

1,000,000,000 CHF investment

7,000,874 hours of work

6,587 experiments

423 researchers

1 medicine



With Prof Susan M Gasser
and Prof Olivier Michelin

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



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 throughput

26.10.23 *screening assays_ multiple parallel parameters optimization MDO*

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*

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 *Preclinical research ends up with IDB's, FDA guidelines for FIH*

AAC108

Session 10: **Clinical research_ phase 0, phase I, II, III, IV**

30.11.23 *The longest and complex experimental procedures with human patients*

AAC108

Session 11: **Intellectual property_ integrity in research_my genome vs our genomes**

07.12.23 *Why are patents essential to new medicine/biotech development*

AAC108

Session 12: **Health Hackathon – Hacking medicine I** with Dr Greg Michelin MD

14.12.23 *Pitches –building teams – hacking problem - 5Ws – brainstorm*

starts @ 2PM ! MED21522

Session 13: **Health Hackathon – Hacking medicine II** with Prof O. Michelin MD - Prof SM Gasser PhD judges

21.12.23 *Building up solutions – make it better - final presentations*

starts @ 2PM ! AAC231

! NON EXHAUSTIVE LISTING - SUGGESTIONS WELCOME !

sessions	no	workshops	speaker/s
S02 (28-09-23) ! AAC108 !			
historical medicines with Nobel laureates while hopping on giant shoulders	1	vaccine discovery : E. Jenner and smallpox	Danica M
	2	penicillin: impact, whose invention ?	
	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 an emerging field	7	expanding the scope of targeted therapies	
	8	chronotherapy	Pitt
S04 (12-10-23) ! AAC014 !			
therapeutic target identification	9	rare diseases repurposing medicines	Adrien
S04b (19-10-23) ! AAC108 !	10	nosocomial 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 multiple 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 preclinical 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 ! MED21522!		Hacking medicine	all + invitees
S13 (21-12-23) start @ 2 PM ! AAC231 !		Hacking medicine	all + invitees



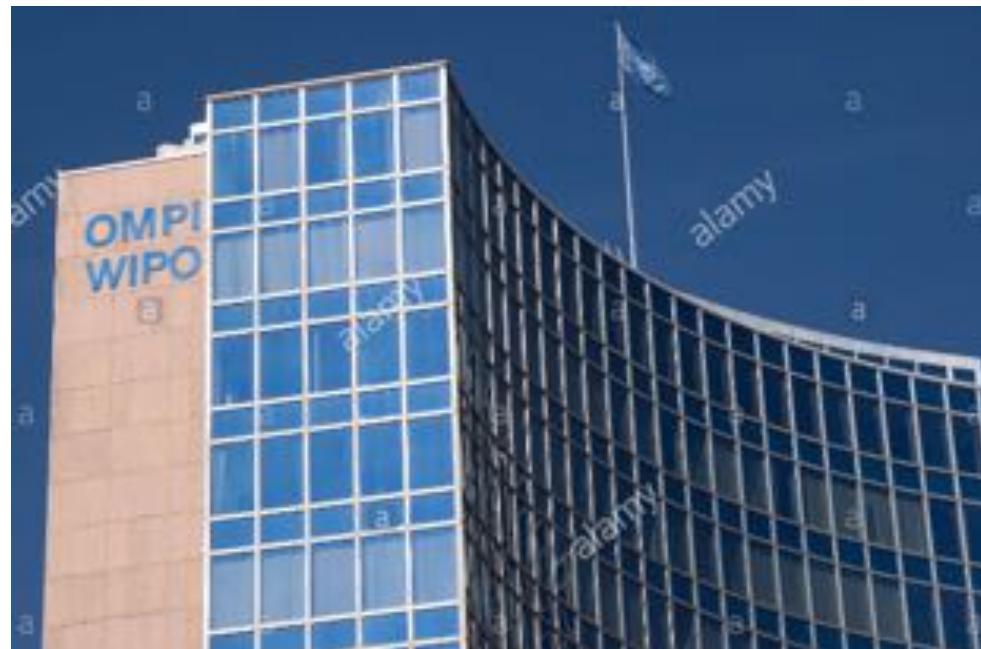
Workshops _ The Making Of An Innovative Medicine

(today's class)





- Intellectual property_patents
- Scientific integrity

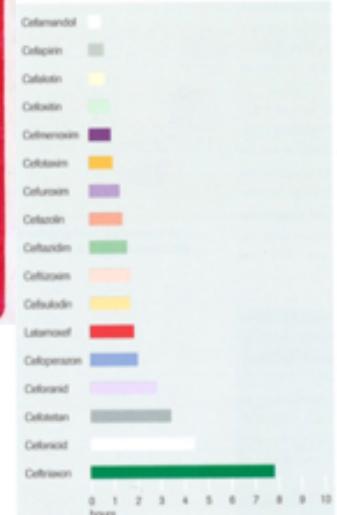


Intellectual property (IP) _ why patents ?

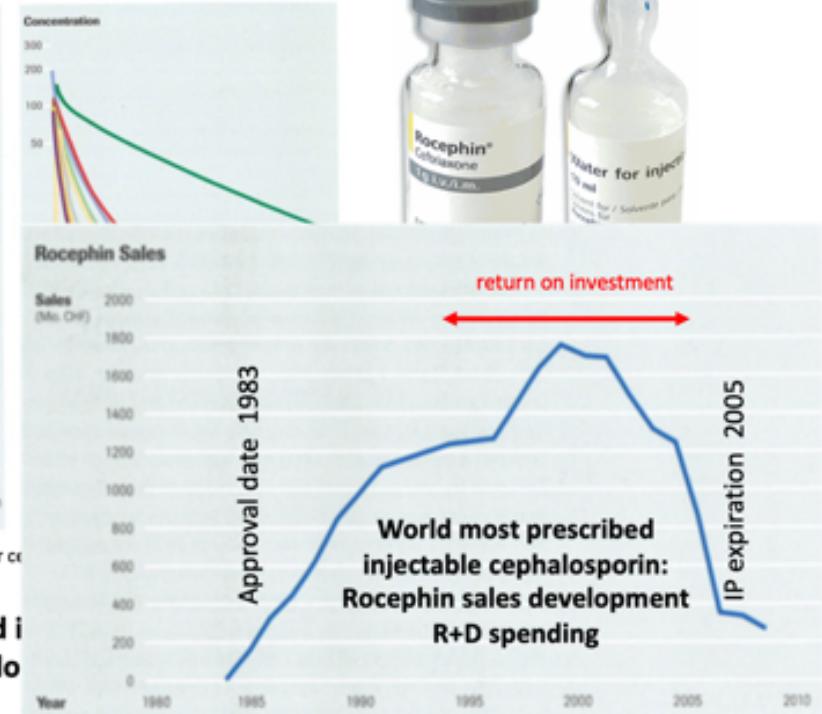


No IP protection, yet unrivalled !
red colour enough ?

Before AMR and antibiotics stewardship : the big pharma business model



World most prescribed i
Rocephin sales develo



No IP protection, no new antimicrobial discovery !

- Patenting is important to protect the large investment and assets of a pharma/start up company. Without patent, likely no pharma, no start up R+D, hence no innovative therapeutic solutions for patients in need.
- A patent is a legal right granted on an invention, something new, prior art, not state-of-the-art, being it pharmaceutical, object, process or use.



**NOW THAT YOU HAVE WORKED FOR >10 YEARS
ON AN INNOVATIVE MEDICINE !**

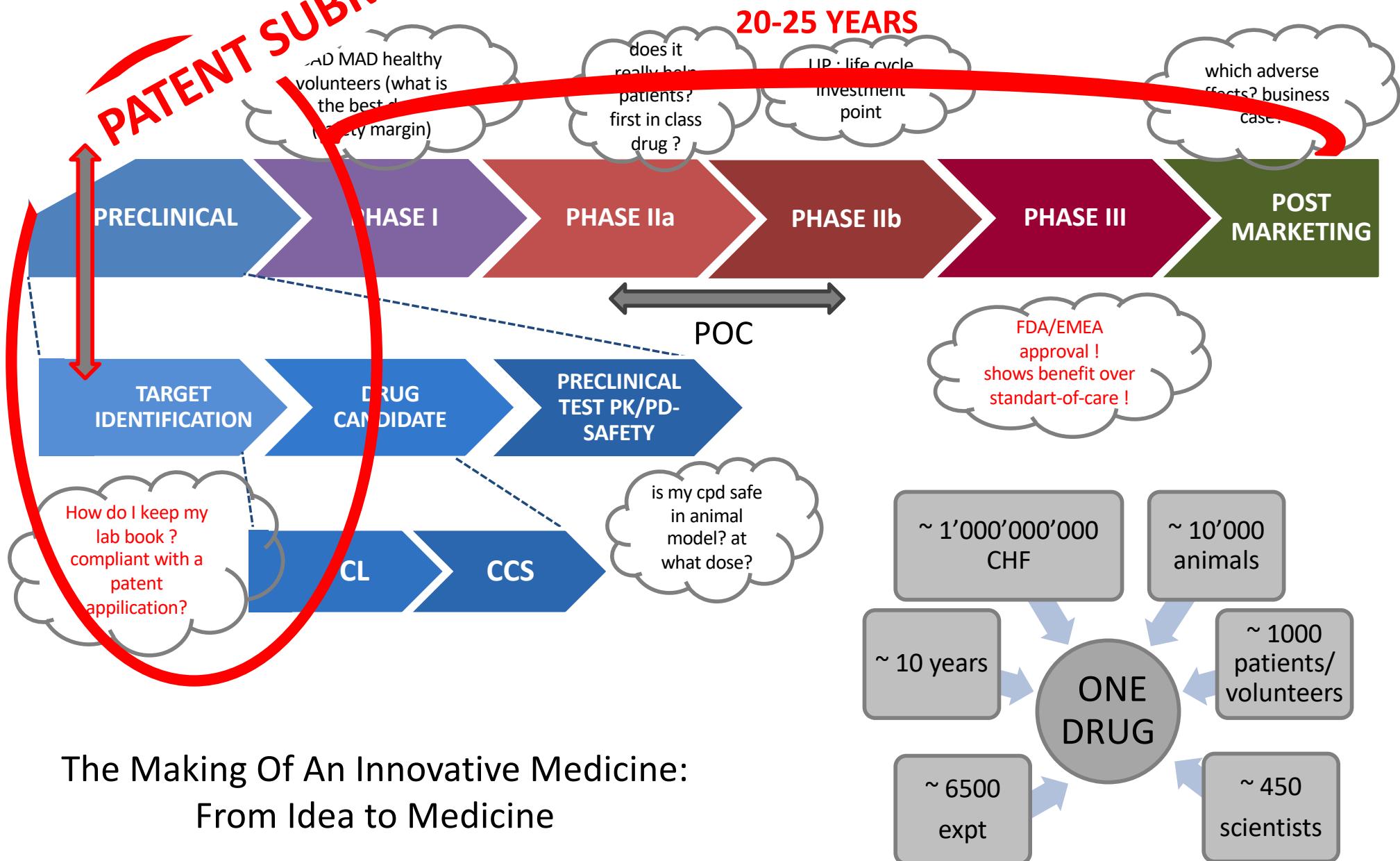
**HOW TO MAKE SURE SOMEBODY ELSE DOES NOT PRODUCE A
COPYCAT VERSION OF YOUR DISCOVERY ?**

WHY PATENTS ARE IMPORTANT IN PHARMA ?

- **Patenting is important to protect the large investment and assets of a pharma/start up company. Without patent , likely no pharma R+D hence no innovative therapeutic solutions for patients in need**
- **A patent is a legal right granted on an invention, something new, prior art, not state-of-the-art, being it pharmaceutical, object, process or use**
- **Systems Biology, O'mics, Molecular Biology, Computational Biology et al. have revolutionized medical practice by making of an innovative medicine possible : intellectual property is key !**



The Value of Patent Submission – Patent submission from Day 1 of your discovery _ PRIOR ART IS KEY !!



Life cycle of an innovative medicine – FIRST BRAND THEN GENERIC



PATENT
SUBMISSION
DAY 1 OF
DISCOVERY

Product life cycle

BRAND

MEDICINE SURVEILLANCE FOR ADVERSE EFFECTS



FDA APPROVAL
DAY 1 MARKET

GENERIC DRUGS ARE MUCH CHEAPER,
BUT SOME CALL FOR CAUTION

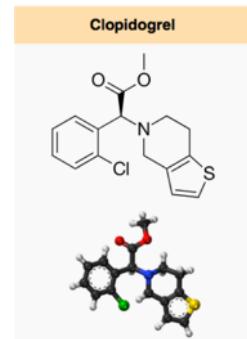


Intellectual property (IP) _ patent infringement



the brand

WHY PATENTS ARE IMPORTANT IN PHARMA ? HOW SERIOUS CAN INFRINGEMENT BE ?



- **Sanofi and Bristol Meyer Squibs awarded 442 millions US \$ by supreme court in Manhatten in damages from Apotex (largest canadian generics company) for Plavix (blood thinner) patent infringement**

THE STAR

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Star Business Journal

Apotex must pay \$442.2 million in Plavix case

Tues., Oct. 19, 2010



Toronto-based Apotex Inc. must pay Sanofi-Aventis SA and Bristol-Myers Squibb Co. \$442.2 million (U.S.) for making a copy of the drug Plavix, a Manhattan court has ruled.

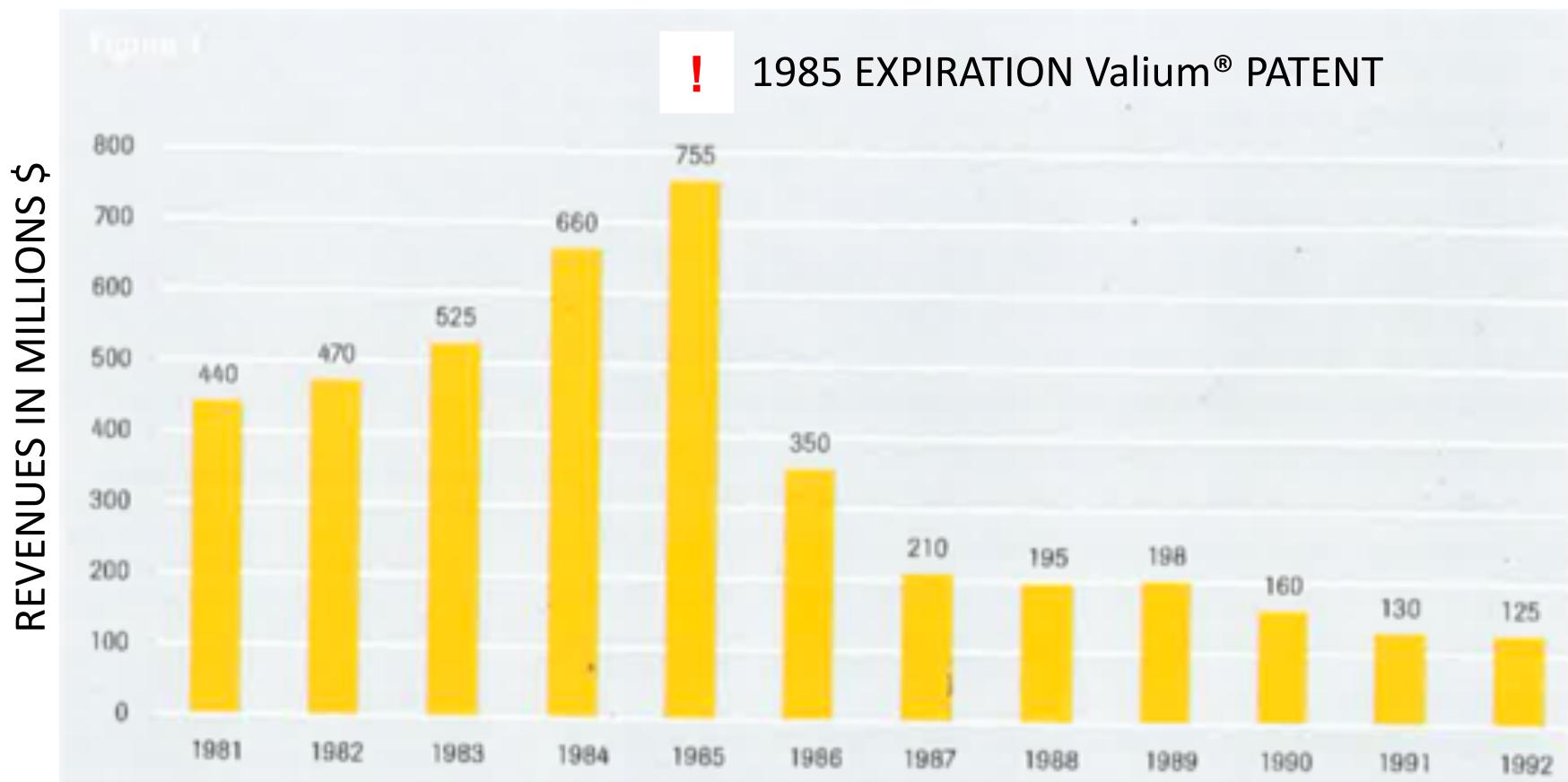
the copycat
(generic)



Intellectual property (IP) _ patent life cycle



WHY PATENTS ARE IMPORTANT IN PHARMA ?



Diazepam (Valium ®) was filed in 1960s by Roche Ltd (10y after chlordiazepoxid first less potent benzodiazepin Librium)

LIFESAVER MEDICINES FOR MILLIONS AND INTELLECTUAL PROTECTION : eg. BENZODIAZEPINE VALIUM®



February 24, 1985

GLORY DAYS END FOR PHARMACEUTICALS

By WINSTON WILLIAMS

LAST month, the privately held Swiss drug company, Hoffmann-La Roche, dealt a harsh blow to its American work force: Disappointed by the flow of new products here and preparing for the imminent expiration of its lucrative patent on Valium, the company said it would lay off 1,000 employees, more than 12 percent of its American payroll.

Source: The New York Times (24.2.1985)

- Patent expiry occurs 20 years and maximal 5 years extension after patent date
- Upon expiry drug sales dramatically drop, generics are taking often over the market
- Commercial aspects of patent expiry and its consequences are not to underestimate : many examples such as Versed Inc sales dropped from 626 M\$ to 19M\$ (97% sales losses) within a few years in the context of thousands of jobs loss



Novartis streamlines

Plant closures and job losses as patent expiries loom

Novartis is to close three plants in Italy and Switzerland and restructure business in the US resulting in the loss of 2000 jobs over the next three-to-five years.

The Switzerland-based pharmaceutical company said 700 new positions would be created in low-cost countries, with expected annual savings of \$200m.

In a video discussing the company's financial results for the third quarter of 2011, Joseph Jimenez, CEO of Novartis, blamed the cost-cutting measures on an "increasingly difficult environment" that was likely to get even tougher over the next five years.

He said, "These actions are necessary to ensure that we adapt our organisation to continue delivering on our mission of bringing innovative new drugs to patients."

Earlier in 2011, Novartis announced the loss of 550 jobs at its plant in the UK, and in December 2010 around 1,400 sales reps were laid off in the US.

The cuts come despite an increase in net profit of 16 per cent (at constant

exchange rates) for the Q3 period, with Novartis making \$3.54bn.

Revenue was up too, increasing by 12 per cent to \$14.84bn for the third quarter of 2011.

However, the company is facing pressures from a strong Swiss franc, and upcoming patent expiries for key drugs. These include blood pressure treatment Diovan (valsartan), which is already feeling the effects of generic competition as patent protection is lost in stages over the next two years. Sales of the drug fell by 7 per cent to \$1.43bn during the quarter.

In its outlook for the rest of 2011, Novartis said it expected to deliver sales growth in the low- to mid-single digits, with volume growth more than offsetting the impact of generic competition and price pressures.

Sales from its Alcon eyecare division, purchased in October 2010, were expected to increase at a mid to high single-digit rate, while generics division Sandoz was projected to deliver high single-digit sales growth.

Intellectual property _ the milestones of patent life





**Vaccines free of charge ?
Global health policies (eg COVAX) vs pharma patent
Medicine pricing ? How to price life saving drugs ?
Intellectual property and health policies**

**How would you defend your inventorship while inventing
new medicines, vaccines ?**

<http://patft.uspto.gov/>

Glivec - Imatinib : patent erosion vs generic versions



Imatinib (a tyrosine kinase bcl-Abl inhibitor) **GLIVEC AS AN EXEMPLARY “HALL OF FAME” OF RARE DISEASE INNOVATIVE MEDICINE DISCOVERY THAT EMERGED AS A BROADER SPECTRUM CANCER MEDICINE**

ONCOLOGY BUSINESS UNIT

	Q4 2016 USD m	Q4 2015 USD m	% change USD cc	FY 2016 USD m	FY 2015 USD m	% change USD cc
Gleevec/Glivec	764	1 219	-37 -36	3 323	4 658	-29 -28
Tasigna	458	432	6 9	1 739	1 632	7 10
Subtotal Bcr-Abl portfolio	1 222	1 651	-26 -24	5 062	6 290	-20 -18
Sandostatin	408	413	-1 1	1 646	1 630	1 3
Afinitor/Votubia	391	382	2 3	1 516	1 607	-6 -5
Exjade/Jadenu	237	248	-4 -3	956	917	4 6
Votrient	192	176	9 10	729	565	nm nm
Tafinlar + Mekinist ¹	178	147	21 24	672	453	nm nm
Promacta/Revolade	178	133	34 35	635	402	nm nm
Jakavi	162	119	36 40	581	410	42 45
Zykadia	22	24	-8 -11	91	79	15 14
Other	217	226	-4 -1	902	951	-5 -3
Total Oncology Business Unit	3 207	3 519	-9 -7	12 790	13 304	-4 -2

¹ Majority of sales for Mekinist and Tafinlar are combination, but both can be used as a monotherapy

nm = not meaningful

Our Bcr-Abl portfolio, consisting of Tasigna and Gleevec/Glivec, generated sales of USD 1.2 billion (-24% cc) in the fourth quarter.

Tasigna (USD 458 million, +9% cc) showed solid growth in the fourth quarter across key markets globally. Tasigna is approved for the treatment of adult patients newly diagnosed with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in the chronic phase, and is also approved for the treatment of adult patients with CML in the imatinib or accelerated phase who are resistant or intolerant to at least one prior therapy including Gleevec/Glivec.

Gleevec/Glivec (USD 764 million, -36% cc) declined, driven by the US, where multiple generic versions have entered the market. Gleevec/Glivec is approved in more than 110 countries for the treatment of adult patients in all phases of Ph+ CML, for the treatment of patients with KIT (CD117)-positive gastrointestinal tumors (KIT+ GIST), which cannot be surgically removed and/or have metastasized, and for the treatment of adult patients following complete surgical removal of KIT+ GIST. Numerous indications are available in every country.



Glivec fast FDA approval 2001

- 2001-2015 ; 14 years !!
- Out of 25 potential years IP protection
- Invention day is key !!
- Pharma business strategies !
- Line extension !
- Back up molecules !
- Generic for image

Biologicals – patent trial pending 2023 with far reaching impact on NBE's the case of PCSK9, a «cash cow” in metabolic diseases



starts to count carbon-footprint assessments, this will take years," he says. "As soon as you have a few carbon-footprint assessments here and there in different countries or different infrastructures, you start to have a pretty good idea of what you need to do."

One way to push things forward would be for institutions to ask scientists for emissions-reduction strategies as a condition of grants or jobs. But this is challenging for research institutions that are not used to

considering their emissions, says Knud Jahnke, a cosmologist at the Max Planck Institute for Astronomy in Heidelberg, Germany. "It's fundamentally human and fundamentally challenging for big organizations because if they're big, they're well-oiled in the way they're used to operate."

1. Qin, Y. *et al.* *Nature Genet.* **54**, 134–142 (2022).
2. Martin, P. *et al.* *Nature Astron.* **6**, 1219–1222 (2022).
3. Adshead, F. *et al.* *Lancet* **398**, 281–282 (2021).
4. Subaiya, S., Hogg, E. & Roberts, I. *Trials* **12**, 31 (2011).

PATENT ROW COULD HAVE FAR-REACHING IMPACT ON BIOTECH

The results of a US case on therapeutic antibodies could dictate how broad patents are.

By Heidi Ledford

An unusual patent case before the US Supreme Court could have wide-ranging implications for drug prices and technology.

On 27 March, the court heard arguments in a dispute over rights to antibodies that are used to treat high cholesterol in people at risk of cardiovascular disease. Although the court's justices spent much of their time wrestling with the details of how these therapeutic antibodies are isolated, their decision – expected by the end of June – could affect how specific patents, of any ilk, must be when they describe an invention, and how broad they can be.

"It could spill over into all types of biotechnology cases," says Sean Tu, a legal scholar at West Virginia University in Morgantown. "Today we're talking about antibodies, tomorrow we might be talking about CRISPR or CAR-T-cell therapies."

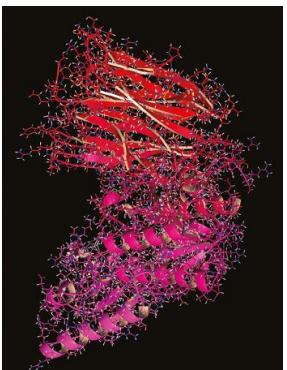
Cholesterol clearance

At the core of the current case are antibodies that bind to a protein called PCSK9, which decreases the clearance of 'bad' cholesterol from the blood. The antibodies block PCSK9 activity, resulting in lower levels of this cholesterol. Several PCSK9 antibody therapies have come to market, including Repatha (evolocumab) made by Amgen in Thousand Oaks, California, that was approved in August 2015.

In the case before the US Supreme Court, Amgen is appealing against a federal court ruling that struck down one of its key patents on Repatha. The patent claims not only a handful of specific antibodies, as defined by

an amino-acid sequence, but also any antibodies, regardless of their structure, that bind to the same region of the PCSK9 protein.

This, said the lower court, was insufficiently detailed. US law requires that a patent contain a written description of the invention that provides enough detail for someone "skilled in the art" to use the patent as a recipe to recreate the invention. But Amgen's patent, the federal court argued, merely disclosed how to sift through antibodies found in mouse serum for those that bind to a region of the PCSK9 protein, rather than first specifying what the sequence of those antibodies would be.



The PCSK9 protein is the target of antibodies that are used to treat high cholesterol.

A win by Amgen could hinder the development of new medicines by restricting competition and discouraging the development of multiple antibodies that bind to the same target, says Gregory Winter, a molecular biologist at the University of Cambridge, UK. The availability of different antibodies helps to keep the price of drugs in check, and can provide treatment options for people who develop an immune response to a particular drug.

In 2018, Winter shared the Nobel Prize in Chemistry for his work on therapeutic antibodies. When a colleague showed him the Supreme Court case, he decided to submit a brief to the court explaining the underlying science. In the brief, Winter and his co-authors compare antibodies to an attempt to make calorie-free ice cream. Amgen, they said, made vanilla and chocolate ice cream that it determined, after the fact, to contain no calories. "But rather than patent only those two flavors, Amgen claims to have invented all calorie-free frozen dessert, be it ice cream, sorbet, sherbet, or gelato," they wrote.

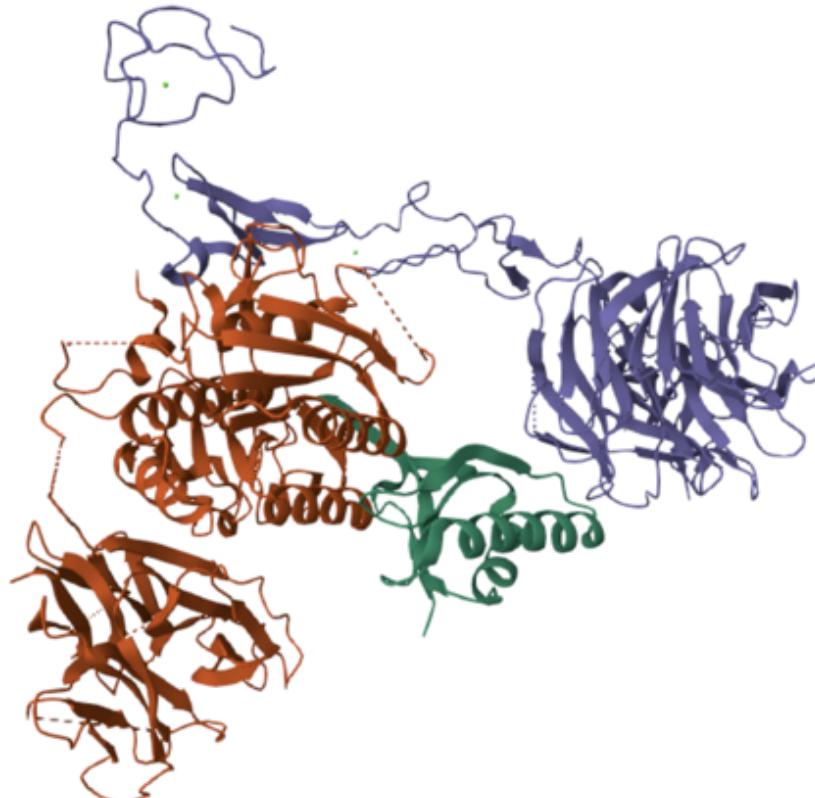
Amgen's attorneys have argued that striking down its patent will harm future development of therapeutic antibodies. Broad patent protection is necessary to justify the company's investment in a specific medicine, said attorney Jeffrey Lamken, who represented Amgen in the Supreme Court. "You can't invest \$2.6 billion in the breadth of your claims is such that it means you can't get adequate protection."

Patents 'squeezed'

A decision against Amgen could discourage investors from taking a risk on other biotechnology companies as well, said Michael Penn, vice-president of intellectual property at Instil Bio, a company that is developing cell therapies in Dallas, Texas, at a meeting hosted by the American University Washington College of Law in Washington DC after oral arguments. "When they see patents getting squeezed and patent breadth getting squeezed year for year, that investment goes elsewhere," he said.

The debate divides the industry into those that focus on drug targets, and favour broad patent protection, and those that develop specific molecules against the targets, says Ulrich Storz, an attorney at the Michalski Hürtzman and Partner law firm in Düsseldorf, Germany. Universities are more likely to patent targets than candidate drugs, and the Association of University Technology Managers in Washington DC has filed a brief supporting Amgen.

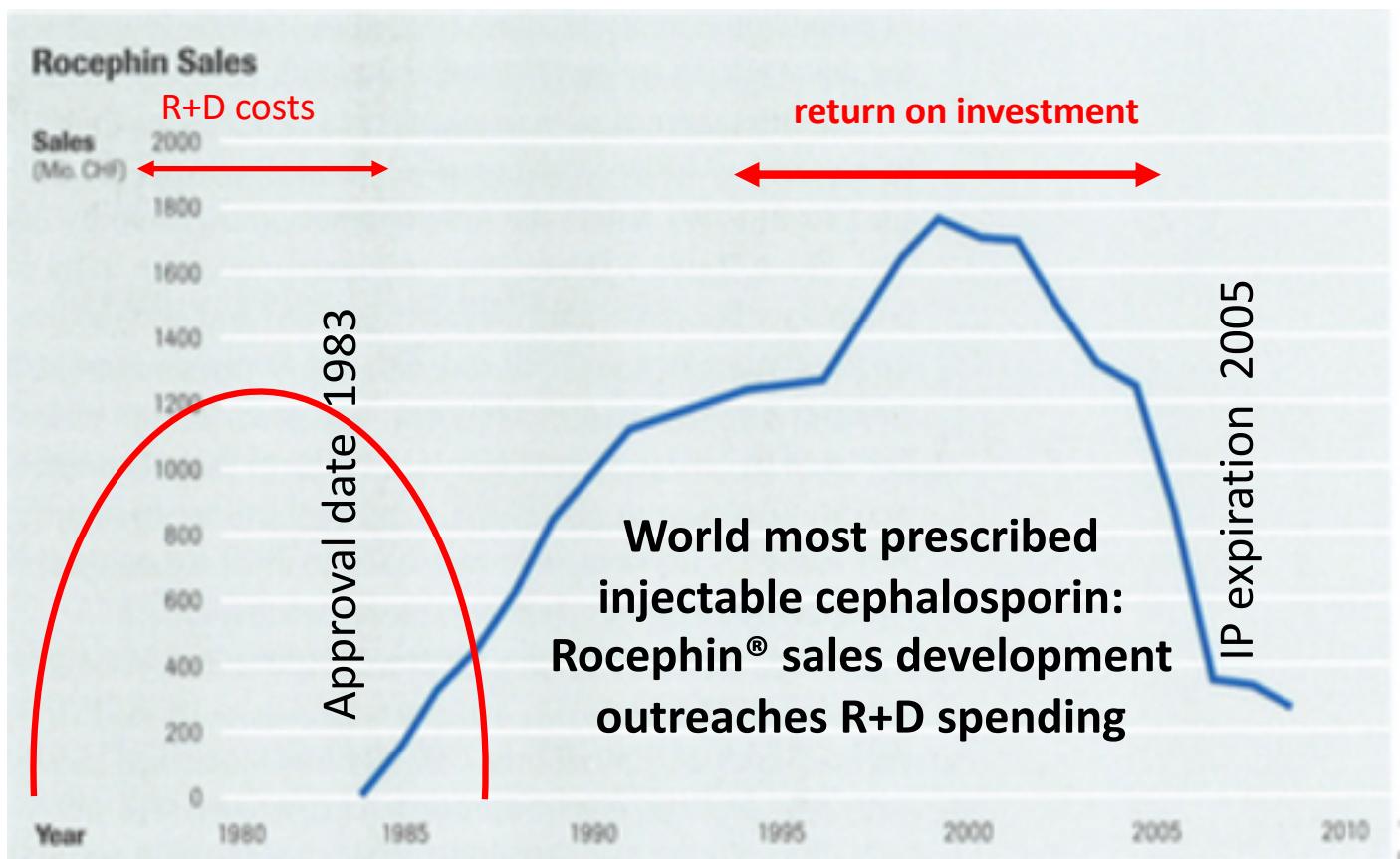
Even so, there is little evidence that the prevailing practice – which over the past few years has favoured relatively narrow patent claims on antibodies – needs to change to allow such broad patents, says Tu, especially given the potential effect on drug prices and treatment options. "The system that we have right now is working pretty well," he says. "Everybody's getting paid."



PCSK9

LDLr

«Life and death» of a live saving medicine -ceftriaxone : the pharma business model



**World most prescribed injectable cephalosporin:
Rocephin® sales development & R+D spending**

No patent protection means essential medicine shortage : the pharma business model



Suisse: plus de 900
médicaments en rupture
d'approvisionnement

January 2023



World most prescribed medicine unavailable (when cost of goods are no longer covered by medicine pricing even as generics)



**practical examples of patentable data in biomedical research
when, how much, claim validity
chemistry vs biology patents
patenting genes, mice strains etc ?
gene reporter assays ?**

How would you defend your inventorship ?

<http://patft.uspto.gov/>

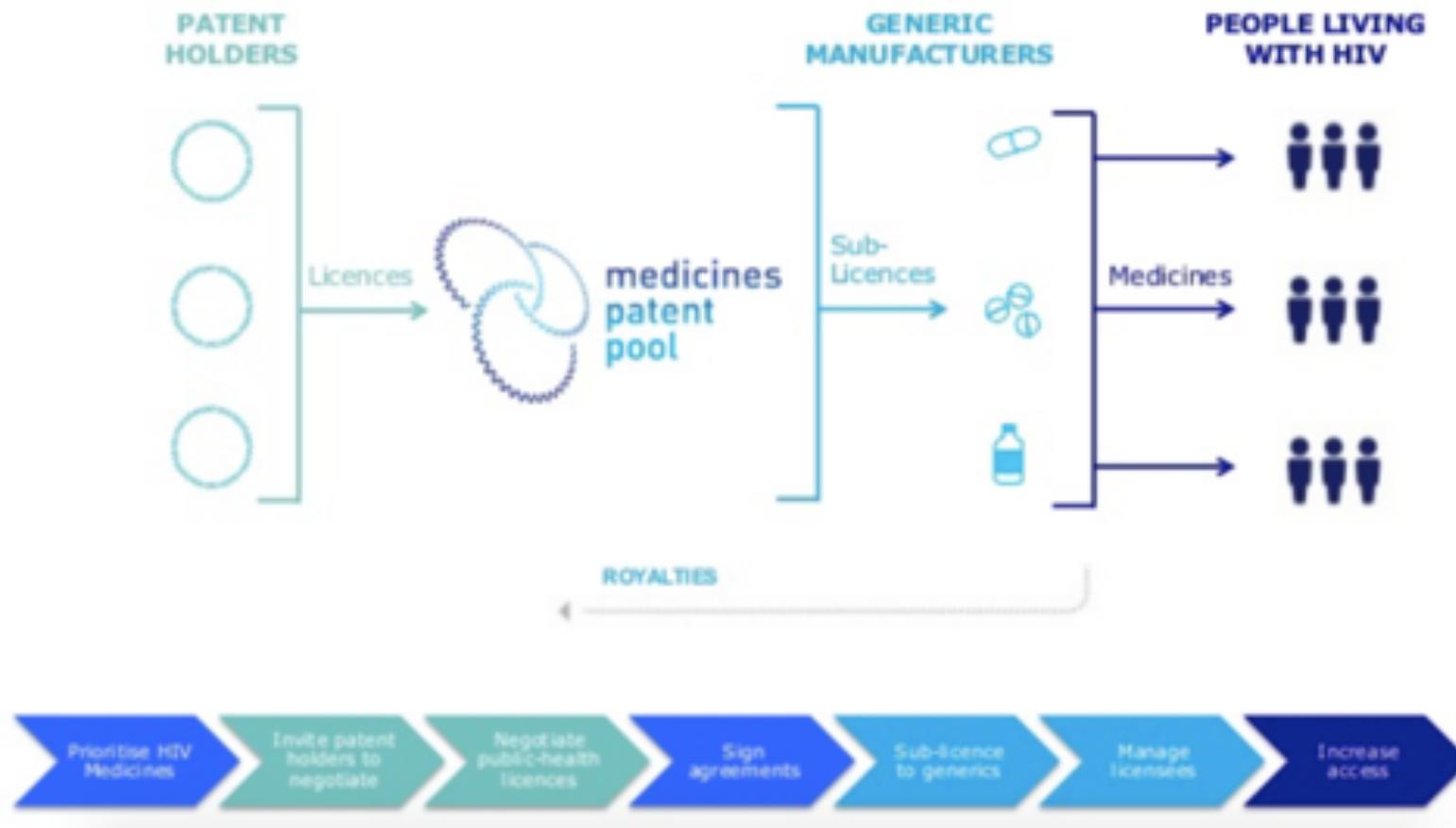
Medicines patent pool : enabling access to sub-licences

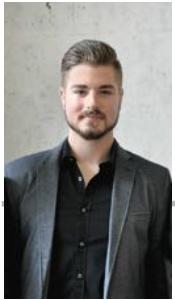


<https://medicineslawandpolicy.org/covid-19/>



How the MPP works





Career jump : create a spin off / pharma start up



- Ruben Herrendorff PhD at UNIBAS made his dream come true : the creation of a pharma start up during his PhD thesis @ UNIBAS Dept of Pharmaceutical Sciences
- 2015 “his” START-UP was born : Polyneuron Pharmaceuticals Inc.
- Business case built up on a glycopolymers platform to block/decoy autoantibodies in rare autoimmune diseases (www.polyneuron.com)
- Debilitating demyelination of motor and sensory neurons





- Ruben Herrendorff PhD at UNIBAS made his dream come true : the creation of a pharma start up during his PhD thesis @ UNIBAS

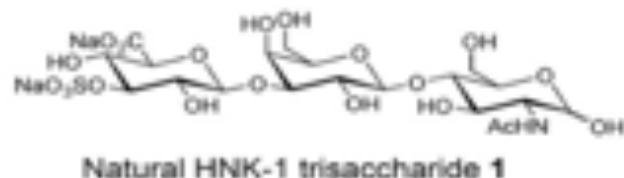
PNAS

Selective *in vivo* removal of pathogenic anti-MAG autoantibodies, an antigen-specific treatment option for anti-MAG neuropathy

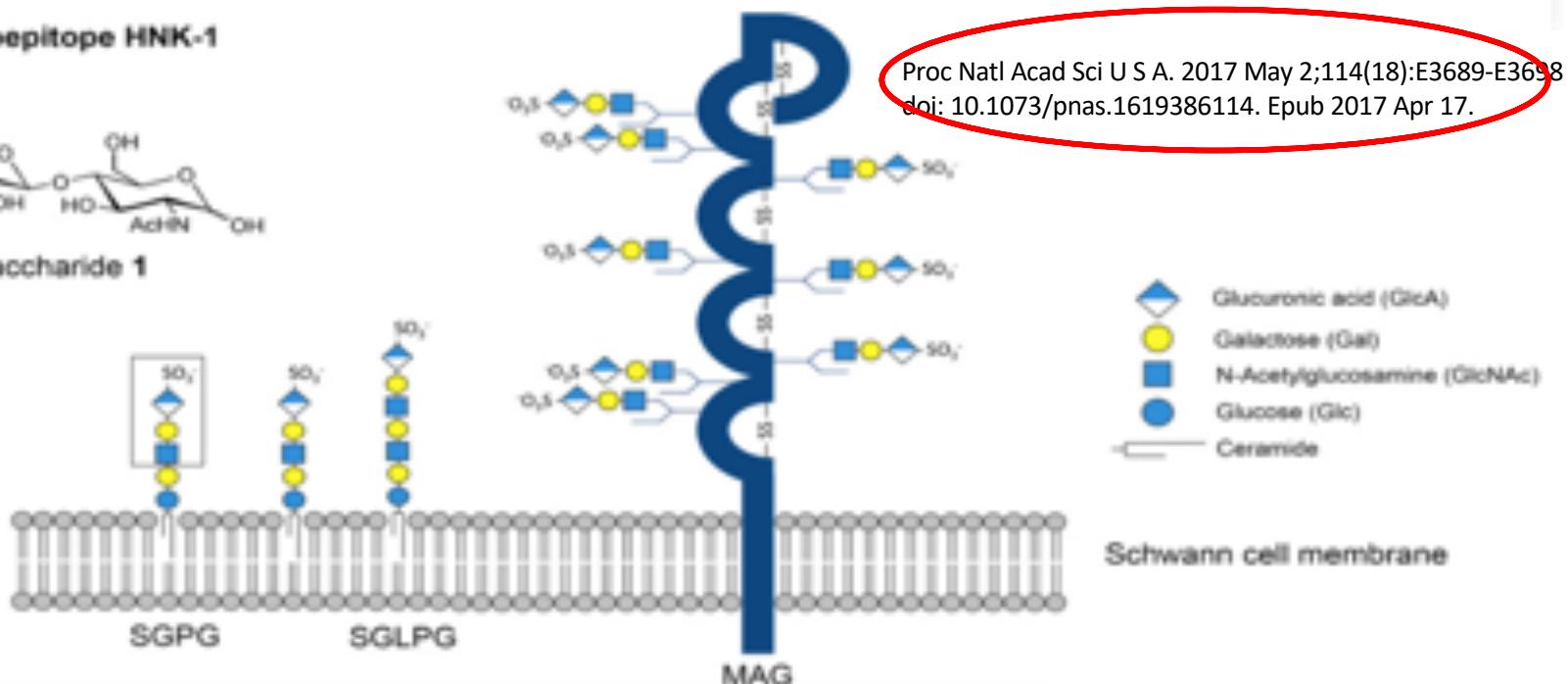
Ruben Herrendorff^a, Pascal Hänggi^a, Hélène Pfister^a, Fan Yang^a, Delphine Demeestere^a, Fabienne Hunziker^a, Samuel Frey^a, Nicole Schaeren-Wiemers^b, Andreas J. Steck^{b,c}, and Beat Ernst^{a,1}

^aInstitute of Molecular Pharmacy, Pharmacenter, University of Basel, 4056 Basel, Switzerland; ^bDepartment of Biomedicine, University Hospital Basel, University of Basel, 4031 Basel, Switzerland; and ^cClinic of Neurology, Department of Medicine, University Hospital Basel, University of Basel, 4031 Basel, Switzerland

A Antigenic myelin glycoepitope HNK-1



Natural HNK-1 trisaccharide 1



B *in vivo* removal of HNK-1

no start up/ no biotech added value without intellectual property :
First patent your invention then publish in best journal!



US009994605B2

(12) **United States Patent**
Ernst et al.

(10) **Patent No.:** US 9,994,605 B2
(45) **Date of Patent:** Jun. 12, 2018

(54) **CARBOHYDRATE LIGANDS THAT BIND TO
IGM ANTIBODIES AGAINST
MYELIN-ASSOCIATED GLYCOPROTEIN**

(71) **Applicant:** UNIVERSITAET BASEL, Basel (CH)

(72) **Inventors:** Beat Ernst, Magden (CH); Ruedi Herrendorff, Basel (CH); Andreas Steck, Epalinges (CH); Fan Yang, Basel (CH)

(73) **Assignee:** UNIVERSITAET BASEL, Basel (CH)

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days. days.

(21) **Appl. No.:** 15/124,715

(22) **PCT Filed:** Mar. 12, 2015

(86) **PCT No.:** PCT/EP2015/055140

§ 371 (c)(1),

(2) **Date:** Sep. 9, 2016

(87) **PCT Pub. No.:** WO2015/136027

PCT Pub. Date: Sep. 17, 2015

FOREIGN PATENT DOCUMENTS

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WO/0020871 * 4/2000

OTHER PUBLICATIONS

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Herrendorff et al., "Selective *in vivo* removal of pathogenic anti-MAG autoantibodies, an antigen-specific treatment option for anti-MAG neuropathy," *Proceedings of the National Academy of Sciences USA* 114(18):E3689-E3698 (2017).

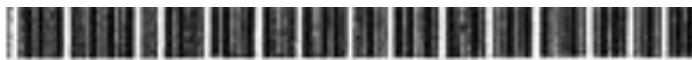
Sarkar et al., "Synthesis and glycosaminoglycan priming activity of three disaccharides related to the linkage region tetrasaccharide of proteoglycans," *Carbohydrate Research* 279:161-171 (1995).

Simon-Halldi et al., "Identification of a peptide mimic of the L2/HNK-1 carbohydrate epitope," *Journal of Neurochemistry* 83(6):1380-1388 (2002).

eg RARE disease anti MAG start up !

Primary Examiner — Traviss C McIntosh, III

How a patent looks like _closer look at the NF κ B patent: "enough details for someone skilled in the art to use the patent as recipe to recreate the invention"



US006410516B1

(12) **United States Patent**
Baltimore et al.

(10) Patent No.: **US 6,410,516 B1**
(45) Date of Patent: **Jun. 25, 2002**

(54) **NUCLEAR FACTORS ASSOCIATED WITH TRANSCRIPTIONAL REGULATION**

(75) Inventors: David Baltimore, New York, NY (US); Ranjan Sen, Cambridge; Phillip A. Sharp, Newton, both of MA (US); Harinder Singh, Chicago, IL (US); Louis Staudt, Silver Springs, MD (US); Jonathan H. Lebowitz, Indianapolis, IN (US); Albert S. Baldwin, Jr., Chapel Hill, NC (US); Roger G. Clerc, Binningen (CH); Lynn M. Corcoran, Port Melbourne (AU); Patrick A. Baumerle, Eichstätt (DE); Michael J. Lenardo, Potomac, MD (US); Chen-Ming Fan, San Francisco; Thomas P. Maniatis, Belmont, both of MA (US)

(73) Assignees: President & Fellows of Harvard College; Massachusetts Institute of Technology; Whitehead Institute for Biomedical Research, all of Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/464,364**

(22) Filed: **Jun. 5, 1995**

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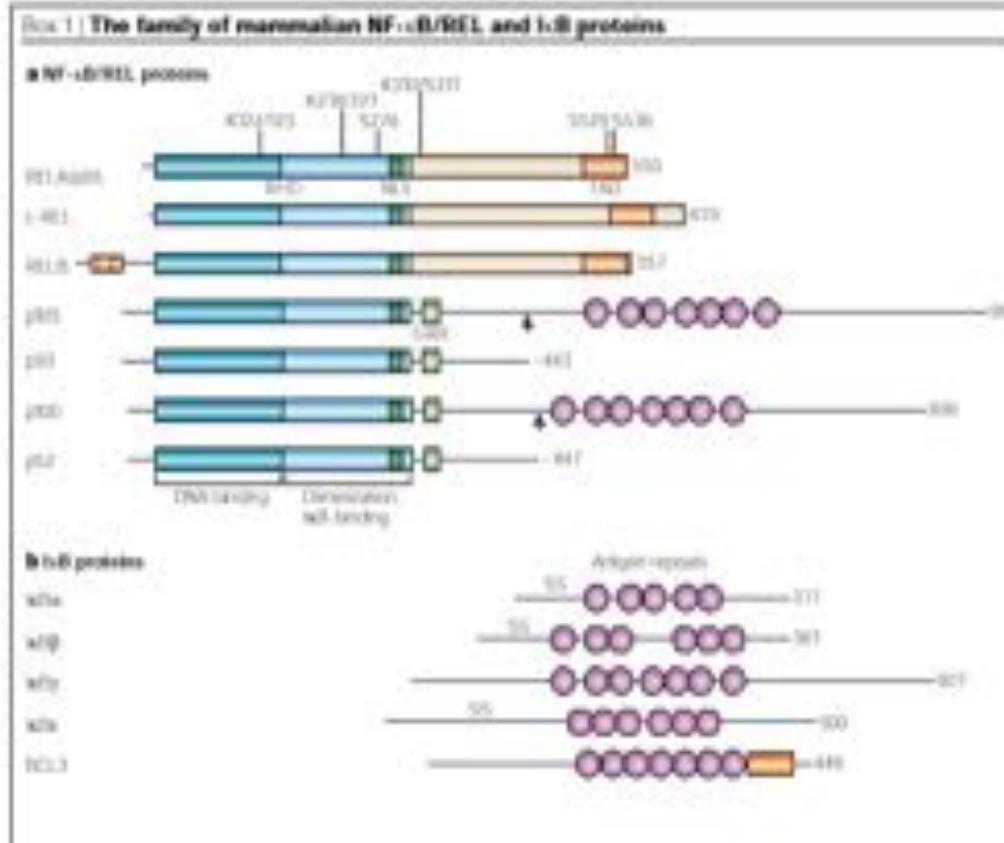
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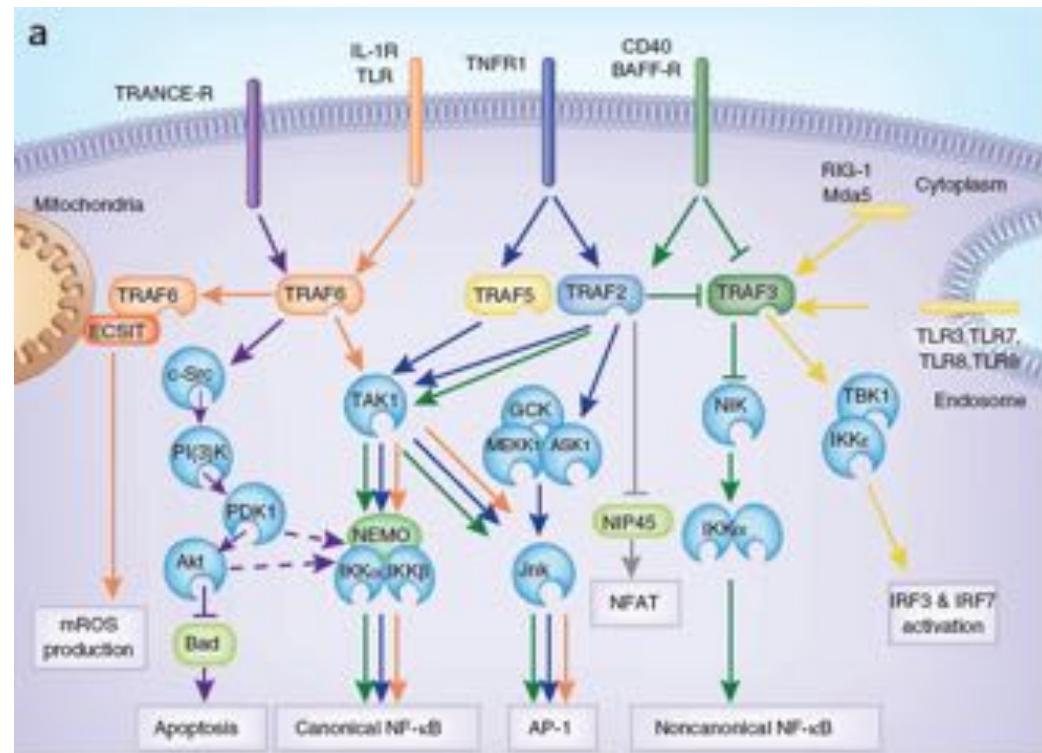
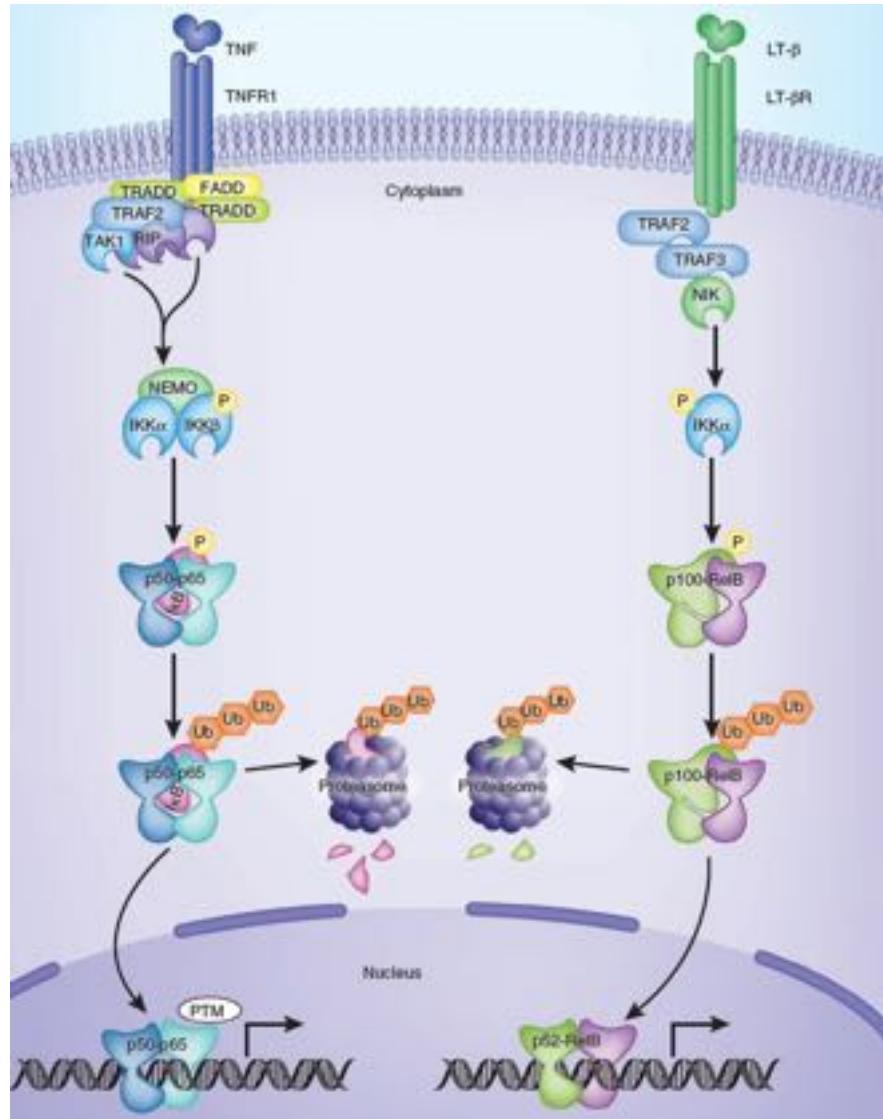
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The NF κ B/REL Family and I κ B Proteins



The NF κ B System: Signal Induced Degradation of Cytosolic Inhibitor Proteins Which Activates the TF



TRX factors such as NF κ B are final effectors of various cellular signaling pathways :
25 years on !

Prototypical inflammatory signal pathway

Oeckinghaus A, Hayden M, Ghosh S (2011) Nature Immunology 12:695-708



TNF- and Cancer Therapy-Induced Apoptosis: Potentiation by Inhibition of NF- κ B

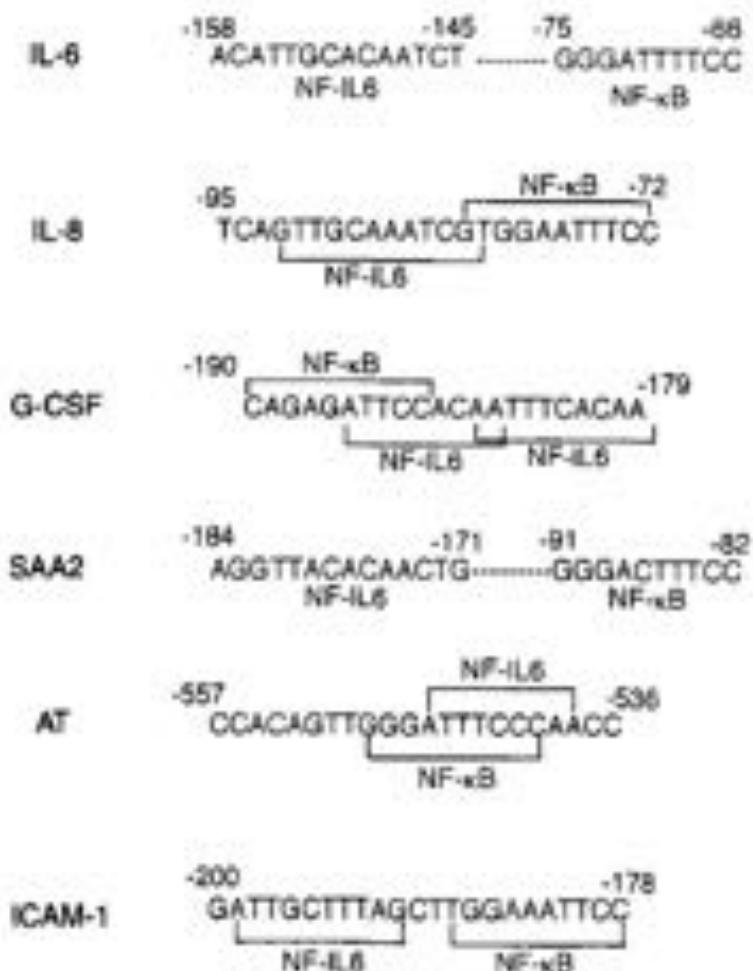
Cun-Yu Wang, Marty W. Mayo, Albert S. Baldwin

NF-IL6 AND NF- κ B IN CYTOKINE GENE REGULATION

Many cells are resistant to stimuli that can induce apoptosis, but the mechanisms involved are not fully understood. The activation of the transcription factor-kappa B (NF- κ B) by tumor necrosis factor (TNF), ionizing radiation, or the drug rubicin (a cancer chemotherapeutic compound), was found to protect fibroblasts from apoptosis. Inhibition of NF- κ B nuclear translocation enhanced apoptotic killing by TNF and rubicin, but not by apoptotic stimuli that do not activate NF- κ B. These results suggest that NF- κ B activation may be a common mechanism for TNF- and drug-induced apoptosis.

Table 1. Chronic inflammatory diseases associated with NF- κ B activation

NF- κ B activation in human inflammatory diseases	
Rheumatoid arthritis	G-CSF
Atherosclerosis	SAA2
Chronic obstructive pulmonary disease (COPD)	AT
Asthma	
Multiple sclerosis	
Inflammatory bowel disease (IBD)	
Ulcerative colitis	



Adapted from Tak and Firestein 2001.

**Table 1.** Autoimmune Diseases Associated with Dysregulated Nuclear Factor (NF)- κ B Activation.

Disease	Dysregulation	Reference
Rheumatoid arthritis (RA)	Constitutive NF- κ B activation seen in the synovium. Increased NF- κ B DNA binding activity in RA patients.	28, 29
Systemic lupus erythematosus (SLE)	Abnormal NF- κ B activity in T cells with increased expression of c-Rel and decreased p65 expression. NF- κ B binding activity is absent in a subset of SLE patients.	33–35
Type 1 diabetes mellitus (T1D)	Increased NF- κ B activation in peripheral blood mononuclear cells. RelA, p50, c-Rel, and RelB DNA binding are impaired in DCs, while p65 and RelB are constitutively activated in monocytes in T1D patients.	221, 222
Ulcerative colitis (UC)	NF- κ B activation is seen in inflamed UC mucosa, predominantly in macrophages and epithelial cells.	30, 31
Crohn's disease	Increased NF- κ B activation in the inflamed bowel, localized to macrophages and lymphocytes. Increased nuclear levels of p65 seen in the lamina propria.	30–32
Multiple sclerosis (MS)	NF- κ B activation seen in MS brain tissue, predominantly in astrocytes, microglia, oligodendrocytes, and infiltrating macrophages. Increased nuclear levels of p65, c-Rel, p50, and I κ B α seen in macrophages in active MS lesions.	223, 224



**(13) United States Patent
Baltimore et al.**

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Louis Stuuli, Silver Spring, MD (US);
Jonathan H. Lubowitz, Zionsville, IN
(US); Alan E. Johnson, Chapel
Hill, NC (US); Roger G. Clerc,
Research (US); Lynn M. Grossman,
Post Molecular Biology, Inc., Chapel
Hill, NC (US); Michael J.
Lessard, Potomac, MD (US);
Chen-Ming Fan, San Francisco;
Thomas P. Massie, Belmont, both of
MA (US)



Lilly loses Evista, Xigris patent case; will appeal

5th May 2006

by

PharmaTimes

Eli Lilly has been defeated in a patent infringement lawsuit, brought by Ariad Pharmaceuticals, that could see it having to pay royalties on its Evista osteoporosis drug and Xigris for sepsis.

The plaintiffs' claims were based on the discovery of a messenger cell, called NF- κ B, that controls the proteins a cell makes and in what quantities, thus playing a major role in several diseases. Harvard, MIT and Whitehead licensed the patent to Ariad, based in Cambridge.

In early May, a federal jury awarded at least \$65.2 million to Ariad Pharmaceuticals Inc. after finding that Eli Lilly's Evista and Xigris products infringed on an Ariad patent. Eli Lilly said it would take the case the U.S. Court of Appeals for the Federal Circuit if it has to.



Biopharmaceutical injectable fusion peptide between TNF receptor of IG1 for blockade In vivo of TNF (150 kDa) Rheumatoid arthritis Dermatology psoriasis

Q3 '15 Enbrel® Sales Grew 30% YoY



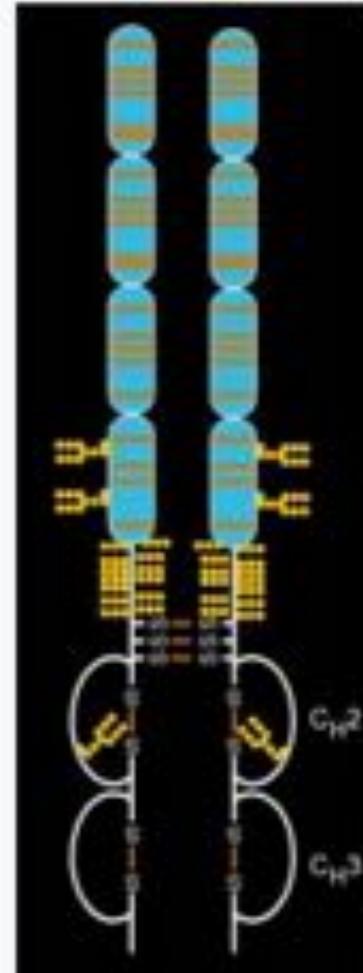
Highlights

- YoY sales growth driven by net selling price* and low inventory levels in the prior year period, offset partially by the impact of competition
- Rheumatology and dermatology segments grew YoY 25% and 38%, respectively, on a value basis
- Rheumatology share was relatively stable QoQ at 28%, while dermatology share was down 2 points QoQ to 24%
 - New dermatology entrants growing the market



Note: Net selling price represents the impact of list price changes as well as contracting and access changes.
Note: Inventory represents wholesale and, based on prescription data, end-user inventories.
Prescription inventories (2001, 2002), are cast of year-end prescription and in quantity.
By month, Company financial reporting, preliminary, actual results may vary.
*Excludes generic introductions, sales data in millions. 11

AMGEN



Clinical data

Trade names

Editorial

soluble TNFRII-human Fc fusion

2005-2007: Dr. Clerc 's hearing US Federal Court LosAngeles CA (USA)



Amgen's attempt to clear its products, Enbrel and Kineret, will now go forward after Judge Kent A. Jordan denied Ariad's motion to dismiss the case. The drugs have generated huge revenues for the company, which pulled in more than \$12.3 billion in revenue in 2005.

Ariad's attorneys, from the Los Angeles office of Irell & Manella LLP, filed a motion to dismiss the case on June 14, in which they argued that Amgen had failed to demonstrate that an "actual controversy" existed to support a declaratory judgment.

In the same motion, Ariad also argued the Amgen had failed to "join indispensable parties to the suit," namely Harvard University, the Massachusetts Institute of Technology and MIT's independent Whitehead Institute.

The three institutions collectively own the Ariad patent targeted in the lawsuit.



03 United States Patent Baltimore et al.

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NFkB patent infringement : Dr. Clerc 's hearing @ US Federal Court LosAngeles CA (USA)



“Es ist alles andere als alltäglich, dass der Dozent vor dem Federal Court sein Patent verteidigen musste” *dixit Rafael Müller MScPharm University of Basel Switzerland*



***NFkB patent infringement : Dr. Clerc 's hearing @ US Federal Court
LosAngeles CA (USA)***



“Es ist alles andere als alltäglich, dass der Dozent vor dem Federal Court sein Patent verteidigen musste” *dixit Rafael Müller MScPharm University of Basel Switzerland*

JUL 10 2007

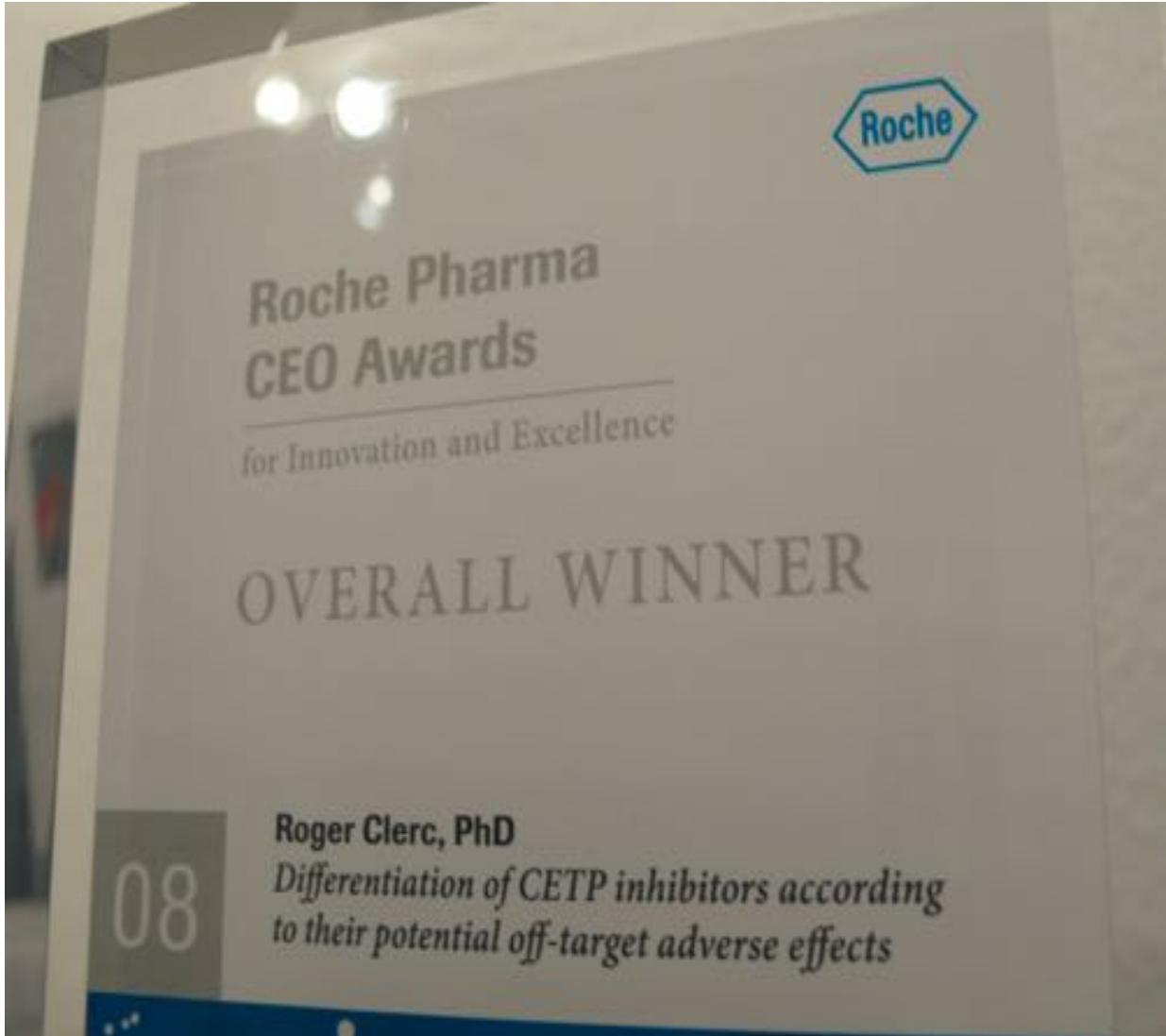
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Biomedical research : team work is a must !



Clerc lab (2016) Roche pRED Basel and University of Basel Switzerland
“the ability to work together towards a common vision”

Biomedical research : team work is a must Intellectual property belongs to the team !



Breaking news : who owns a Crispr/Cas9 case patent ? debate !



NEWS IN FOCUS

INTELLECTUAL PROPERTY

Titanic clash over CRISPR patents turns ugly

Accusations of impropriety feature in escalating dispute.

News and Views : Nature (2017) 543:296-297

East coast vs west coast ?

Whose discovery is it ? the CRISPR heroes !

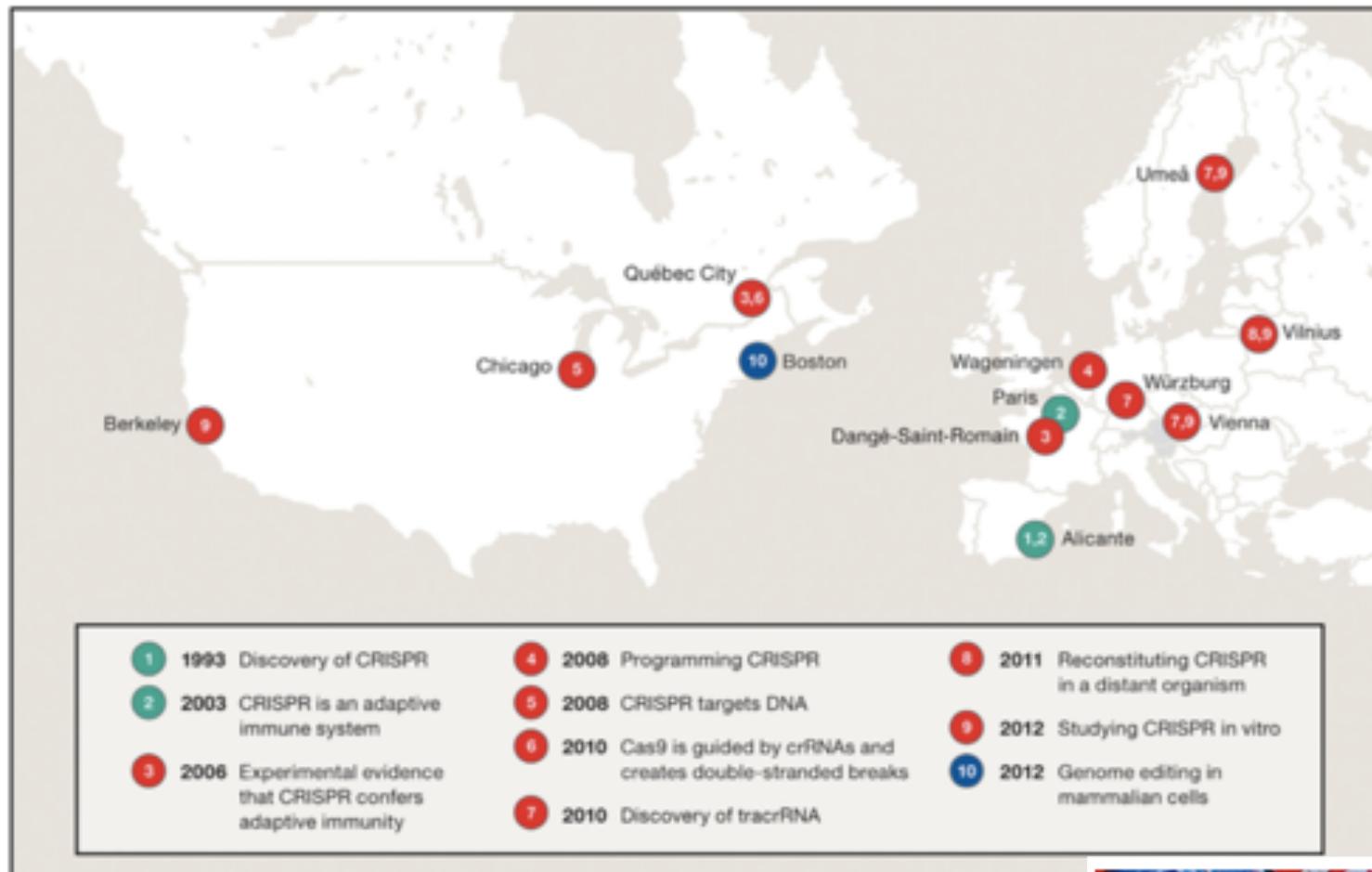


Figure 2. The Twenty-Year Story of CRISPR Unfolded across Twelve Cities in Nine Countries



Patent trial_Crispr/Cas9 case_hot debate today !



RESEARCH MANAGEMENT

A delicate balance

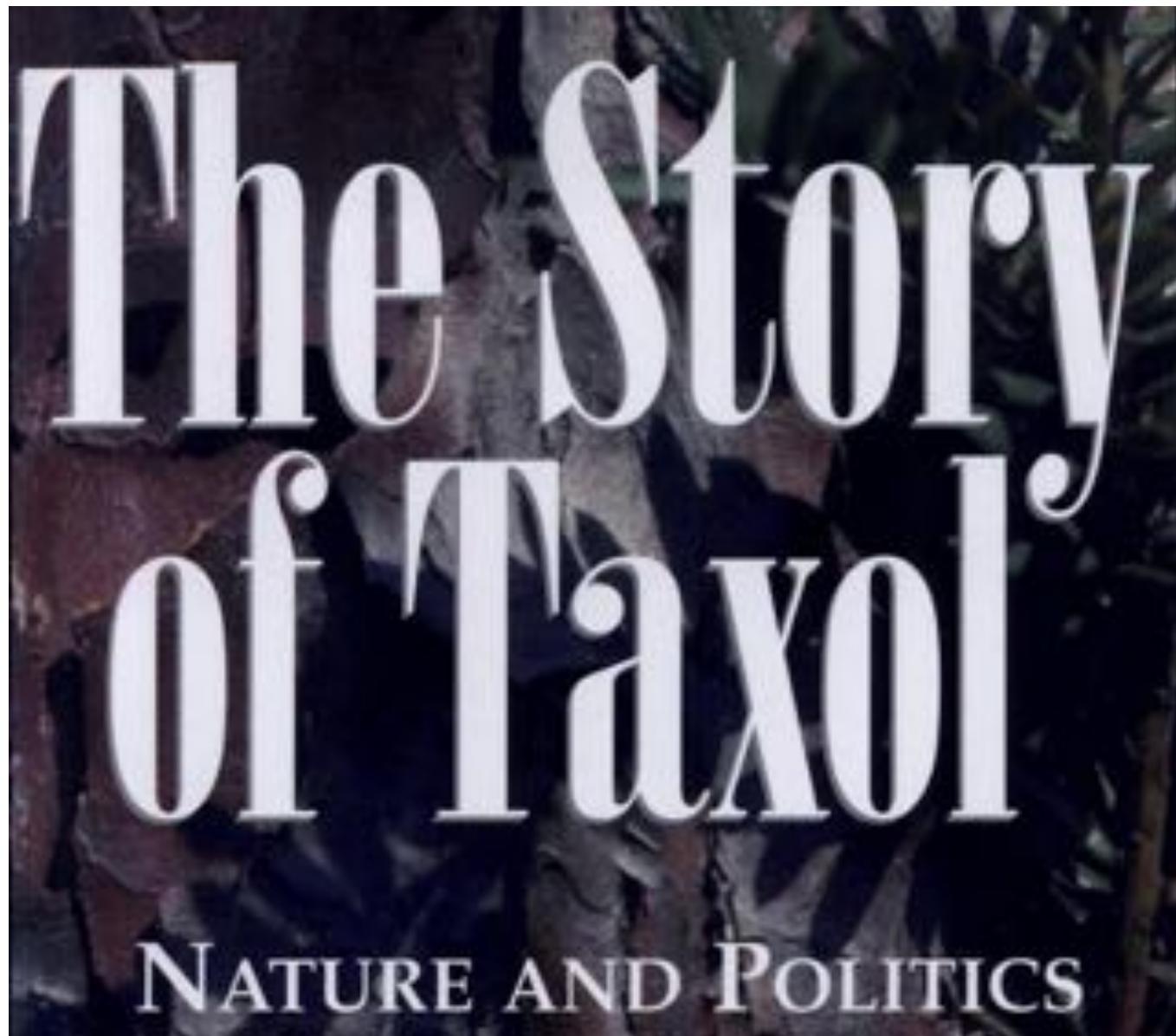
Natural products intellectual property- eg taxol



taxol became Taxol®



Natural products property



WORKSHOP



taxol became Taxol[®]

The discovery of taxol, its characterization and synthetic production

How changing ownership of the mostly used anti-cancer drug affects pharma and the patients

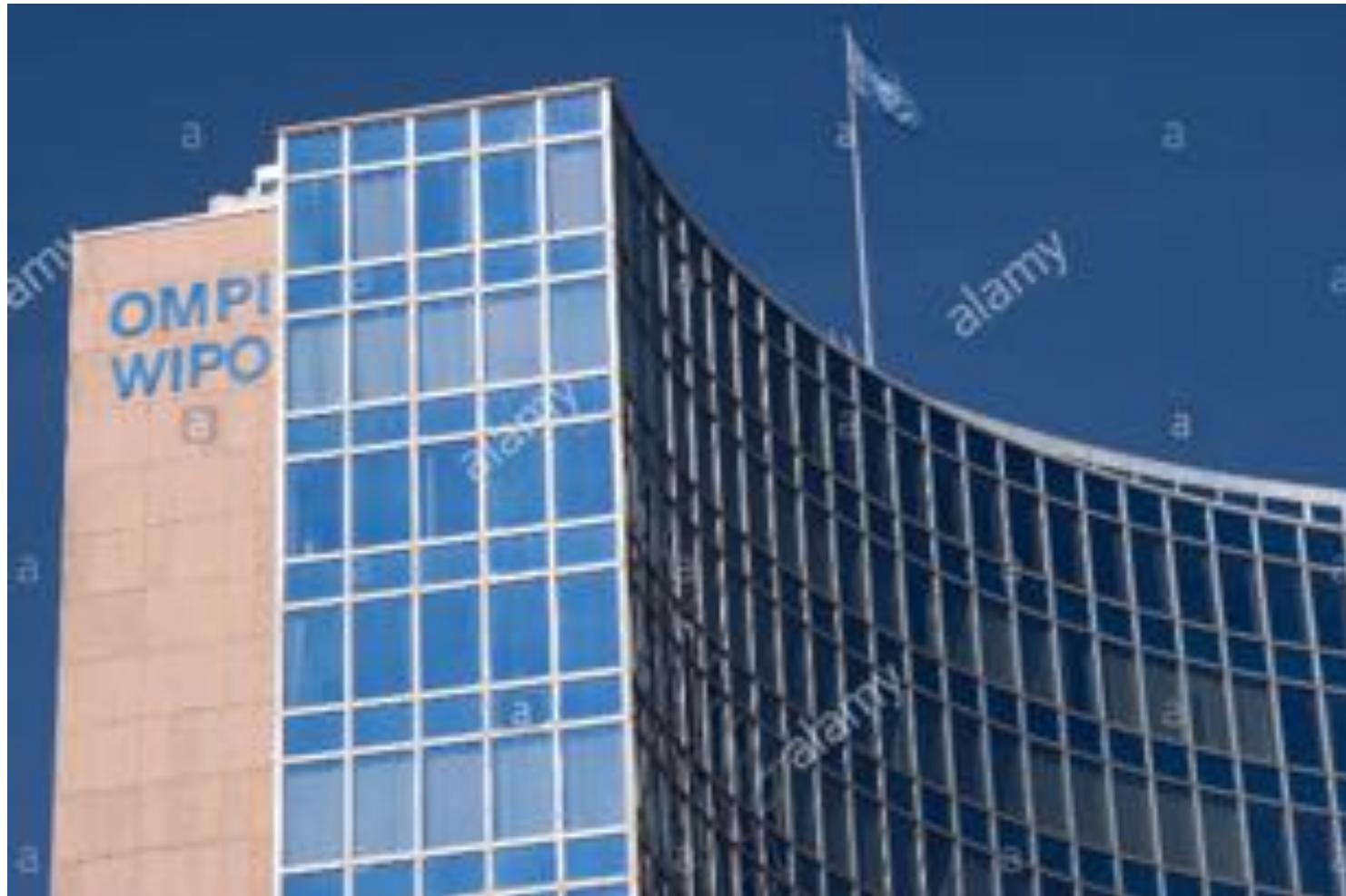
How do you address the intellectual property of natural products used in the pharmacopoeia

Effect of privatization of intellectual property affects the pricing of medicine and patients at large



natural product became NATURALPRODUCT®

WORKSHOP



Older and newly marketed medicines : planned obsolescence ? A consequence of patent life ?



Médecine Modifié à 08:04



L'obsolescence programmée existe aussi dans le domaine pharmaceutique



L'obsolescence programmée existe aussi dans le domaine pharmaceutique Audio de l'info / 1 min. / hier à 07:00

Les brevets qui protègent les nouveaux médicaments permettent à l'industrie pharmaceutique d'engranger des bénéfices. Au terme des vingt ans de couverture, les fabricants n'hésitent pas à dénigrer leur propre produit.

Breaking news RTS/SSR 2018

Older and newly marketed medicines : planned obsolescence ? A consequence of patent life and consequences on healthcare costs



PHOTOGRAPH BY

Allen Frances, M.D., Contributor

Allen Frances MD is Professor Emeritus of Psychiatry and former Chair at Duke University



New Drugs Are Often Bad For Patients, Great For Pharma

10/07/2016 08:22 pm ET | Updated Oct 08, 2017

The business model that generates huge profits for the drug industry depends on planned obsolescence. The big bucks are earned when a drug is still on patent, free of competition, and can be outrageously priced.

Pharma has developed all sorts of devious tricks to extend the duration of its patent monopoly on older drugs and also works hard to develop new "me too" drugs that provide no advantage to patients, but protect its monopoly pricing power.

Pharma research has failed to produce much real progress in fighting disease, largely because curing disease is not its mission. Instead, most Pharma research is tied to marketing and lobbying- with the primary goal of generating profit, not helping patients.



Medicine pricing : how much may life saving drugs cost ? what is the price of a living human ?



Medicine pricing : how much may life saving drugs cost ? is $121 > 10^6$ Euro the price tag of a human life ?



121 Millionen Euro hat Chelsea für Enzo Fernández an Benfica Lissabon bezahlt. Das ist englischer Rekord.

Pedro Nunes / Reuters



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[OECD Home](#) > [Topics](#) > Pharmaceutical Pricing Policy project

Pharmaceutical Pricing Policy project

The OECD Pharmaceutical Pricing Policy project had two main objectives:

- To add to the base of information about pharmaceutical pricing policy in OECD countries and develop a taxonomy and framework for making international comparisons of policies
- To analyse cross-national impacts and implications of policies, particularly with respect to the impacts on pharmaceutical prices paid in other countries and on pharmaceutical R&D



Section 11



THANK YOU.....

DO YOU HAVE ANY QUESTIONS ?

