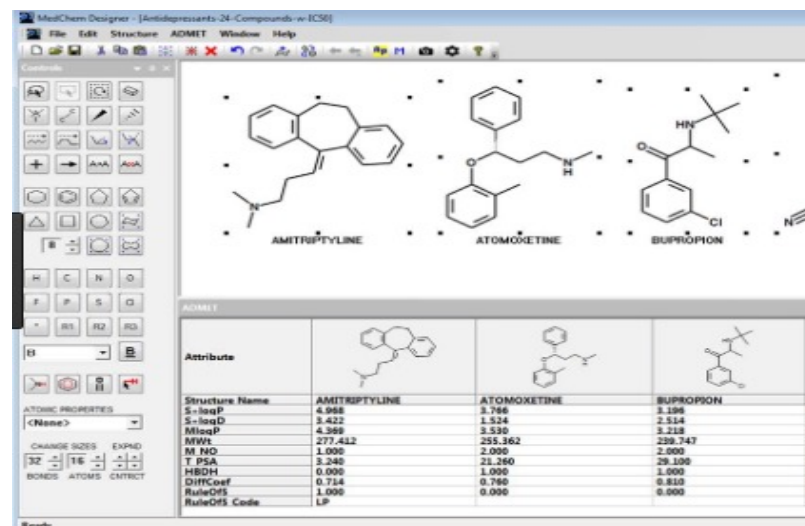
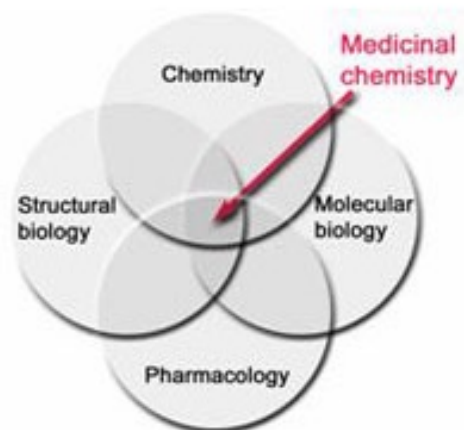
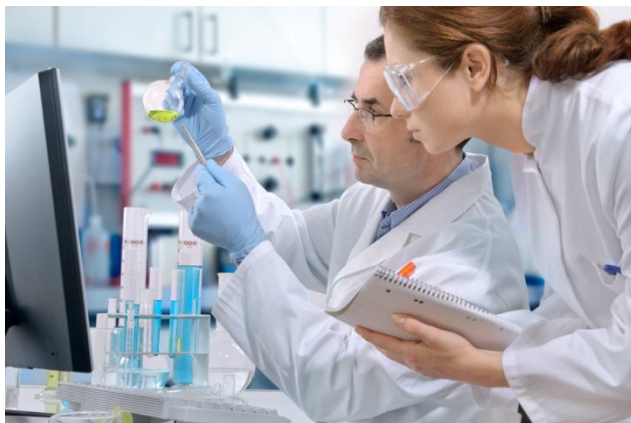
Current State Entities



Timeline



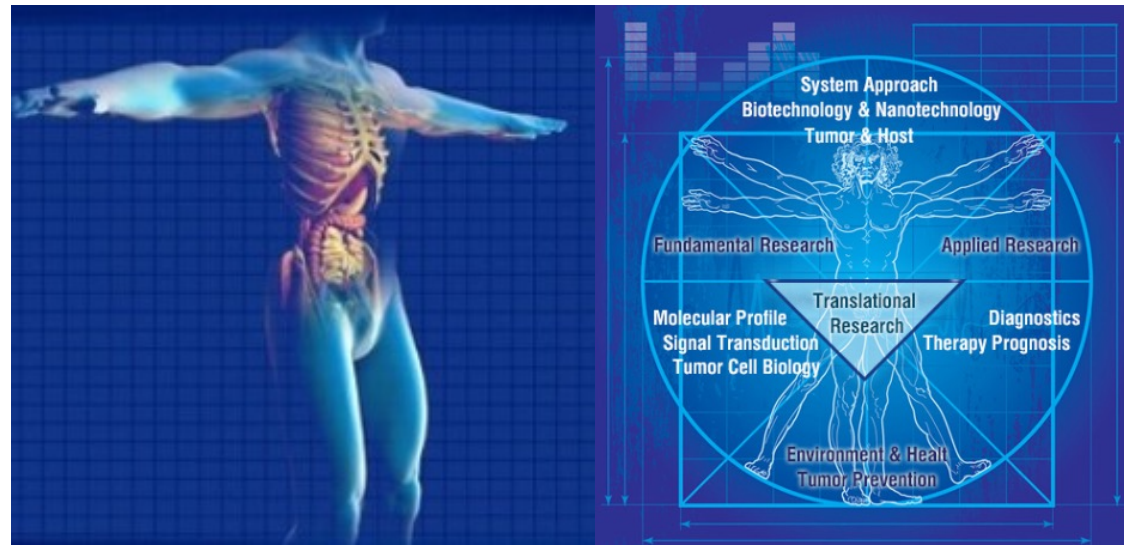
Translational research – challenges and critics



Biomedical research scientists (the traditional team including medicinal chemists, pharmacologists and mol biologists) heavily focused on animal pharm models for validating an innovative medicine ??



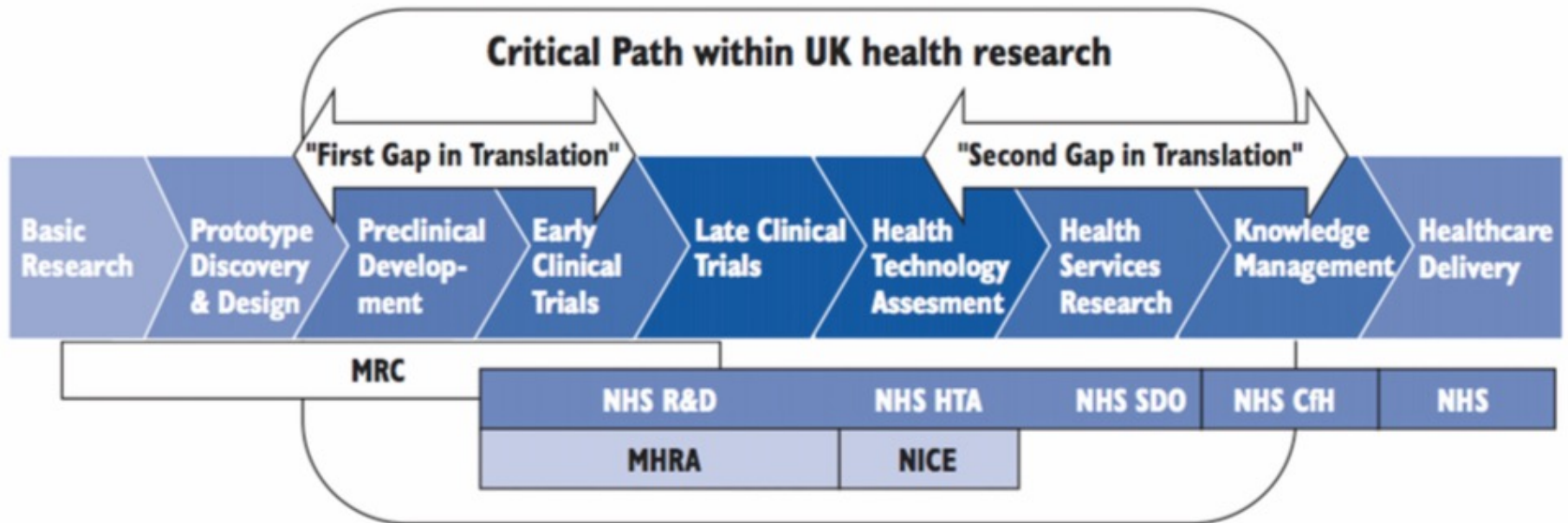
- Making unrealistic promises for quick discoveries in rodents and cures may damage the credibility of science in the eyes of the patients (info vs intox)



Translational research : the road blocks



From bench to bedside and back – healthcare improvement ?

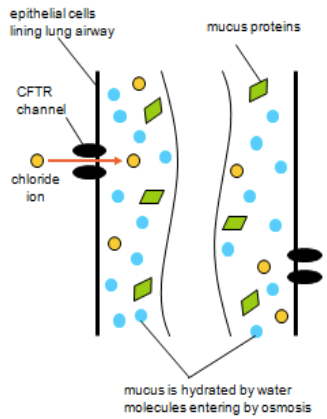


PATIENTS SUPPORTS, GUIDES TRANSLATIONAL RESEARCH AT MAINLY TWO STEPS OF THE DEVELOPMENT OF INNOVATIVE MEDICINES

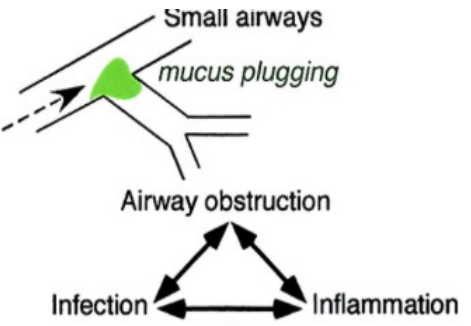
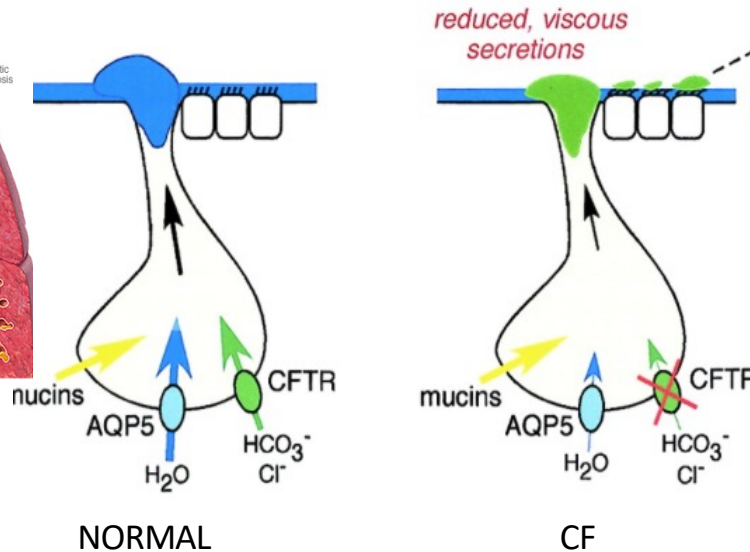
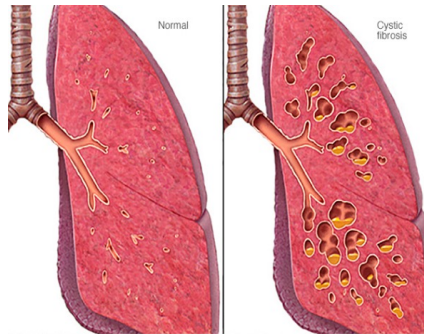
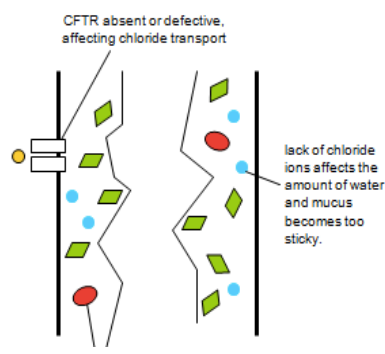
Cystic fibrosis – sticky mucus trap pathogens in the airway



Lung airway of unaffected person

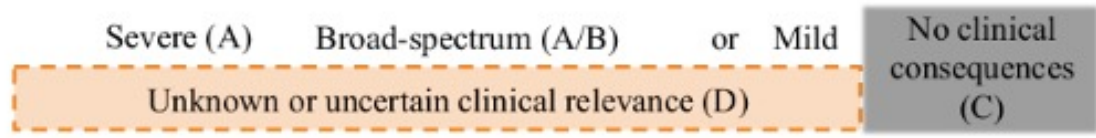


Lung airway of person with cystic fibrosis

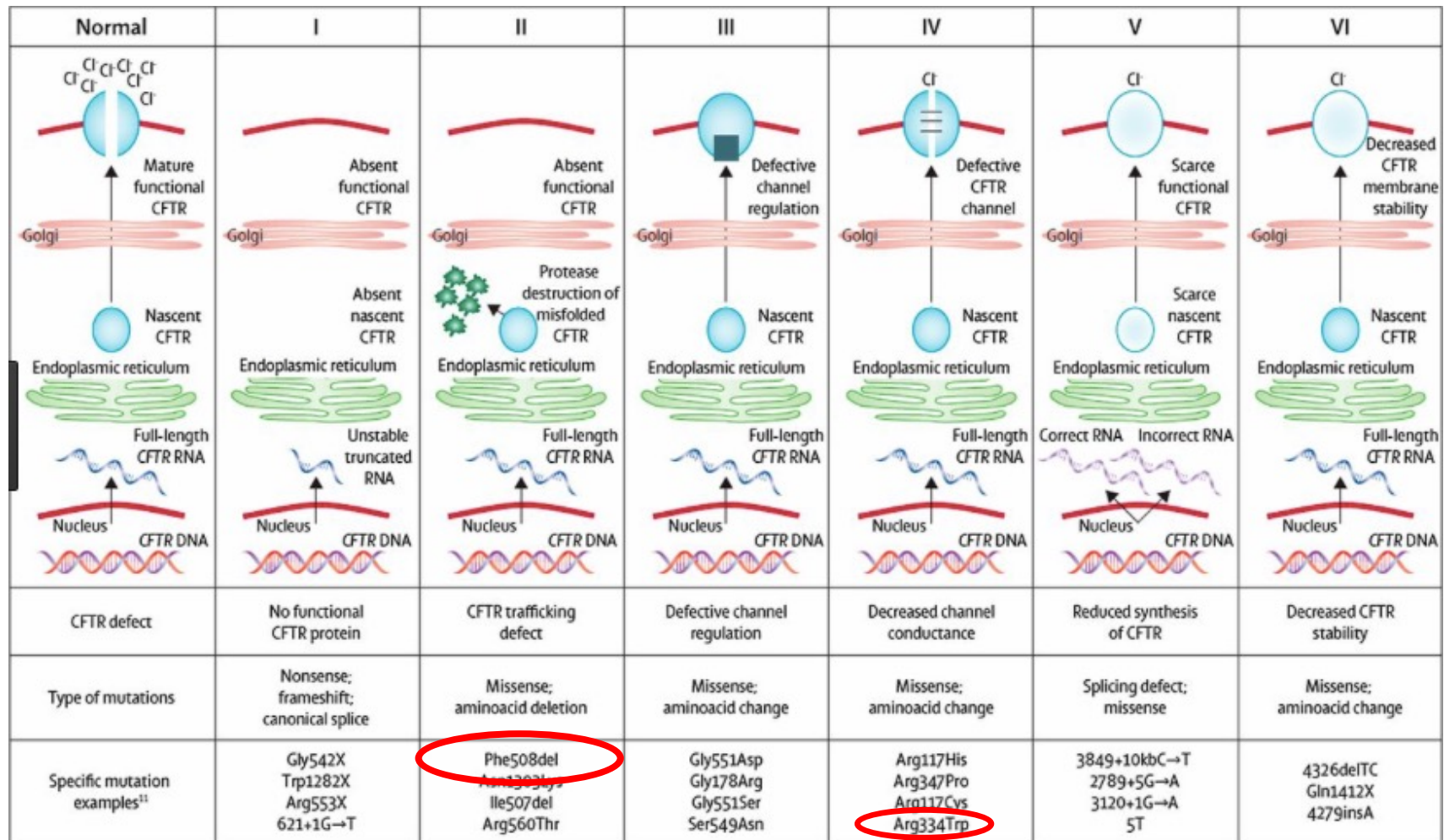


Reduced lung function
antimicrobials
Ibuprofen NSAID
Dornase®
Trikafta®

CLINICAL CLASSIFICATION



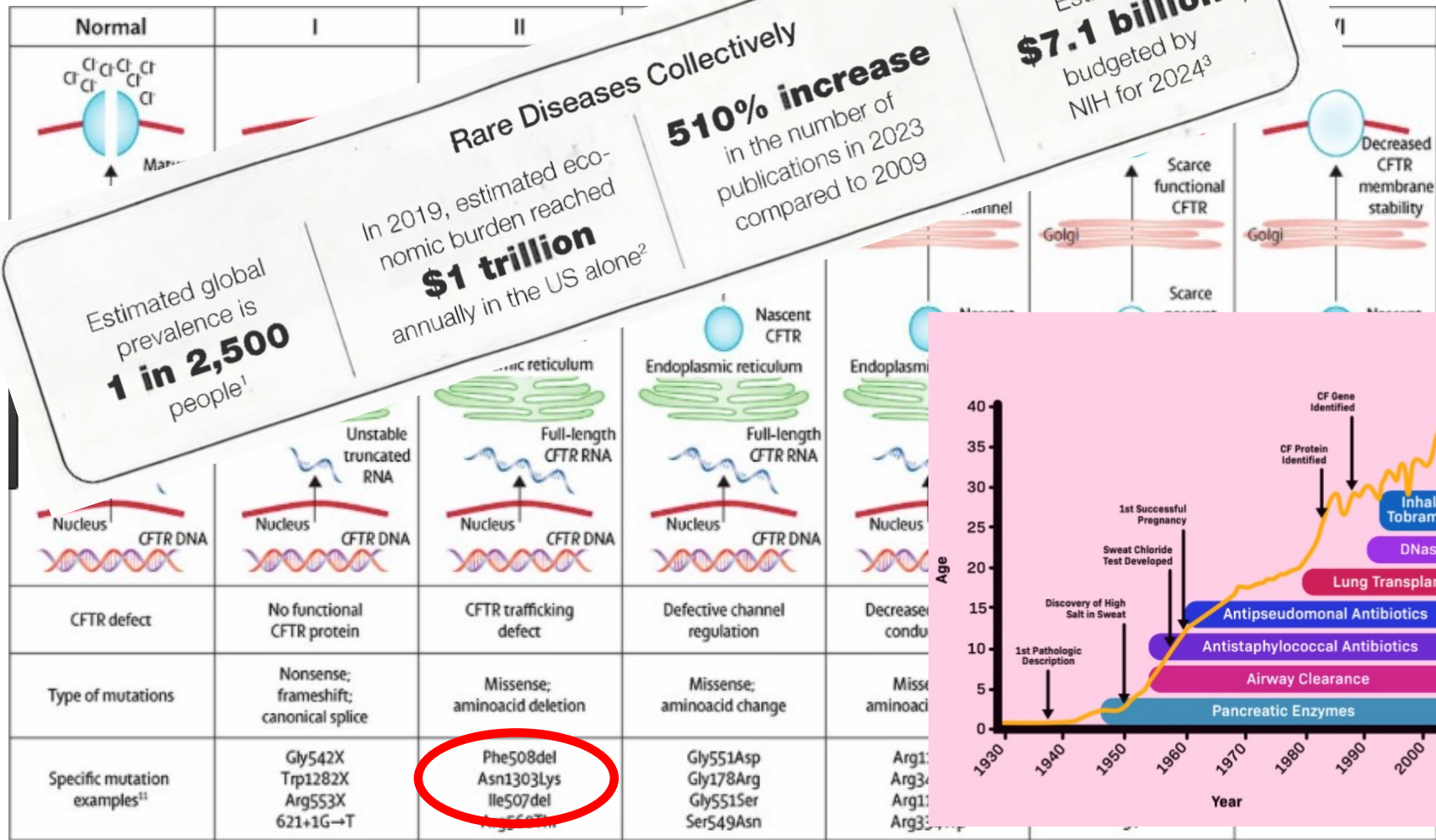
Cystic fibrosis – a rare autosomal recessive disease - when both alleles are mutated



- Most common genetic disease : prevalence : $\approx 1/3000$ newborn in Caucasian Europe
- Life expectancy increased from $\approx 0-40y$ 1930-2010 now 65 with current medicines

Cystic fibrosis – autosomal recessive

when both alleles are

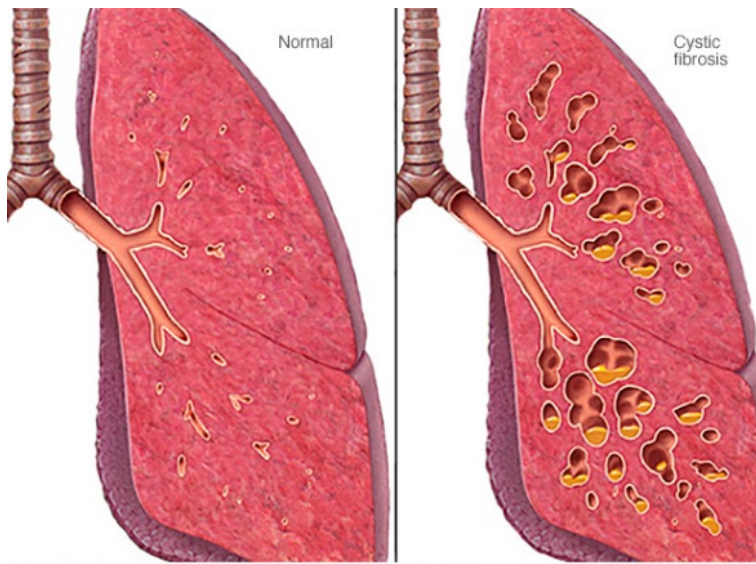


- Most common genetic disease : prevalence : $\approx 1/5000$ newborn in caucasian Europe
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Cystic fibrosis _ innovative translational therapeutic solution



- Many different mutation(s) in the chloride channel CFTR (ABC cassette transporter, water export deficiencies), most common human genetic mutation
- Symptoms are thick mucus, respiratory distress, multiple infections with average reduction of life expectancy
- Recombinant Dnase I reduces the viscosity of cystic fibrosis sputum
- Pulmozyme : a contribution of Molecular Biology to clinical unmet needs
- CFTRs allosteric modulators recently provided a game changer in clinics

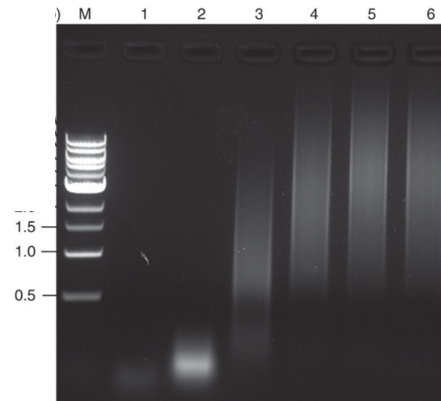


First cystic fibrosis treatment ever : 5 YEARS RECORD timing from an idea to making an innovative medicine in clinical practice !



Genentech
A Member of the Roche Group

5 years from bench
(molecular biology) to
bedside : a world record !



Pulmozyme-the first new treatment approach for cystic fibrosis in 30 years-was developed through a collaborative effort by Genentech, the CF Foundation, CF centers in North America, and the FDA. It is a bioengineered drug: The human protein deoxyribonuclease was isolated and synthesized in the lab at the cost of "several hundred million dollars," according to Genentech's **March, 1988**: Genentech researcher **Dr. Steven Shak** was observing the blood-thinning drug TPA (Activase®) as it dissolved blood clots, and developed the idea to engineer an enzyme that would dissolve mucus plugs in the lungs of CF patients. Research from the 1950s suggested to him that DNase isolated from cows had been effective in breaking up mucus, though its use was discontinued because patients had allergic reactions.

October, 1988 **Dr. Shak** successfully isolated the human gene for DNase and cloned a small amount in the lab. Tests show that the cloned DNase did break down DNA accumulations in CF sputum. He assembled a team of 25 people to develop the drug.

1989: The DNase team began to purify large amounts of the enzyme. Dr. Shak spoke to CFRI about the development process and results to date.

1990: Genentech applied to the FDA for the approval of DNase. With FDA permission, Genentech began an accelerated campaign to test the drug, beginning Phase I testing (for safety in humans) in September and Phase II testing later in the year.

October, 1991: Phase II testing, conducted by Genentech with 181 CF patients at eight U.S. treatment facilities, successfully concluded. Genentech began the construction of a manufacturing facility to produce sufficient quantities of the drug once final approval was granted.

1992: Phase III testing began-over 900 CF patients participated at CF centers all over the U.S.-and took one year to complete. Although increases in lung function in CF patients during Phase III were lower than during the first two phases, the study provided conclusive evidence of an improvement in the incidence of lung infections.

1993: In **March**, Genentech filed its final product application for the approval of DNase, and in August the FDA unanimously approved it under the brand name **Pulmozyme**. The FDA did caution, however, that more research is needed on the effects of Pulmozyme on different populations of CF patients not represented during the clinical trials.

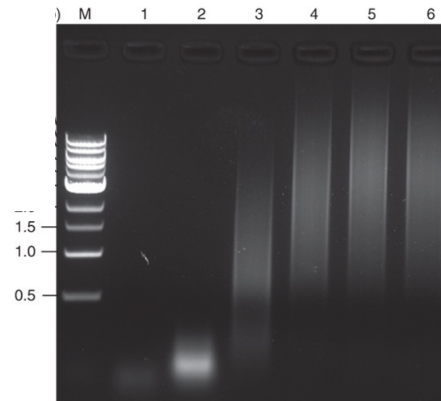
December, 1993: The FDA granted Genentech authorization to deploy Pulmozyme in the clinic.

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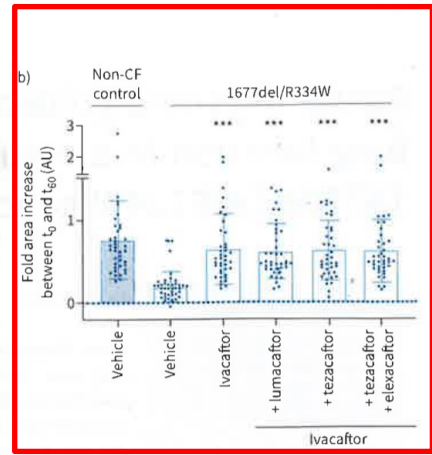
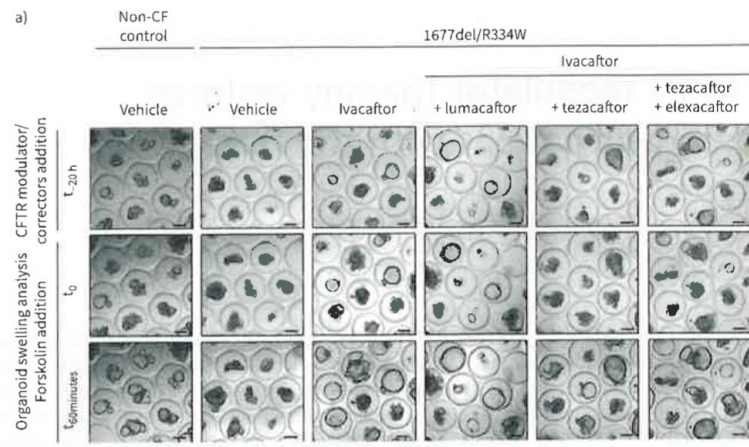


Nathalie Brandenburg
PhD MBA CEO

Organoids for all seasons – whose tissue not included ? Breaking news : organoids enable patient compliance



Cell Reports
Report

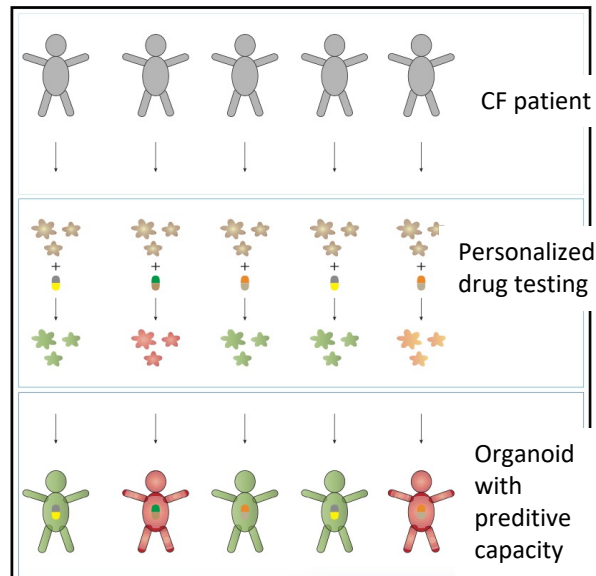


Rectal organoid-guided CFTR modulator therapy restores lung function in a cystic fibrosis patient with the rare 1677delTA/R334W genotype

Rectal Organoids Enable Personalized Treatment of Cystic Fibrosis

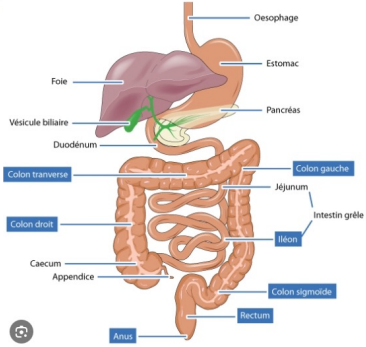
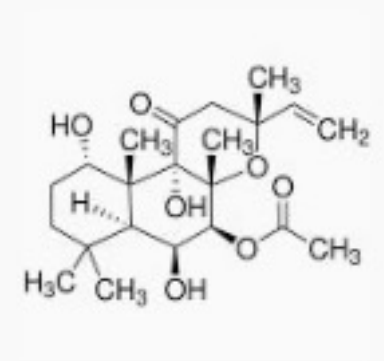
Gitte Berkers,¹ Peter van Mourik,¹ Annelotte M. Vonk,^{1,2} Evelien Kruijselbrink,^{1,2} Johanna F. Dekkers,³ Kerin M. de Winter, de Groot,¹ Hubertus G.M. Azete,¹ Bezemarijn F.P. Merckx, van der Wilt,¹ Jasper S. Diikema,¹

Graphical Abstract



Mitropoulou G ...and Brandenburg N. 2022 Eur Respir J. 60:2201341

cystic fibrosis transmembrane conductance regulator (CFTR), a chloride transporter-channel



...Based on our results, we obtained health insurance coverage for this patient reporting significant improvement of respiratory symptoms...

Cystic fibrosis – CFTR allosteric modulator : a paradigm change treatment for CF patients

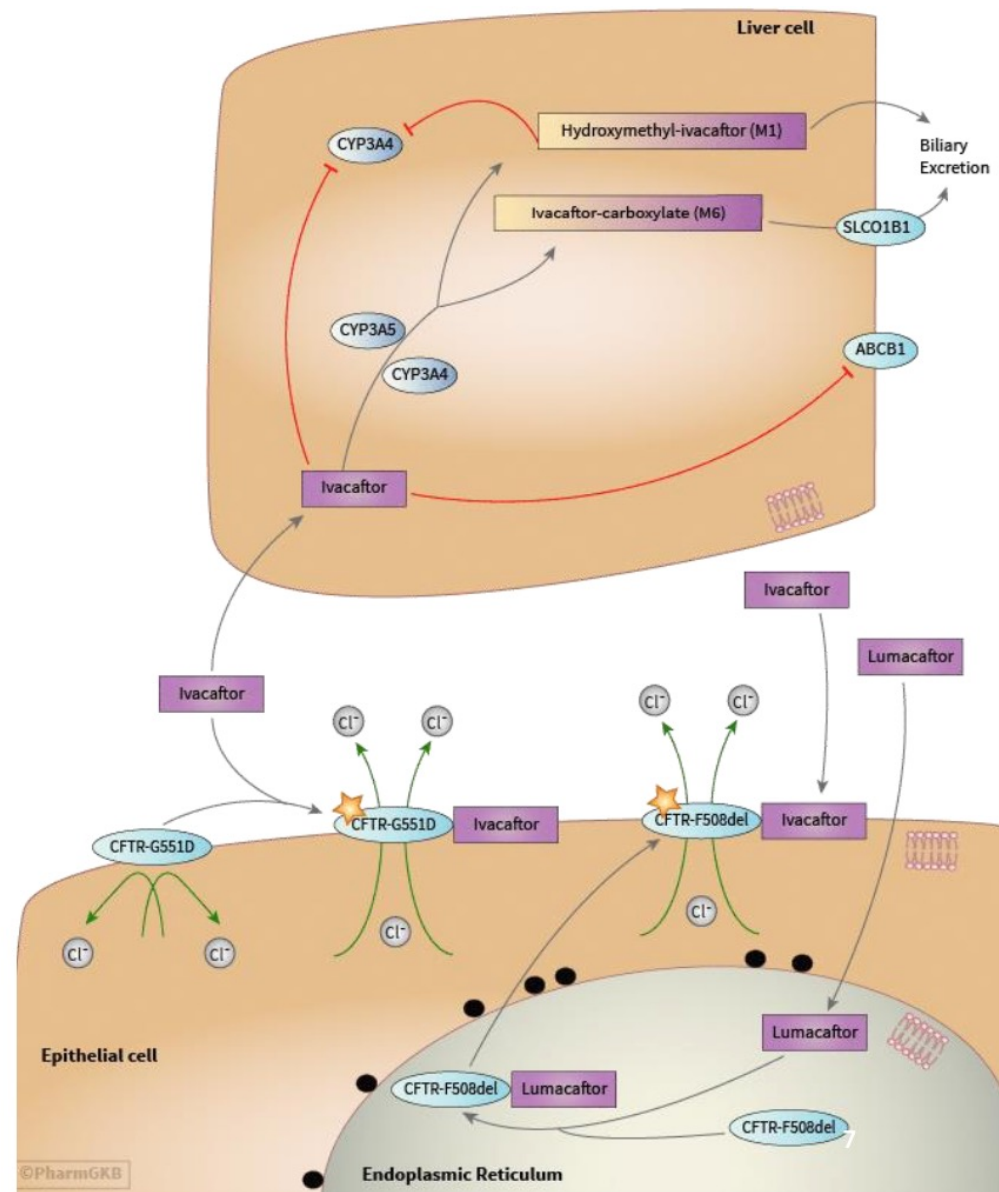


Ivacaftor

- Selective potentiator of CFTR by stabilizing its open state (Allosteric modulator that stabilize the open state of CFTR)
- Metabolized by CYP3A4 and CYP3A5

Lumacaftor

- **Corrector**
- Chaperone that improves maturation and CFTR transport to the membrane

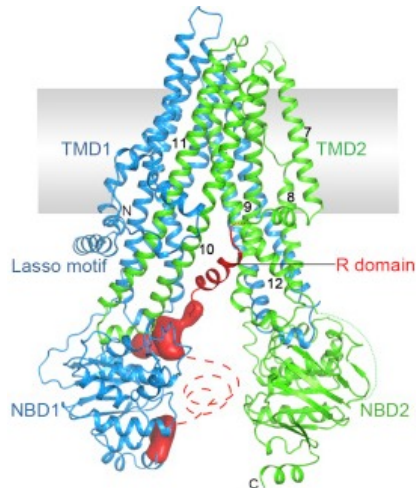


Cystic fibrosis – first tri-therapy for CF patients : a paradigm change



Vertex breakthrough : CFTR allosteric modulators in tri-therapy show a real benefit for CF patients (game changer (!) with even different mutations that represent 90% of the CF population ! FDA approval in 2019

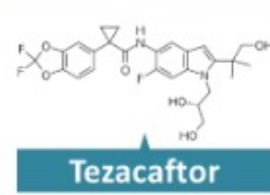
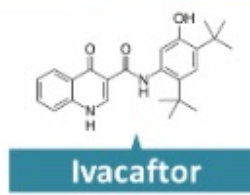
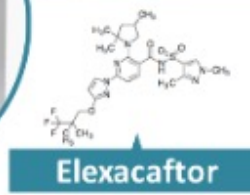
Trikafta : triple combo : elexacaftor/tezacaftor/ivacaftor



PHARMACEUTICAL NEWS

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FDA APPROVES TRIKAFTA, FIRST TRIPLE COMBINATION THERAPY FOR CYSTIC FIBROSIS



Enjoy an inspiring next week end !



Alv Laiets/GR
O. Kubitz, Aug. '16

ZUNÄCHST BERGWETTER





THANK YOU.....



DO YOU HAVE ANY QUESTIONS ?

It is not because things are difficult that we do not dare, it is because we do not dare that they are difficult.

Lucius Annaeus Seneca