Institute for
Interdisciplinary
Innovation in healthcare

ULB

Certificate in Translational Medicine

Brussels, 4-29 January 2016

Institute for
Interdisciplinary
Innovation in healthcare

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Setting the Scene

Michel Goldman, MD, PhD

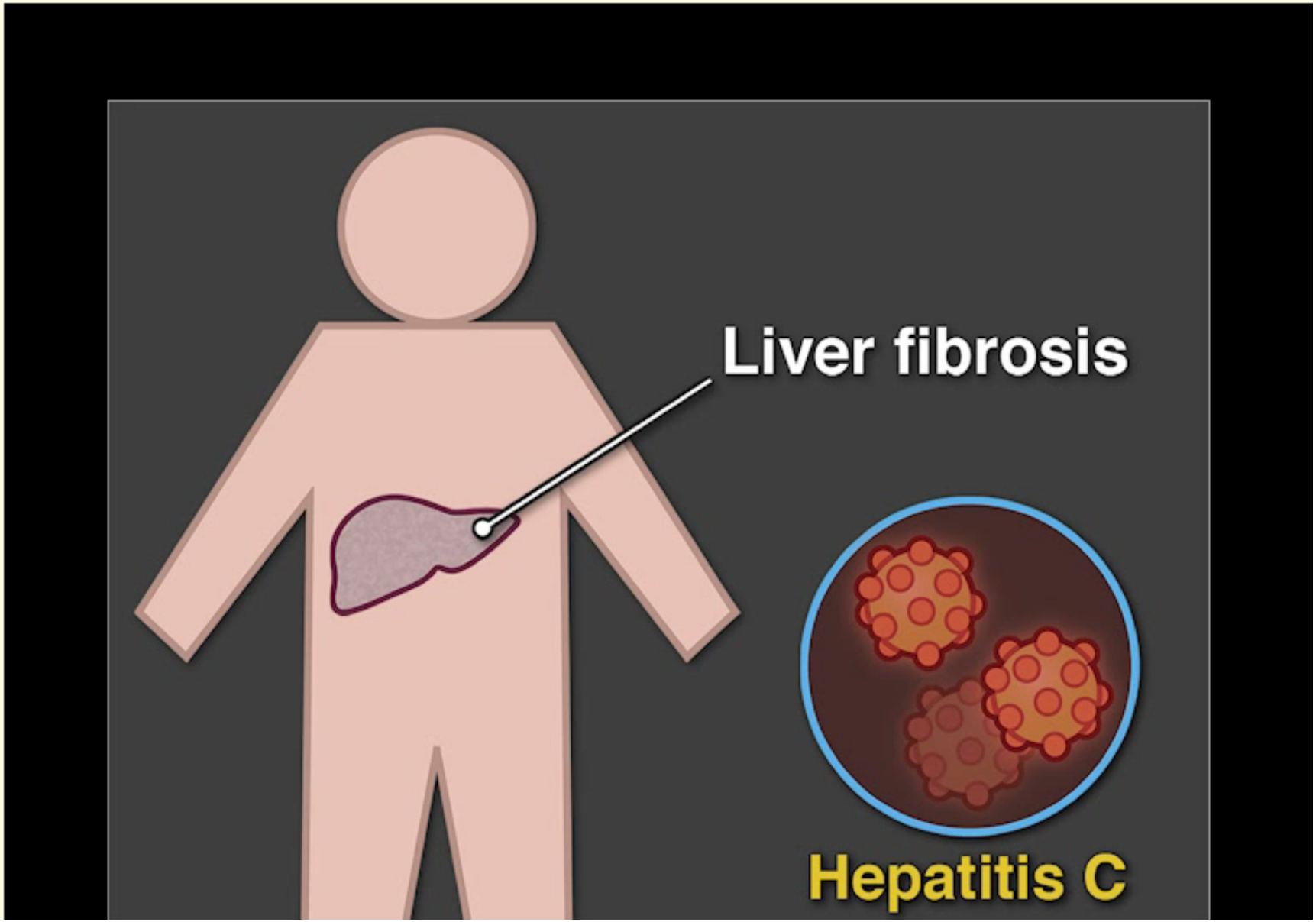
Certificate in Translational Medicine, Brussels, 4-29 January 2016

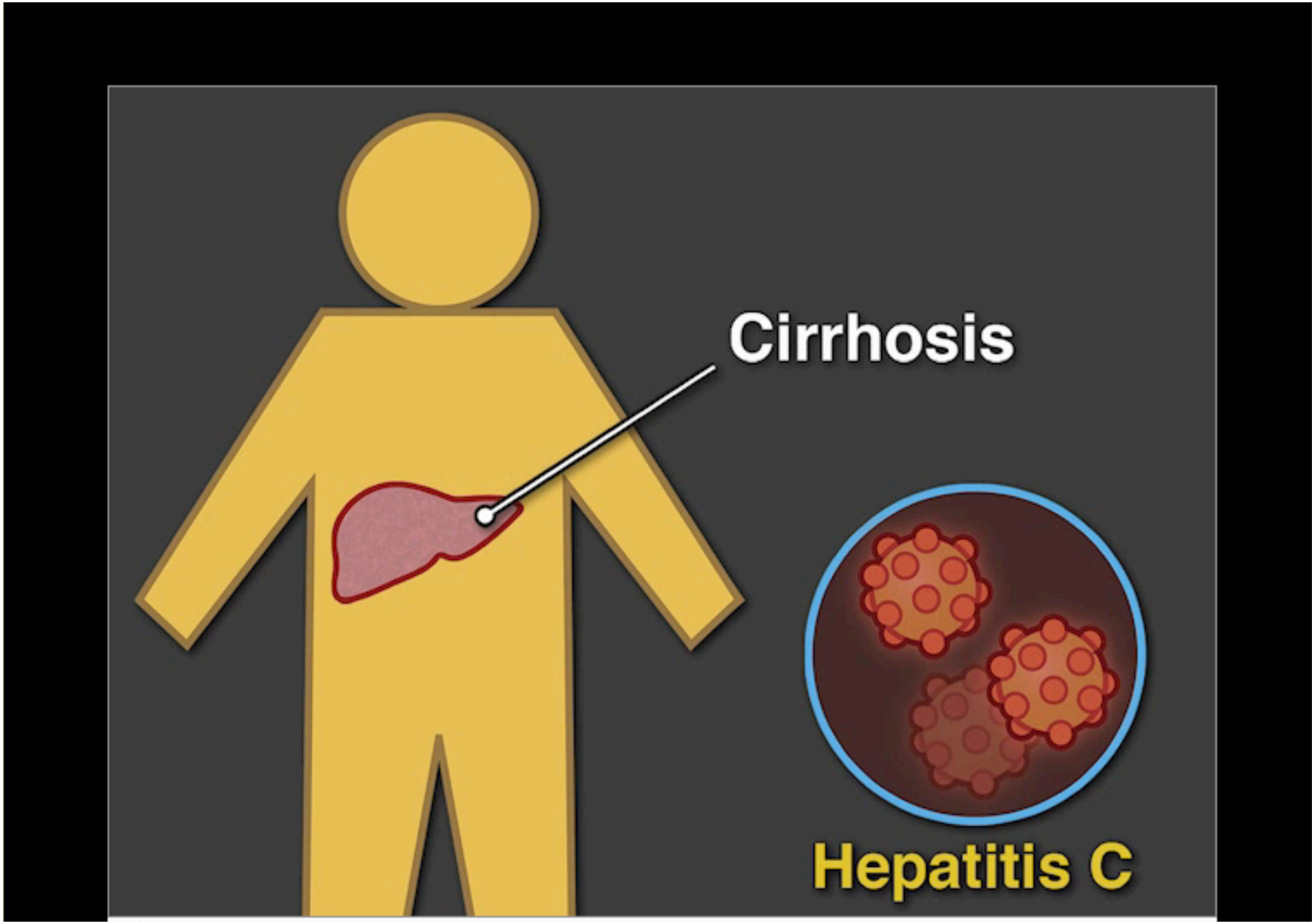
The NEW ENGLAND JOURNAL of MEDICINE

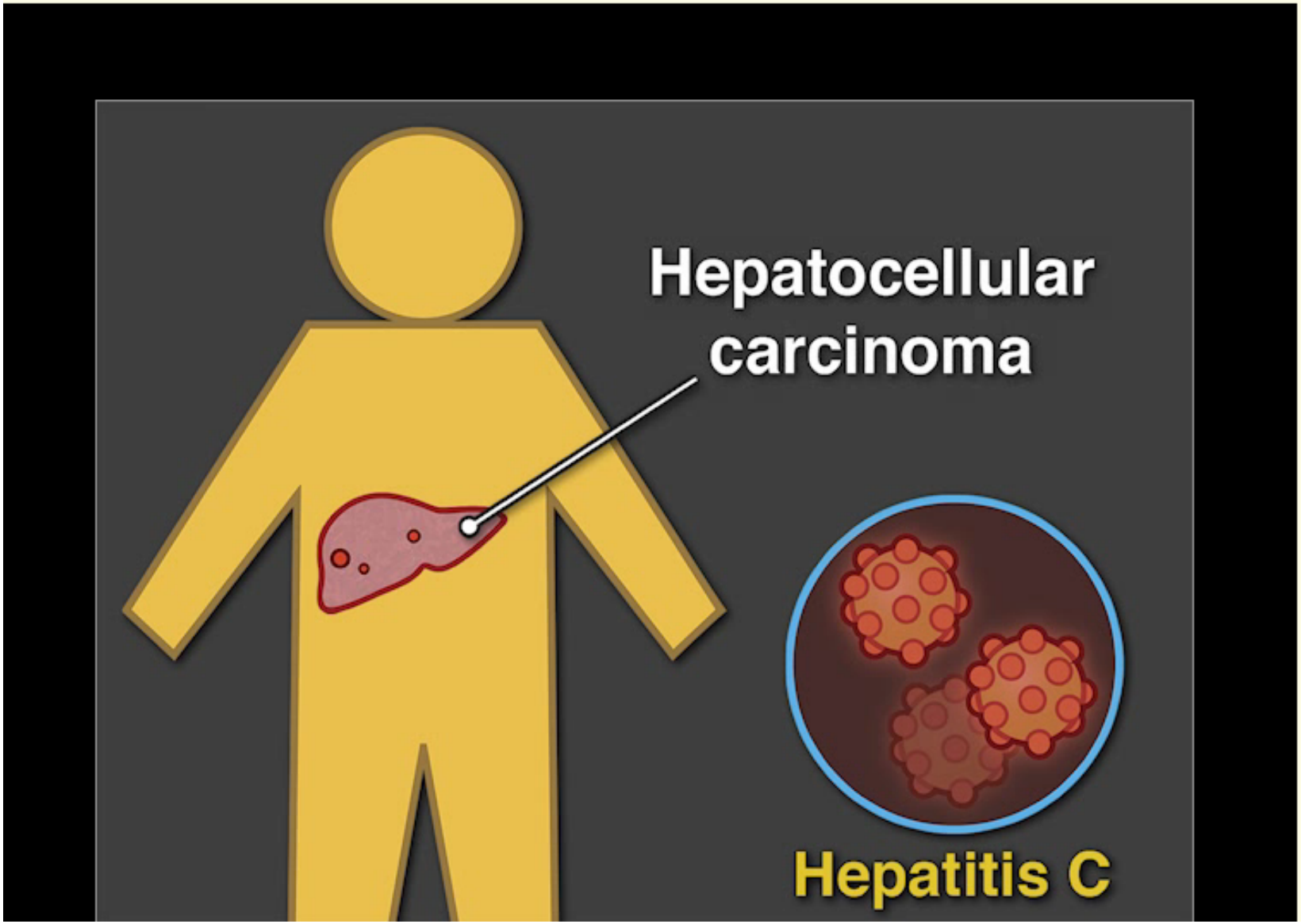
ESTABLISHED IN 1812 DECEMBER 31, 2015 VOL. 373 NO. 27

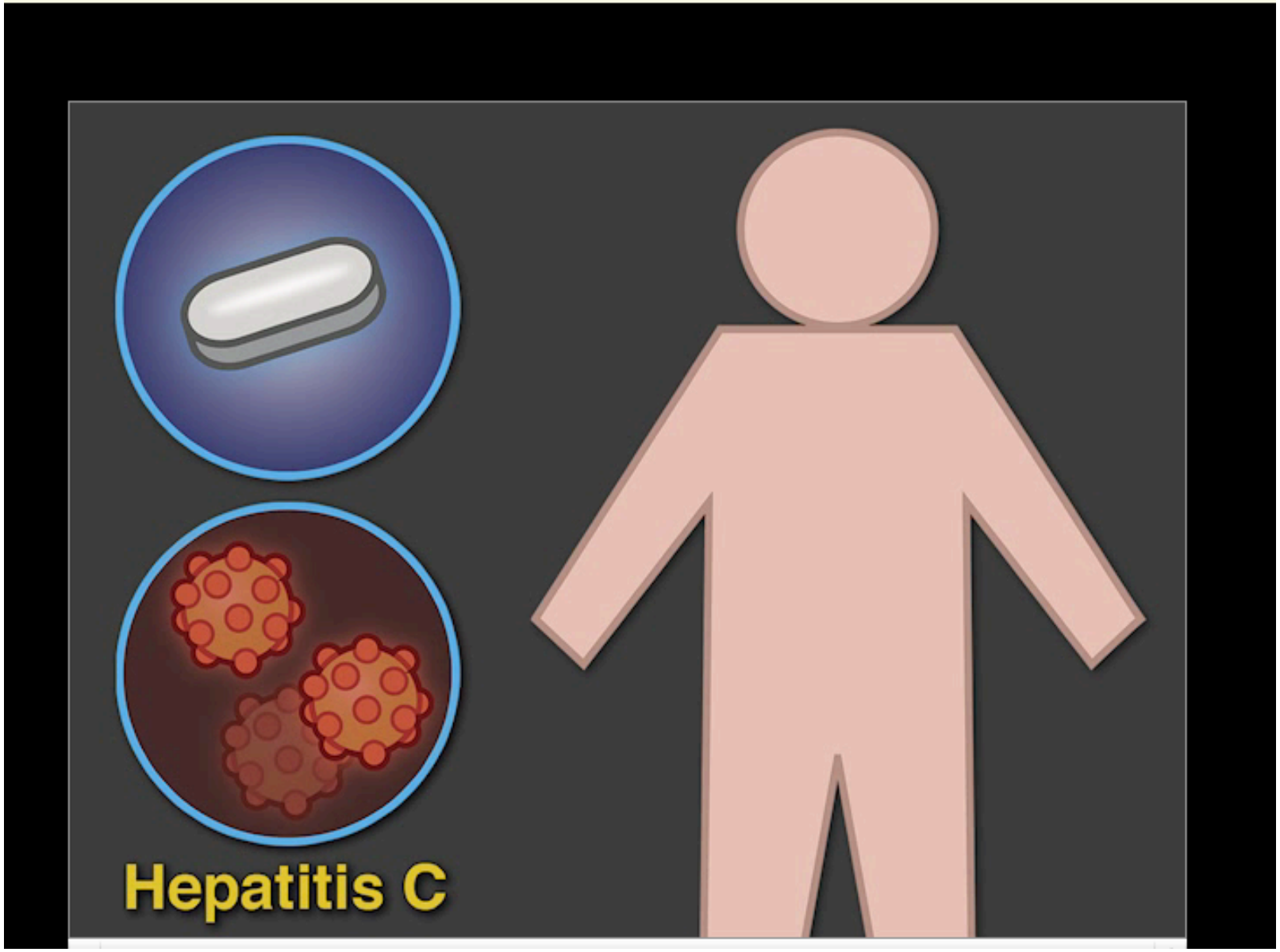
Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection

J.J. Feld, I.M. Jacobson, C. Hézode, T. Asselah, P.J. Ruane, N. Gruener, A. Abergel, A. Mangia, C.-L. Lai, H.L.Y. Chan, F. Mazzotta, C. Moreno, E. Yoshida, S.D. Shafran, W.J. Towner, T.T. Tran, J. McNally, A. Osinusi, E. Svarovskaia, Y. Zhu, D.M. Brainard, J.G. McHutchison, K. Agarwal, and S. Zeuzem, for the ASTRAL-1 Investigators*


Liver fibrosis
Hepatitis C

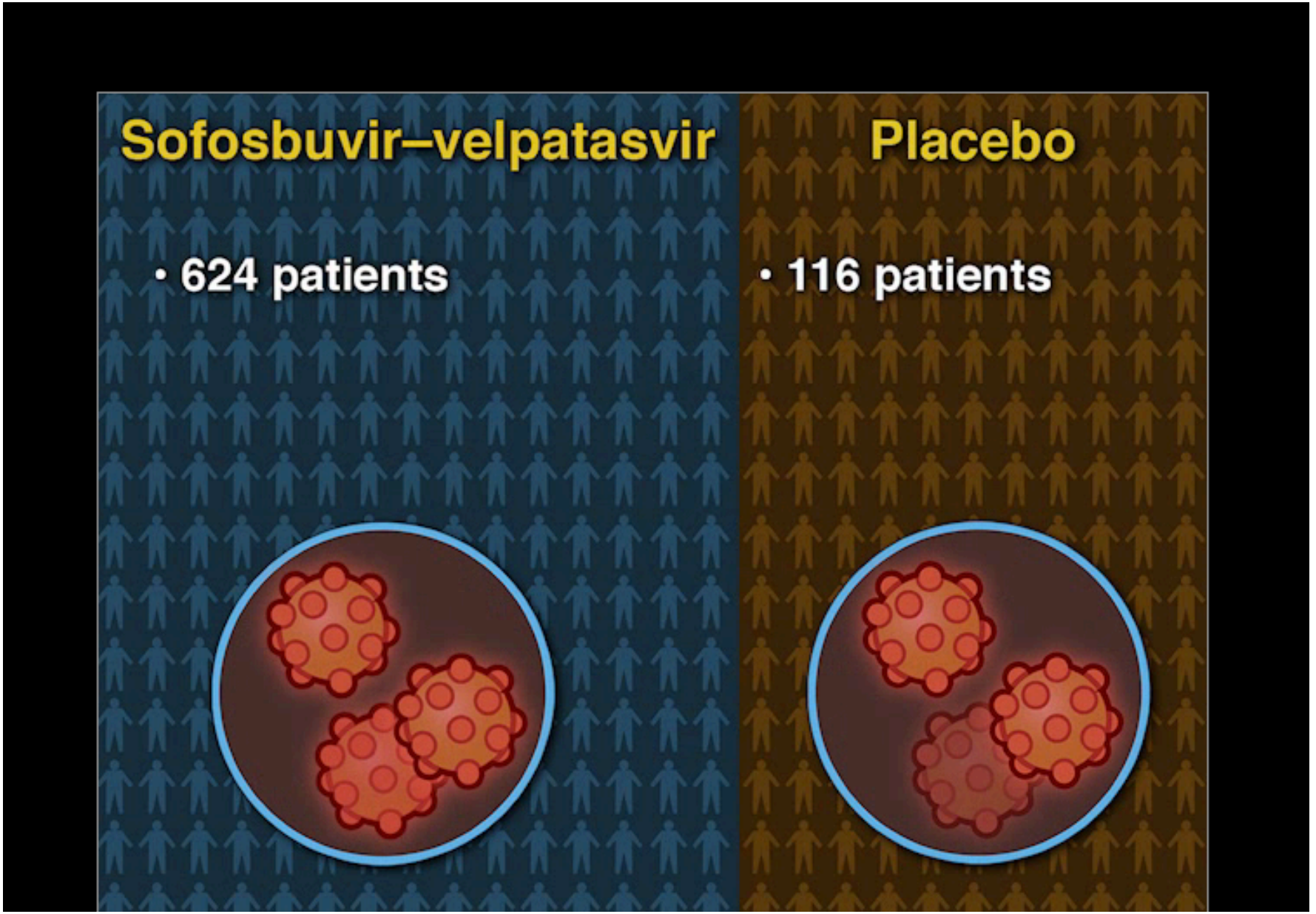

Cirrhosis
Hepatitis C

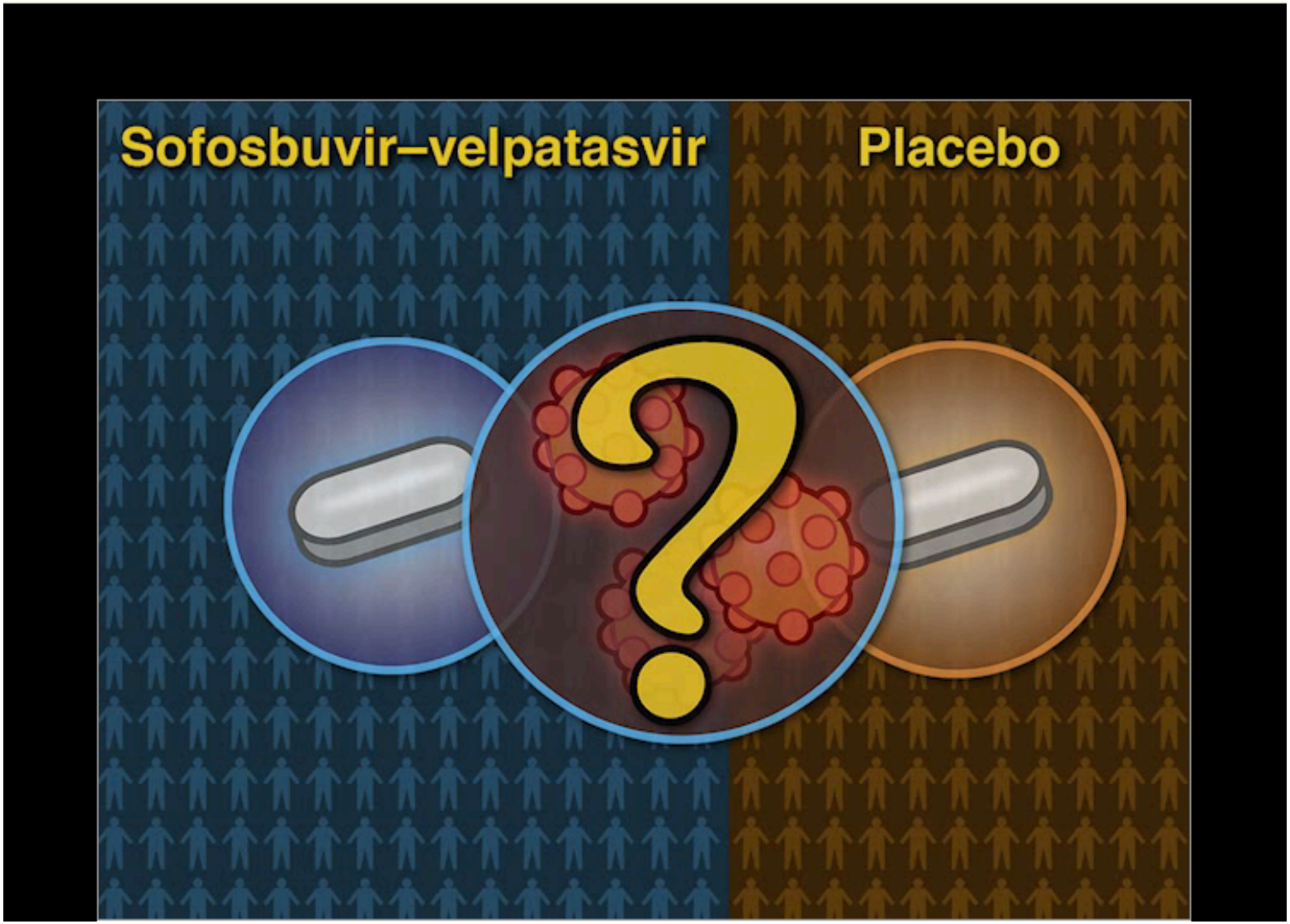

Hepatocellular carcinoma
Hepatitis C



Phase 3, double blind, placebo controlled trial

HCV GENOTYPES 1,2,4,5,6


Sofosbuvir–velpatasvir
• 624 patients
Placebo
• 116 patients


Sofosbuvir–velpatasvir
Placebo

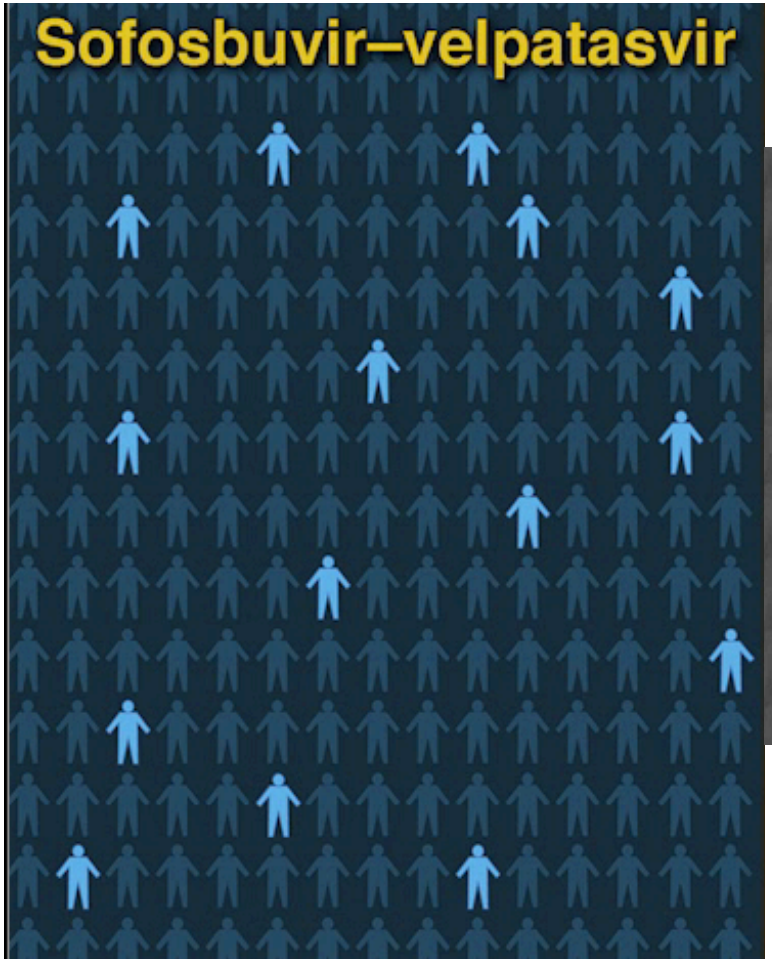
Sofosbuvir–velpatasvir

- 624 patients
- 99% sustained virologic response

Placebo

- 116 patients
- No sustained virologic response

SIDE EFFECTS



- Headache
- Fatigue
- Nasopharyngitis
- Nausea

What is Translational Medicine?

Translational medicine integrates the multiple steps and processes involved in the translation of research findings into standard of care for the benefits of patients and society

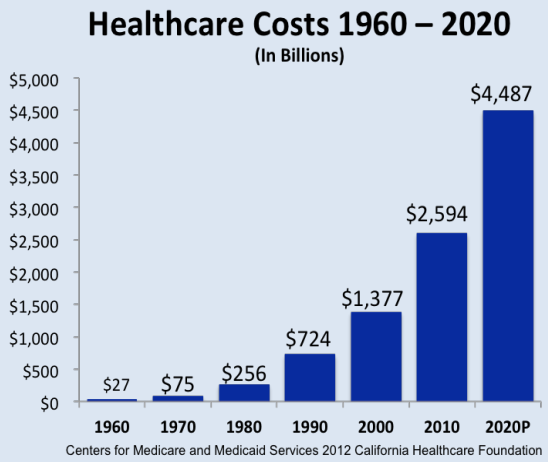
- Delivers innovative tools and products for preventing or treating human diseases at the community level (diagnostics, drugs, biotherapies, vaccines, medical devices…)

- **Interdisciplinary and collaborative by nature**

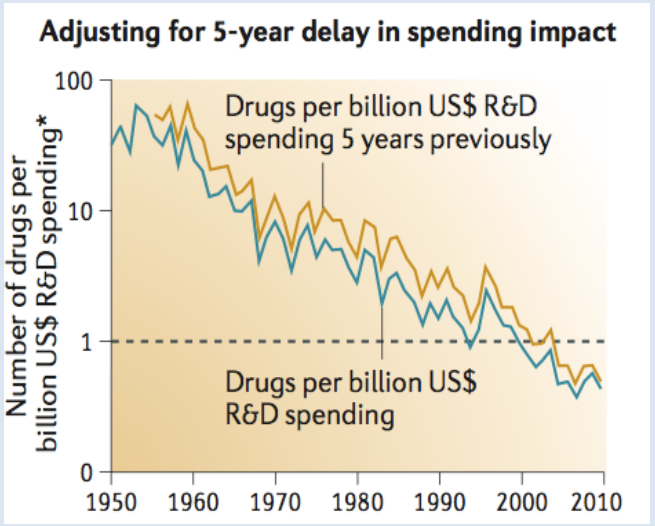
The Healthcare Conundrum

Growing medical needs

Ageing population & increased incidence of chronic diseases



Declining pharma R&D productivity



Source: http://www.phitamerica.org/

Scannell et al. - 2012 - Diagnosing the decline in pharmaceutical R&D efficiency

Alzheimer's disease:
An urgent need for new strategies

Major public health need	Recent failures	Hurdles to drug development
▪ Affects **10m Europeans** (14m by 2040) ▪ Annual cost in EU: **€180b** (€ 250b by 2030)	**Inconclusive results of phase 3 clinical trials:** ▪ Solanezumab ▪ Bapineuzumab ▪ Human Igs	▪ Complexity of brain pathology ▪ Patients' heterogeneity ▪ Lack of validated markers for disease activity

Autism Spectrum Disorders:
A neglected public health need

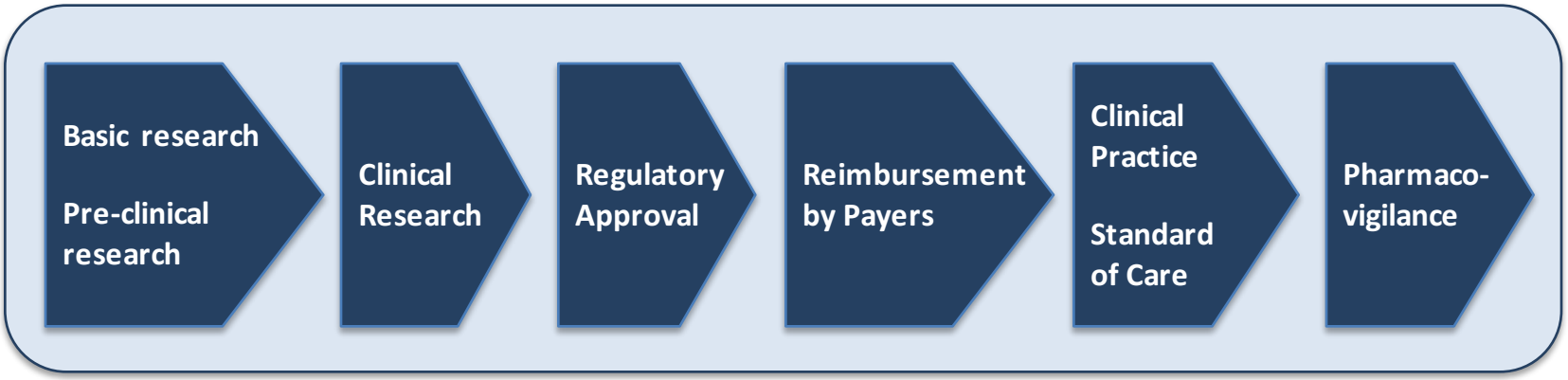
Major public health need	Distrust in past research	Hurdles to drug development
▪ **1% children affected** ▪ **Lifetime cost: €3Mi/patient**	▪ **MMR vaccine allegation** ▪ **Psychoanalytic theories** (France)	▪ Complexity of brain pathology ▪ Patients' heterogeneity ▪ Lack of validated markers for disease activity

The Birth of Experimental Medicine

Vaccination (Edward Jenner, 1749-1823)

Translational Medicine:

From Scientific Breakthrough to Patient Care



Moving Translational Medicine Forward: Education is Key

Mastering Translational Medicine: Interdisciplinary Education for a New Generation

Kyle Kurpinski,[1*] Terry Johnson,[1] Sanjay Kumar,[1] Tejal Desai,[2] Song Li[1*]

Graduate-level education in translational medicine will require more than just scientific research.

www.ScienceTranslationalMedicine.org 8 January 2014 Vol 6 Issue 218 218fs2

American Economic Review 2013 103: 406-411
http://dx.doi.org/10.1257/aer.103.3.406

Can Financial Engineering Cure Cancer?

By DAVID E. FAGNAN, JOSE MARIA FERNANDEZ, ANDREW W. LO, & ROGER STEIN

NBER WORKING PAPER SERIES

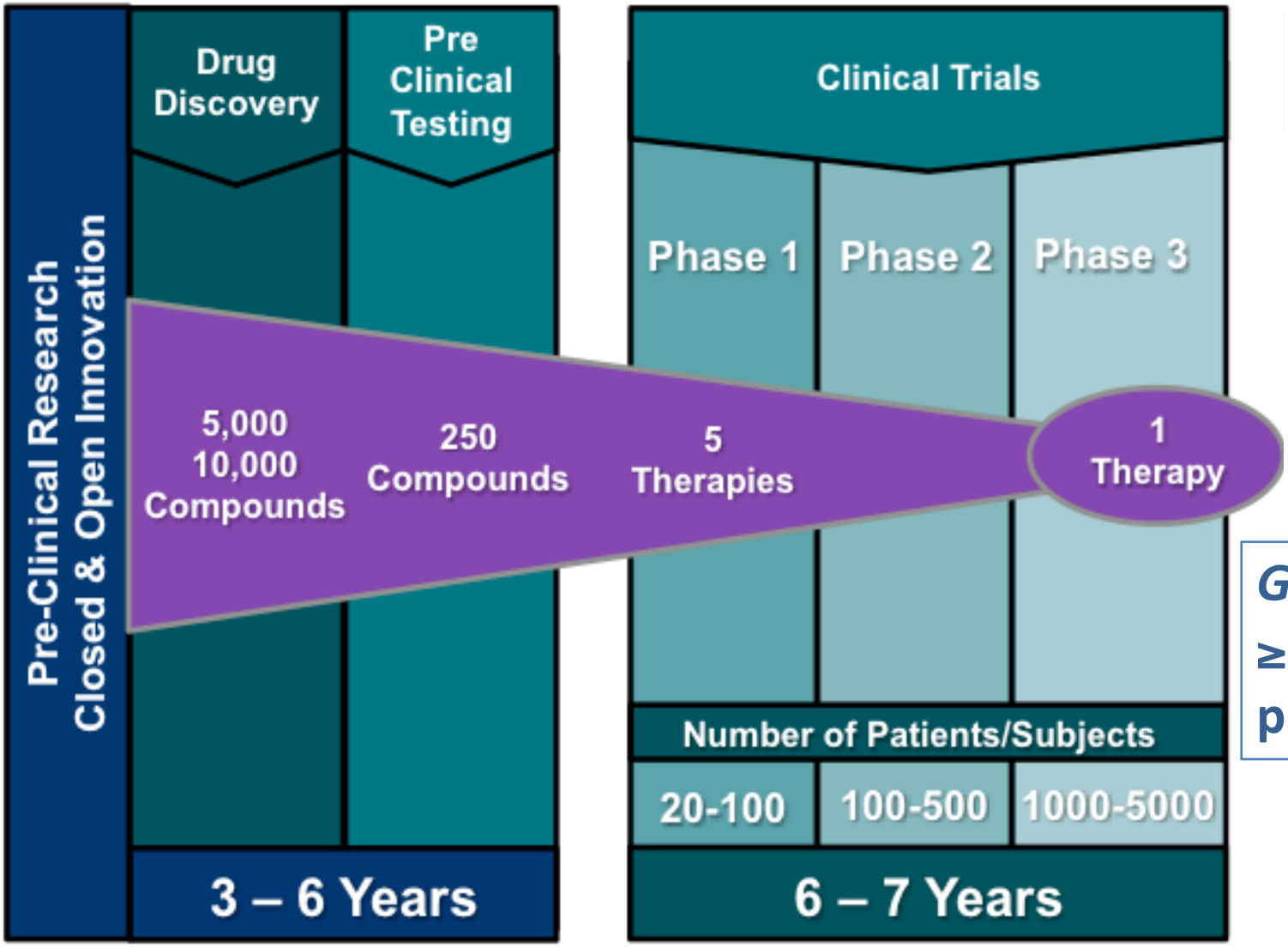
IS THE FDA TOO CONSERVATIVE OR TOO AGGRESSIVE?: A BAYESIAN DECISION ANALYSIS OF CLINICAL TRIAL DESIGN

Vahid Montazerhodjat
Andrew W. Lo

Working Paper 21499
http://www.nber.org/papers/w21499

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
August 2015

Medical Innovation:
Inefficiency of the Conventional Model



Global cost:
≥1 billion €
per new drug

Uncertainty in Healthcare

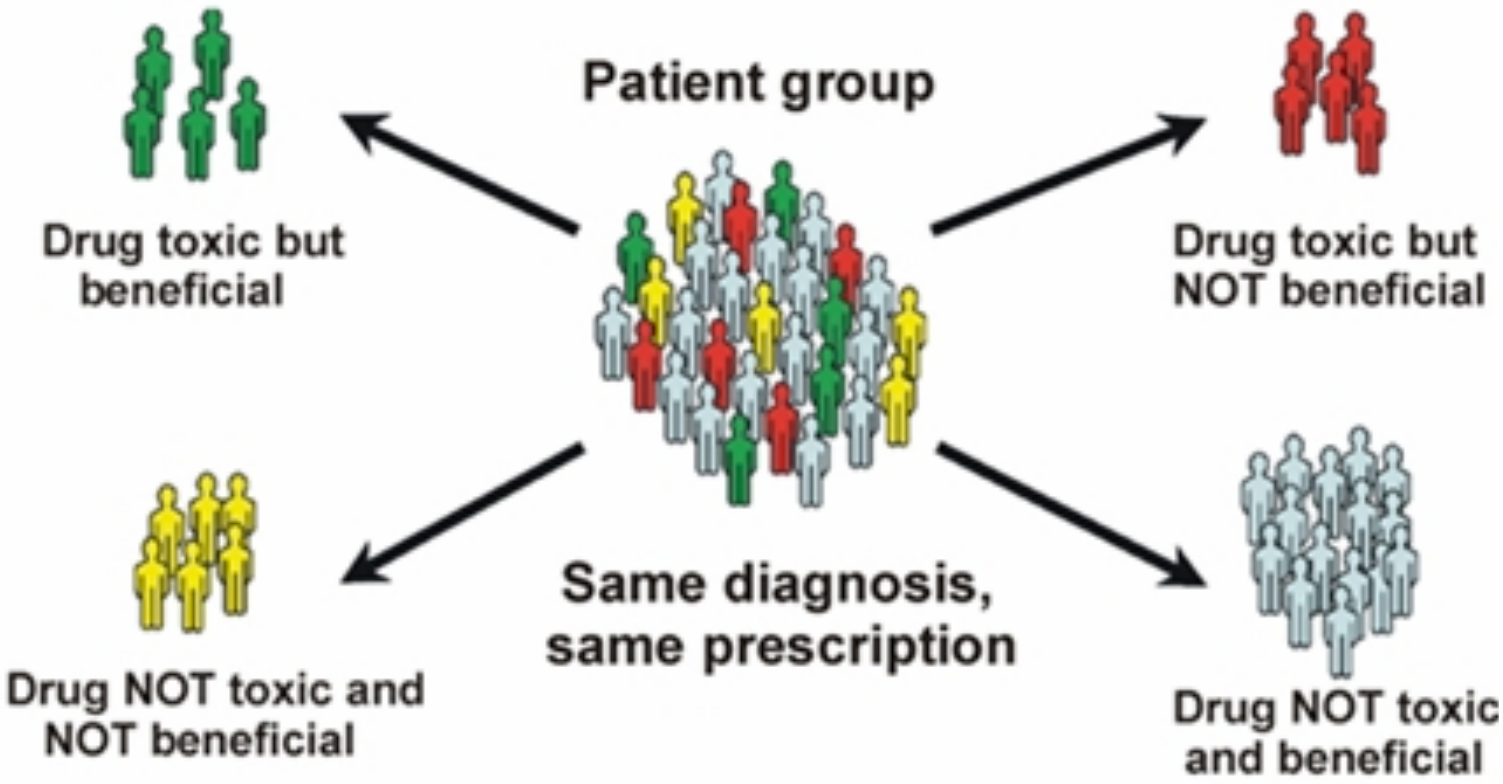
Drug		Efficacy
Anti-Depressants	62 %	
Asthma	60 %	
Diabetes	57 %	
Arthritis	50 %	
Alzheimer	30 %	
Cancer	25 %	

Drug does not work

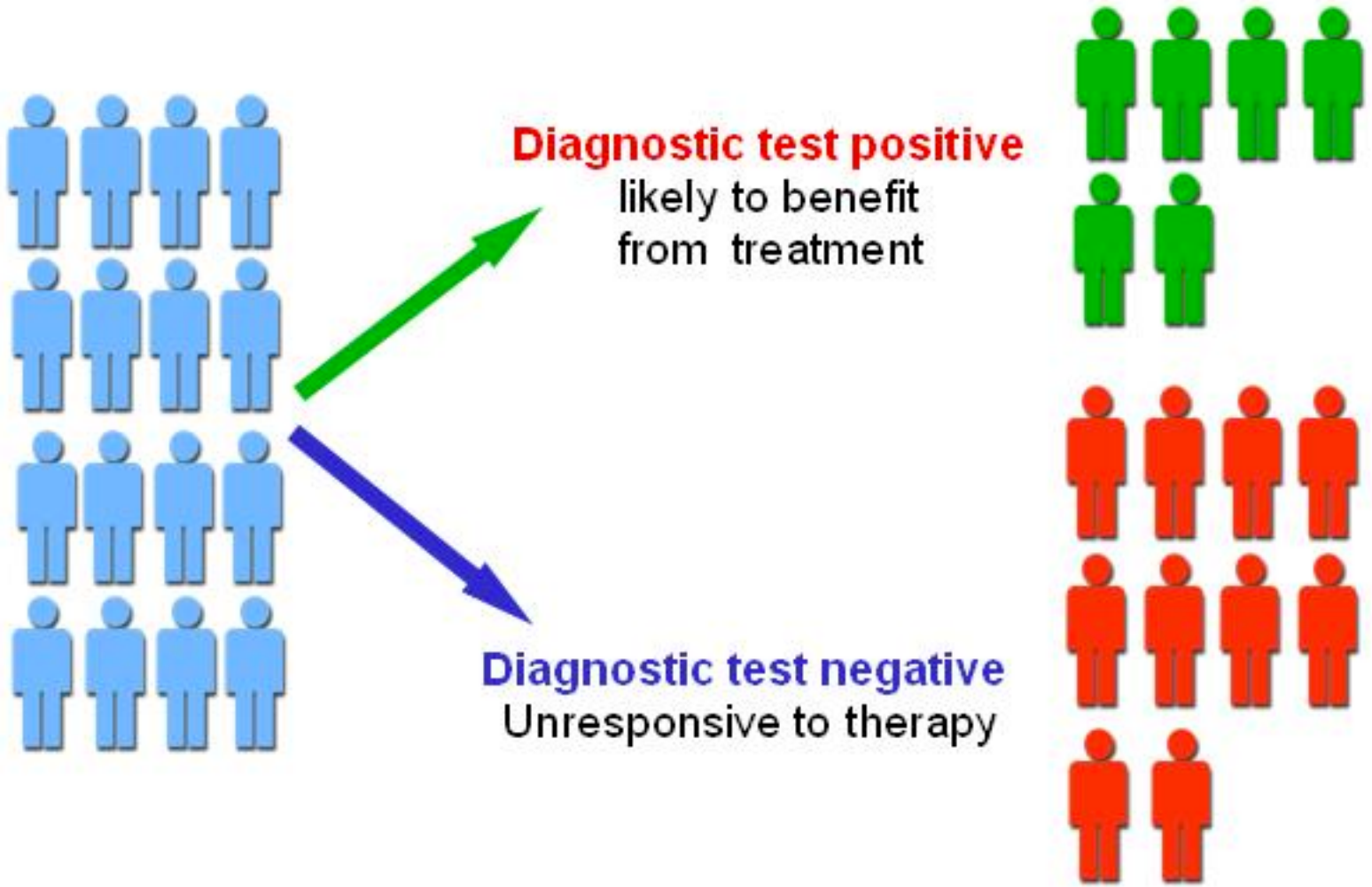
“Medicine is a science of uncertainty and an art of probability.”

Sir William Osler

1849-1919


Patient group
Drug toxic but beneficial
Drug toxic but NOT beneficial
Same diagnosis, same prescription
Drug NOT toxic and NOT beneficial
Drug NOT toxic and beneficial

Personalized Medicine



Personalized Medicine: A new concept ? (1)

It’s far more important to know what person the disease has than what disease the person has.

- Hippocrates -

Personalized Medicine: A new concept ? (2)

The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

Vol. 88, No. 12 — Chicago, Illinois — March 19, 1927

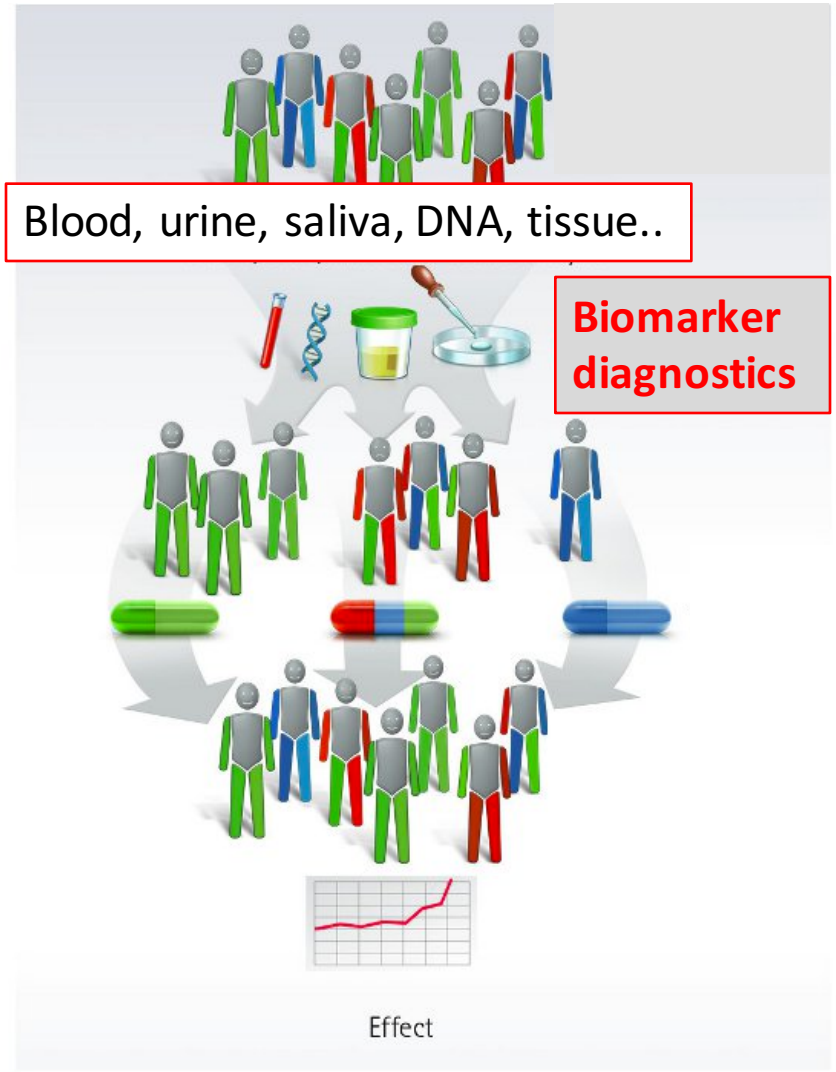
THE CARE OF THE PATIENT *

FRANCIS W. PEABODY, M.D.
BOSTON

It is probably fortunate that systems of education are constantly under the fire of general criticism, for if education were left solely in the hands of teachers science to the diagnosis and treatment of disease is only one limited aspect of medical practice. The practice of medicine in its broadest sense includes the whole relationship of the physician with his patient. It is an art, based to an increasing extent on the medical sciences, but comprising much that still remains outside the realm of any science. The art of medicine and the science of medicine are not antagonistic but supple-

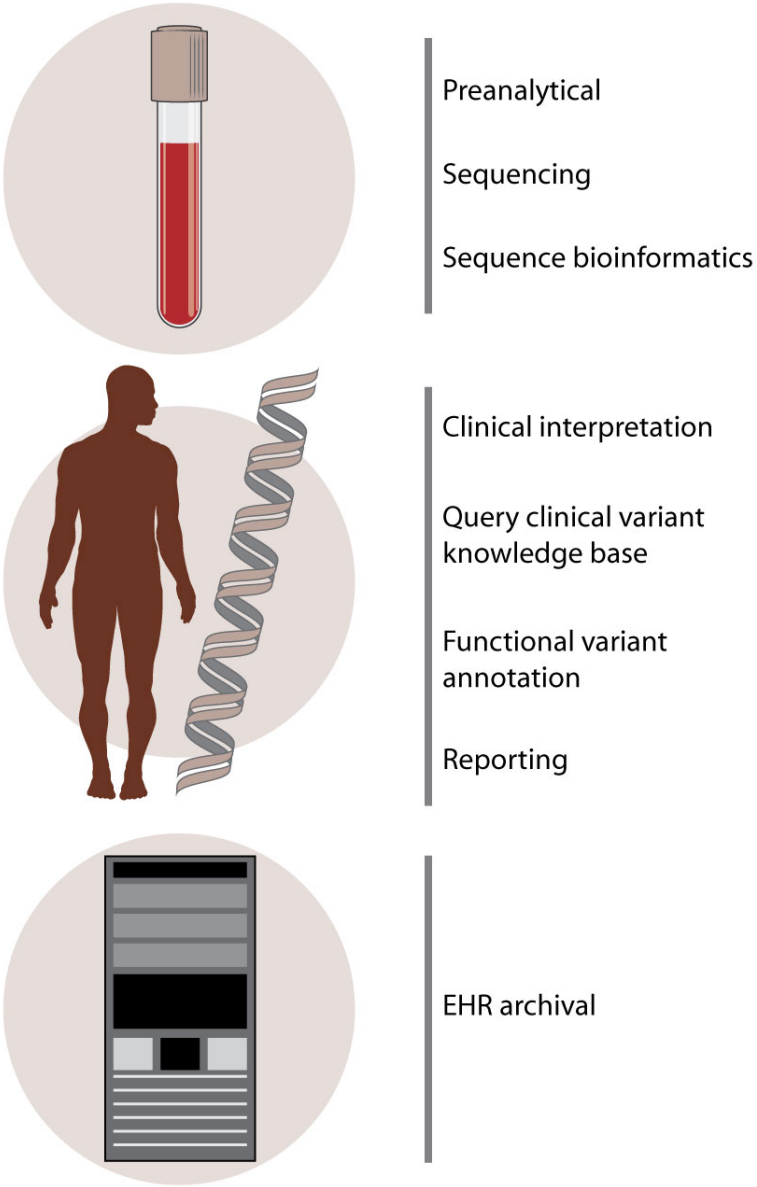
"….the care of a patient must be entirely personal."

Precision Medicine



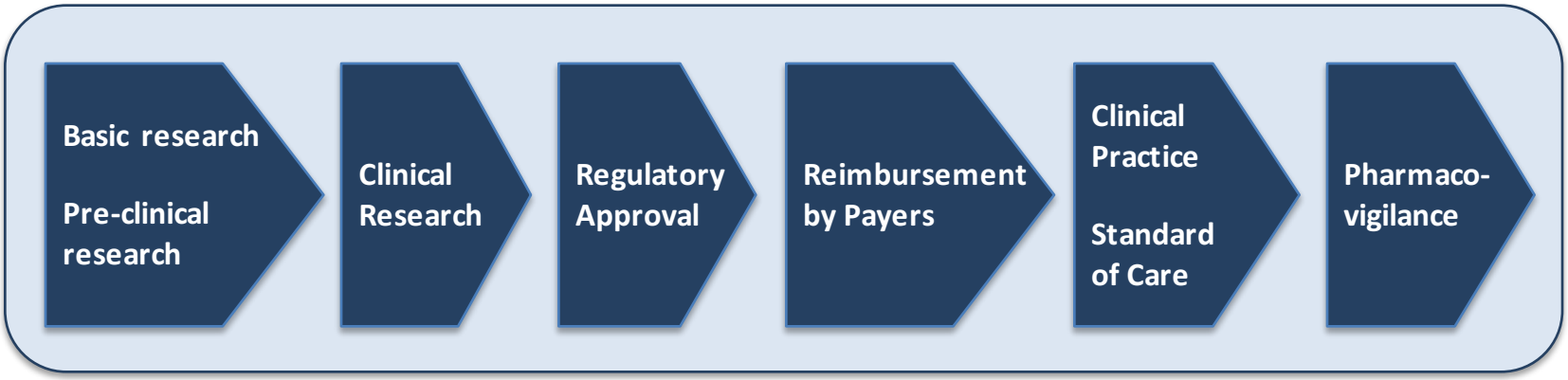
It's all about your genome, and we have something JUST for you.

From Laboratory to Patient to the Cloud

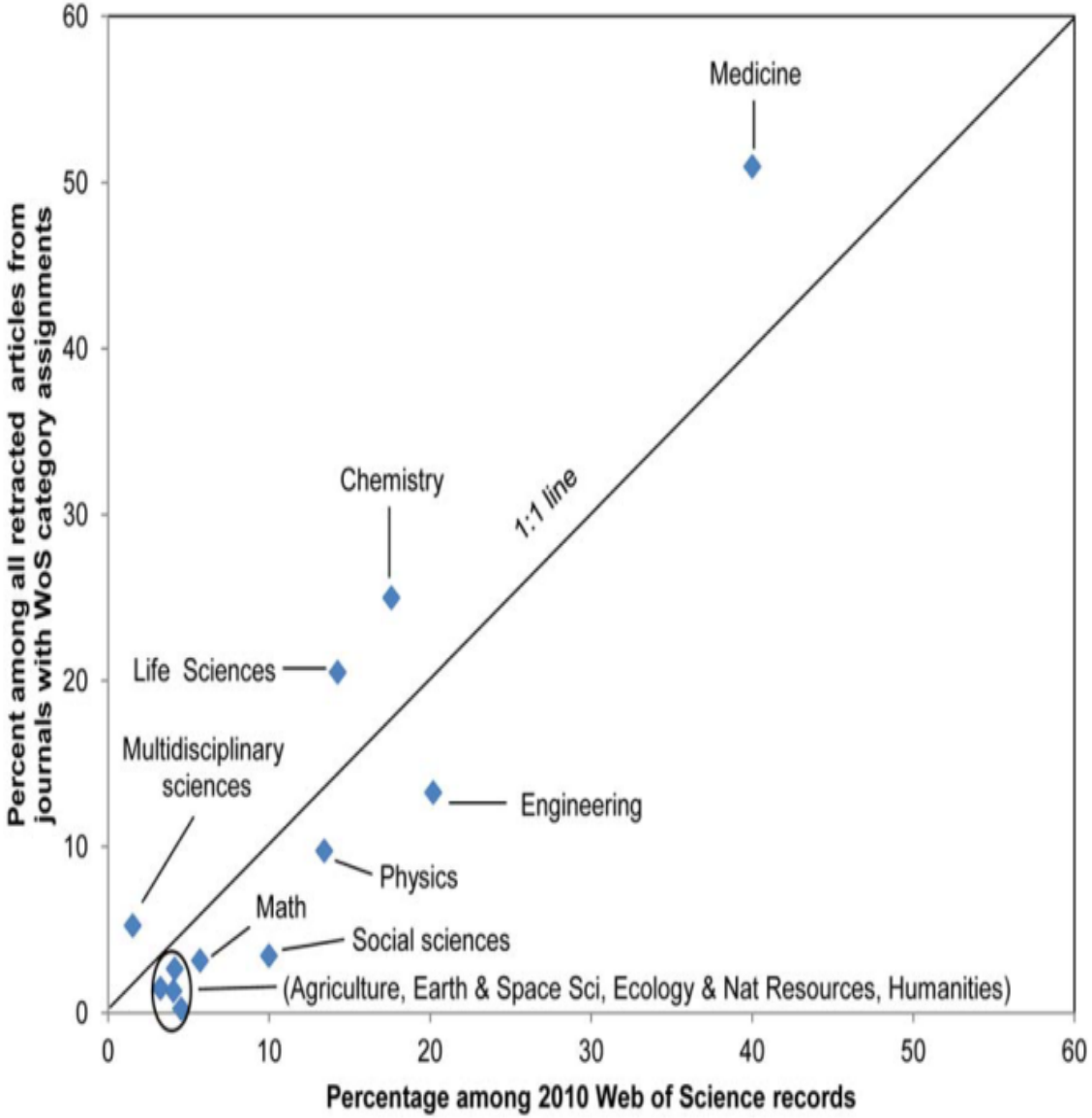


Russ B. Altman et al., Sci Transl Med 2015;7:315ps22

How to move Translational Medicine forward ?



How reliable is biomedical science ?



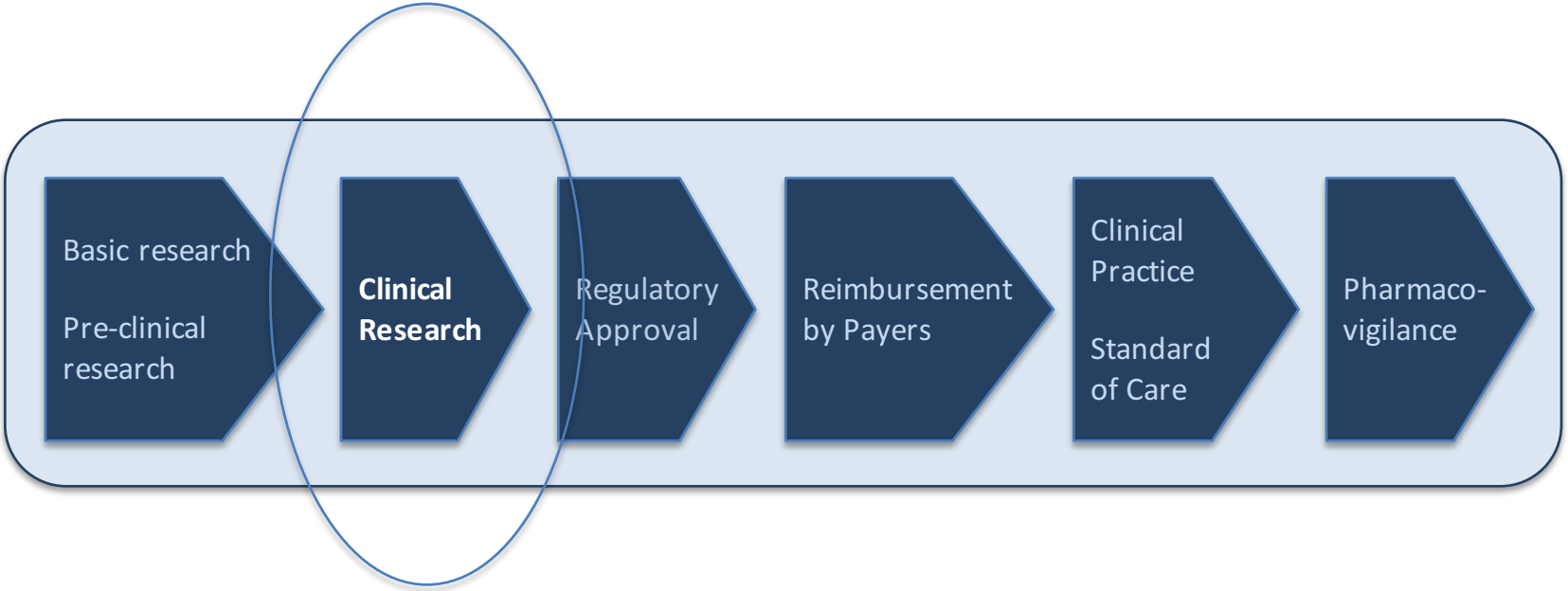
Grieneisen
PlosOne 2012
7: e44118

Retraction rates put lives at risk

Table 1 Summary of the impact of 180 retracted clinical papers

	Number	Average per retracted paper
Citations of retracted papers		
Total citations	5503	30.6
Research-related citations	5143	28.6
Post-retraction citations	1973	11.0
Retraction-related citations	360	2.0
Review papers	1372	7.6
Patient studies	851	4.7
Subjects enrolled in retracted papers		
Total subjects	28 783	160.8
Patients at risk	17 783	99.3
Patients treated	9189	51.3
Subjects enrolled in secondary papers		
Total subjects	445 064	2472.6
Patients at risk	165 588	919.9
Patients treated	70 501	391.7

Steen, R. G. (2011). Retractions in the medical literature: how many patients are put at risk by flawed research?. *Journal of medical ethics*, *37*(11), 688-692.


Basic research
Pre-clinical research
Clinical Research
Regulatory Approval
Reimbursement by Payers
Clinical Practice
Standard of Care
Pharmaco-vigilance

Rare Diseases as Surrogates in Drug Development

Rare Disease	Common disorder	Target	Drug
Familial Hypercholesterolemia	Hypercholesterolemia	HMG CoA	Statins
Hypocholesterolemia		PCSK9	@PSCK9
Cryopyrin-associated periodic syndromes	Rheumatoid arthritis	IL-1β	Rilonacept Canakinumab
Idiopathic Hypereosinophilia	Allergic asthma	IL-5	Mepolizumab
Castleman Disease	Rheumatoid arthritis	IL-6	Tocilizumab
Tuberous sclerosis	Various cancers	mTor	Temsirolimus

The power of data sharing in schizophrenia

- 5 companies (AstraZeneca, J&J, Eli Lilly, Lündbeck, Pfizer)
- 34 clinical trials testing second generation anti-pyschotics
- 11,670 patients
- Budget €25 Million

Drug-placebo differences already significant:

- after 4 vs.6 wks observation
- with 40% less patients

when appropriate gender balance, symptoms and disease duration are selected

Newmeds consortium – IMI
Rabinowitz J et al., J Clin Psychiat 2014, 75: e308-316

Innovative trial designs:
Enablors of therapeutic advances

Randomized registry trials

Pragmatic trials:

- Provide real-world evidence based on patient-reported outcomes

Adaptive trials

- Modifications in the course of the trial according to collected information ("real-time learning")
- Facilitates assessment of combination therapies

Settings standards and promoting responsible data sharing

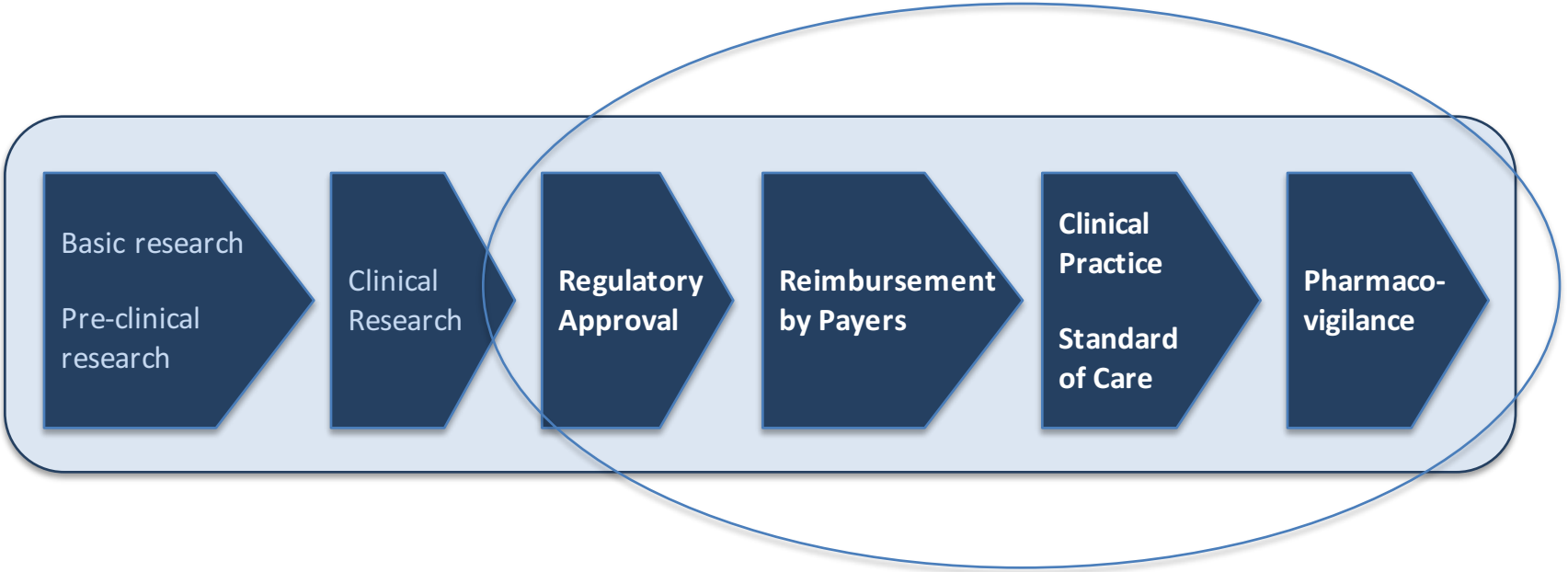
Fostering Responsible Data Sharing through Standards

Rebecca Kush, Ph.D., and Michel Goldman, M.D., Ph.D.

Children with muscular dystrophy and their families make sacrifices to engage in clinical research studies, providing valuable data they expect will contribute to the discovery of a treatment of Alzheimer's disease have led several companies to begin collaboratively developing innovative study designs requiring extensive data sharing.

Unfortunately, the diverse metadata, such confusion is inevitable. Units and other metadata are critical in medical research as well. Standard data and metadata formats are required for efficient aggregation

New Engl J Med 2014, 370:2063


Basic research
Pre-clinical research
Clinical Research
Regulatory Approval
Reimbursement by Payers
Clinical Practice
Standard of Care
Pharmaco-vigilance

PERSPECTIVE | REGULATORY SCIENCE

Unmet needs: Research helps regulators do their jobs

Russ B. Altman[1], Natalia Khuri[2,3], Marc Salit[2,4] and Kathleen M. Giacomini[3,5,*]

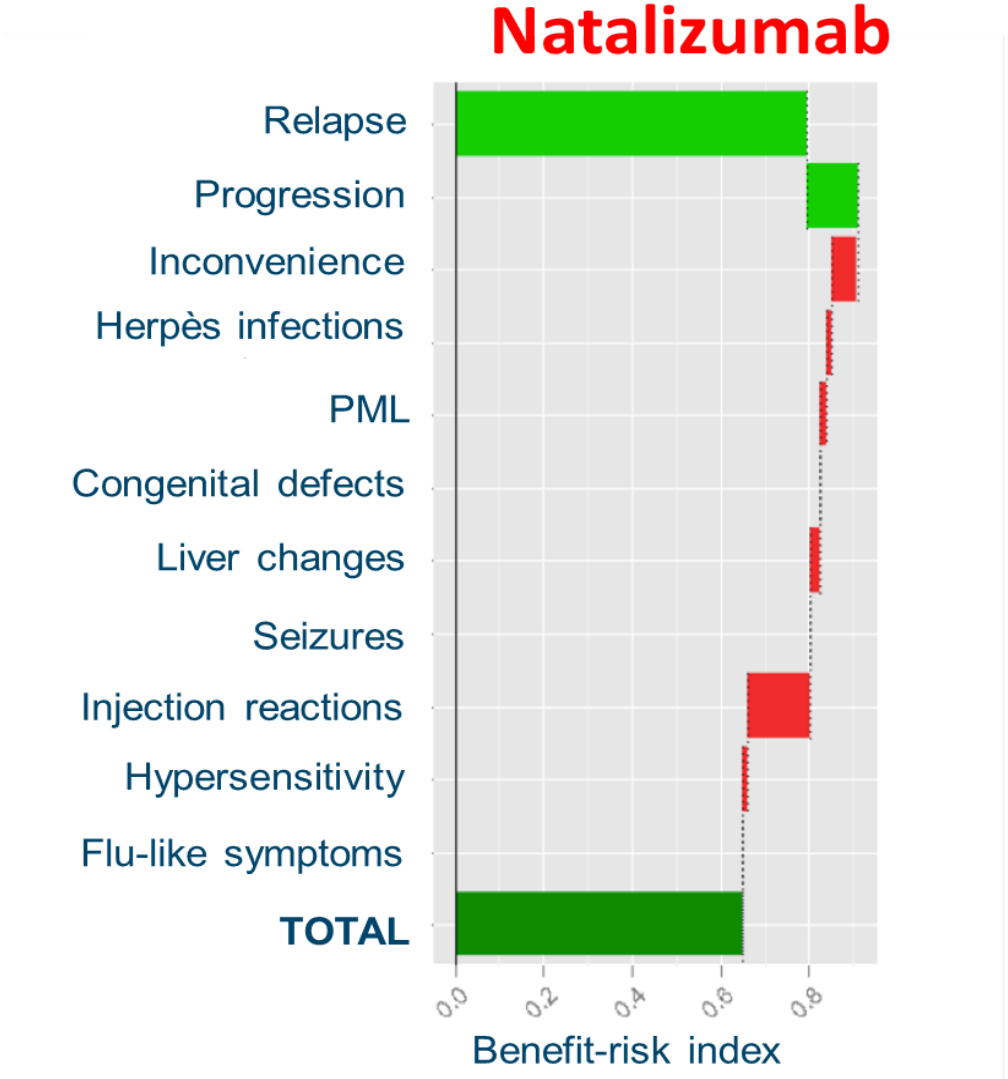
+ Author Affiliations

*Corresponding author. E-mail: kathy.giacomini@ucsf.edu

Science Translational Medicine 25 Nov 2015:
Vol. 7, Issue 315, pp. 315ps22
DOI: 10.1126/scitranslmed.aac4369

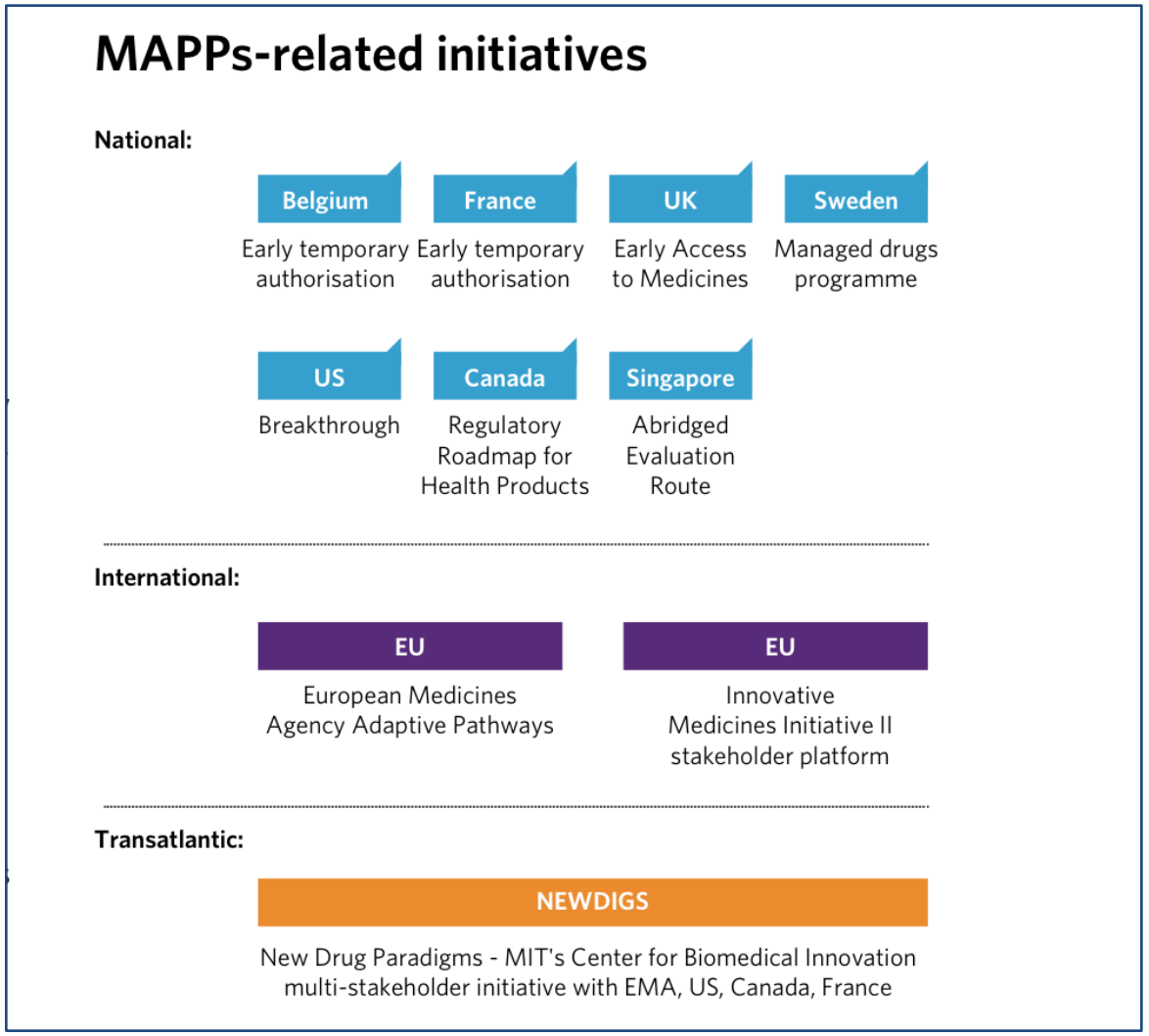
Advancing benefit-risk assessment of medicines

www.imi.europa.eu/content/protect



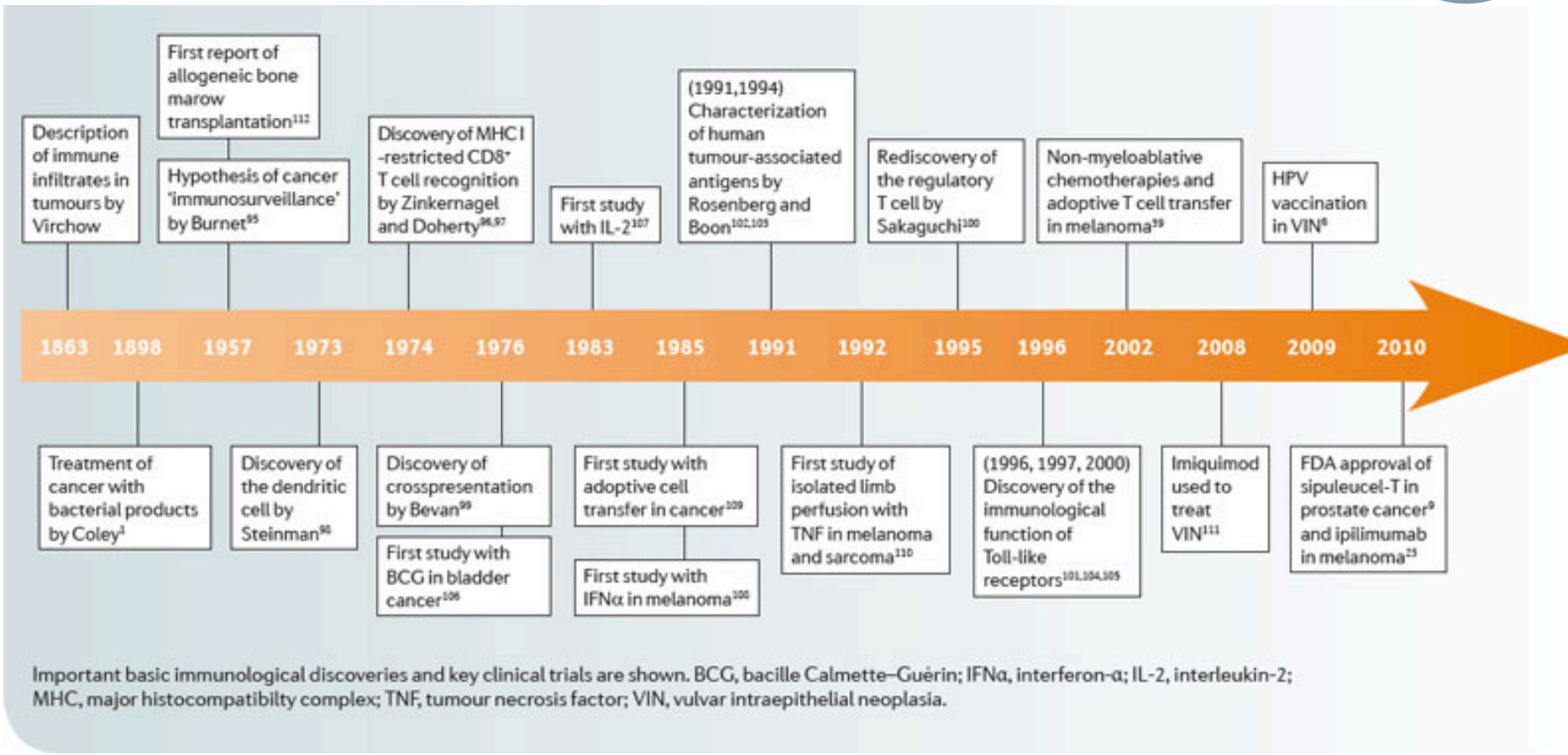
Fast-tracking Innovation:

Medicines adaptive pathways to patients (MAPPs)



P. 'O Donnell
EuropeanVoice 2015
http://bit.ly/1RG3JMW

Cancer Immunotherapy

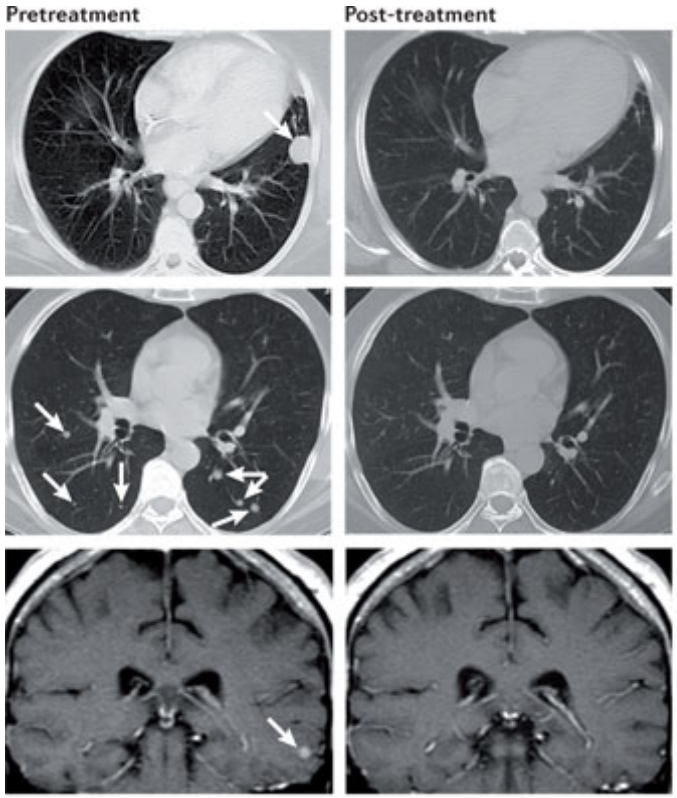


Important basic immunological discoveries and key clinical trials are shown. BCG, bacille Calmette–Guérin; IFNα, interferon-α; IL-2, interleukin-2; MHC, major histocompatibilty complex; TNF, tumour necrosis factor; VIN, vulvar intraepithelial neoplasia.

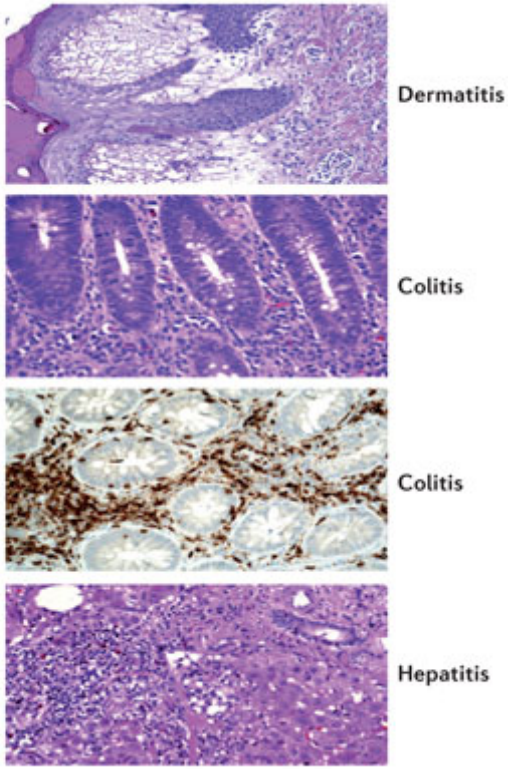
W. Joost Lesterhuis, John B. A. G. Haanen & Cornelis J. A. Punt
Nature Reviews Drug Discovery 10, 591-600, 2011

Immune checkpoint blockade in cancer immunotherapy (ipilumumab)

BENEFITS



ADVERSE EVENTS



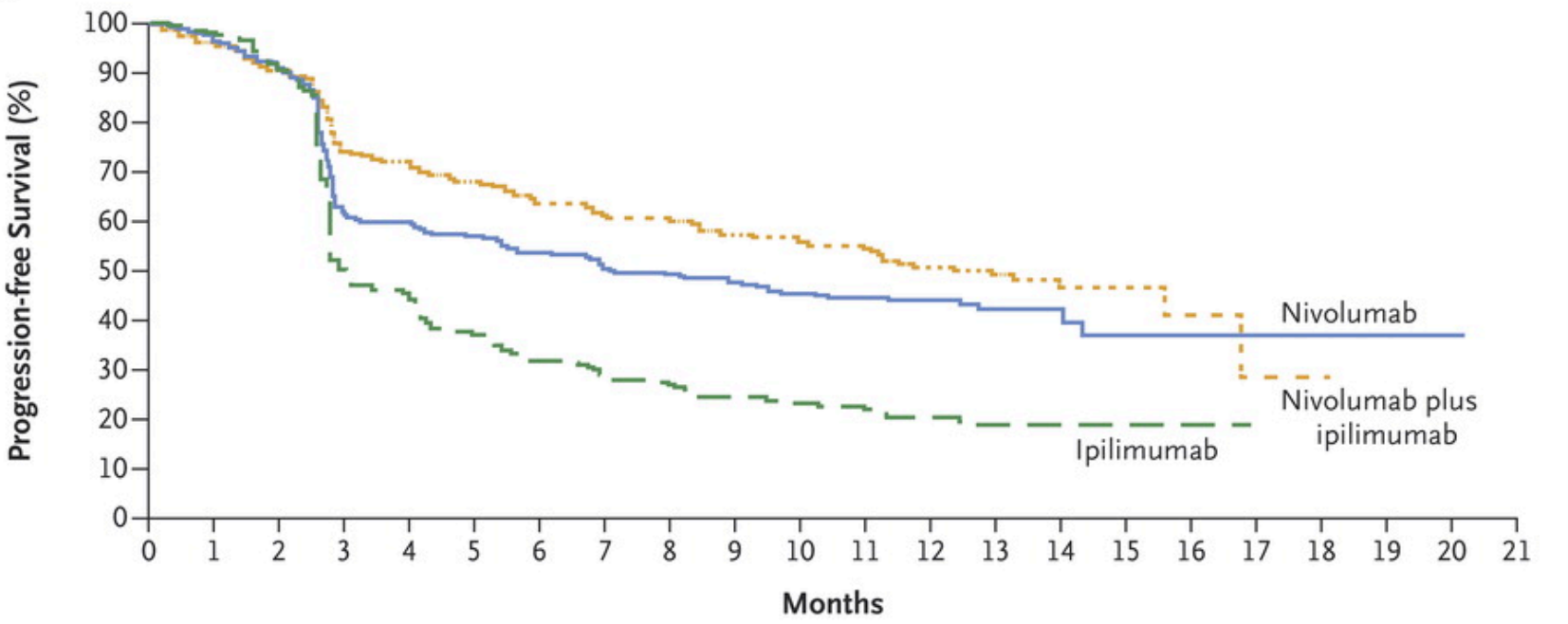
Drew M. Pardoll
Nature Reviews Cancer 12, 252-264 (April 2012) doi:10.1038/nrc323

Latest Developments in Cancer Immunotherapy (1)

The NEW ENGLAND JOURNAL of MEDICINE

April 20, 2015

ORIGINAL ARTICLE



Latest Developments in Cancer Immunotherapy (2)

RESEARCH ARTICLE

CANCER

Trastuzumab emtansine (T-DM1) renders HER2^{+} breast cancer highly susceptible to CTLA-4/PD-1 blockade

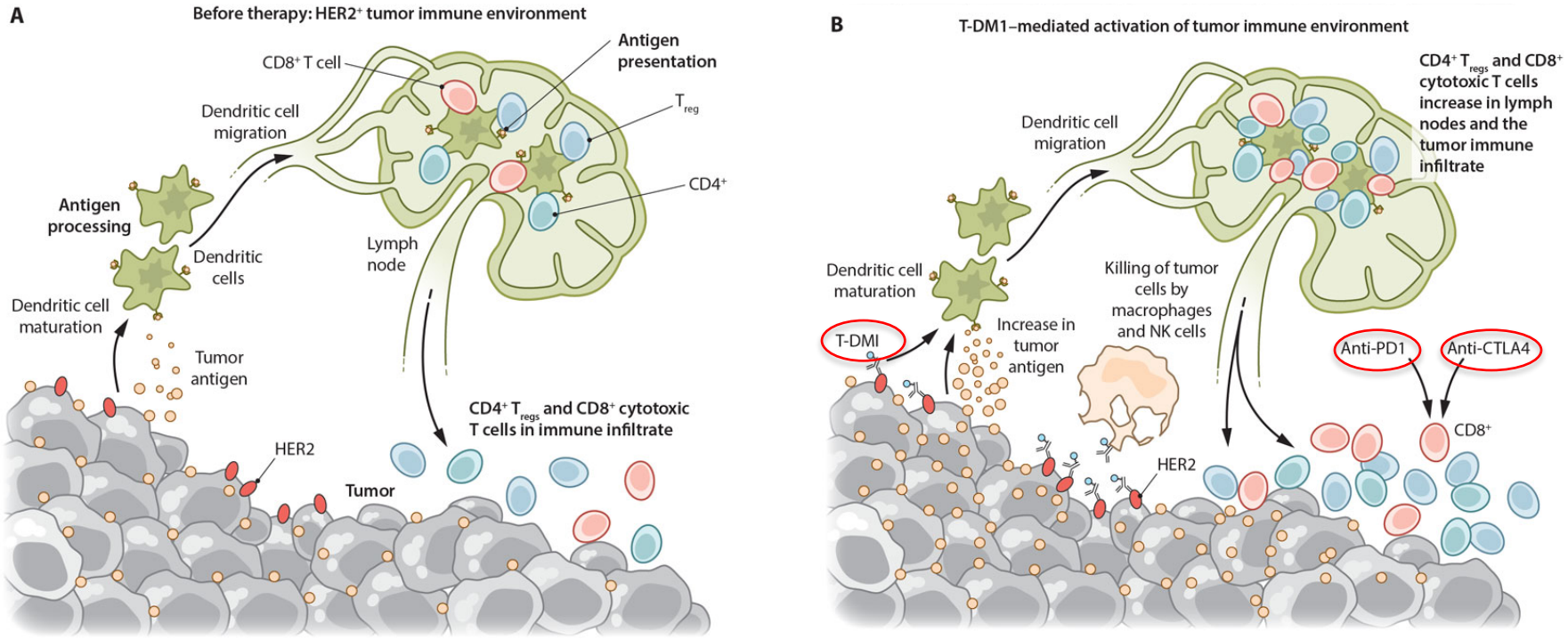
Philipp Müller,[1]* Matthias Kreuzaler,[1] Tarik Khan,[2†] Daniela S. Thommen,[1,3] Kea Martin,[1] Katharina Glatz,[4] Spasenija Savic,[4] Nadia Harbeck,[5,6] Ulrike Nitz,[6,7,8] Oleg Gluz,[6,8] Michael von Bergwelt-Baildon,[9] Hans Kreipe,[6,10] Sai Reddy,[2] Matthias Christgen,[6,10] Alfred Zippelius[1,3]*

www.ScienceTranslationalMedicine.org 25 November 2015 Vol 7 Issue 315 315ra188

Marcia Belvin and Ira Mellman Sci Transl Med 2015;7:315fs48

Published by AAAS

Latest Developments in Cancer Immunotherapy (2)



Marcia Belvin and Ira Mellman Sci Transl Med 2015;7:315fs48

Published by AAAS

Lessons from successes and failures

- Hepatitis C therapy
- Cancer immunotherapy
- Anti-TNF therapy
- Meningococcal vaccines
- Rosiglitazone

Sci Transl Med 29 January 2014:
Vol. 6, Issue 221, p. 221ed2
Sci. Transl. Med. DOI: 10.1126/scitranslmed.3008294

EDITORIAL

DRUG DISCOVERY

Turning the Titanic

Elias A. Zerhouni

"Deciphering the complexity of human diseases and finding safe, cost-effective solutions that help people live healthier lives requires collaboration across scientific and medical communities throughout the health care ecosystem.

Thank you

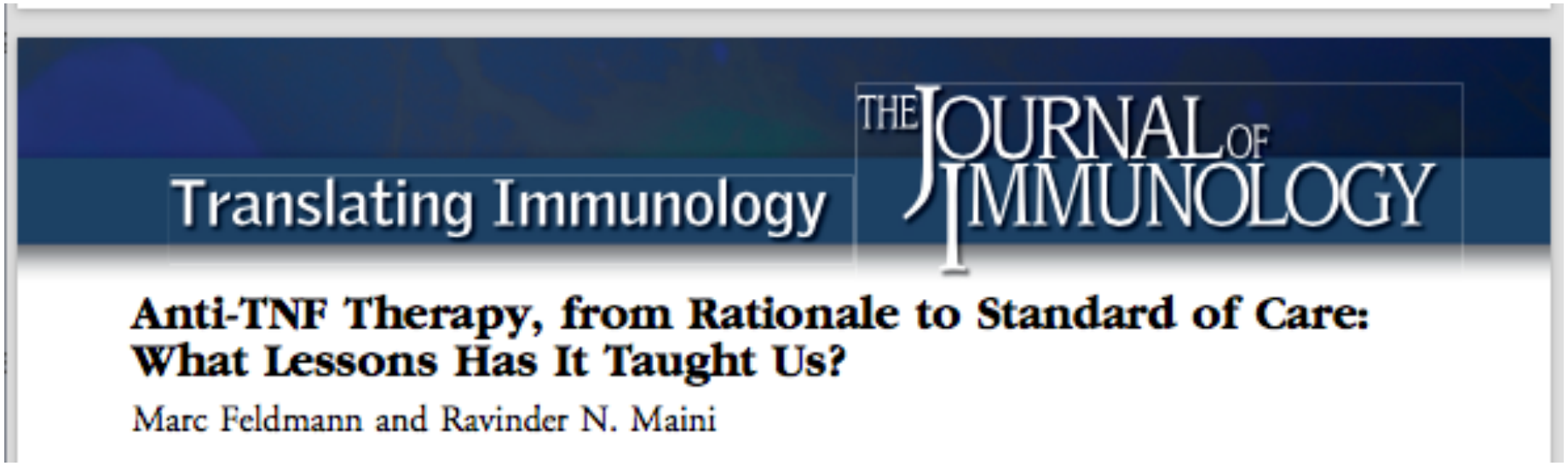
@MichelGoldman

✉ mgoldman@i3health.eu

How to move Translational Medicine forward ?

- Computation
- Data accuracy/reliability
- Data linkage
- Human representation
- Blurred boundaries
- Affordability
- Popular support
- Education

Kohane, IS *Science* 2015; 349:37-38



J Immunol 2010, 185-791

Clinical targeting of the TNF and TNFR superfamilies

Michael Croft[1], Chris A. Benedict[1] and Carl F. Ware[2]

Abstract | Inhibitors of tumour necrosis factor (TNF) are among the most successful protein-based drugs (biologics) and have proven to be clinically efficacious at reducing inflammation associated with several autoimmune diseases. As a result, attention is focusing on the therapeutic potential of additional members of the TNF superfamily of structurally related cytokines. Many of these TNF-related cytokines or their cognate receptors are now in preclinical or clinical development as possible targets for modulating inflammatory diseases and cancer as well as other indications. This Review focuses on the biologics that are currently in clinical trials for immune-related diseases and other syndromes, discusses the successes and failures to date as well as the expanding therapeutic potential of modulating the activity of this superfamily of molecules.

Nat Rev Drug Discov 2013, 12: 147

Scheinberg and Castañeda-Hernández *Arthritis Research & Therapy* 2014, **16**:501
http://arthritis-research.com/content/16/6/501

arthritis research&therapy

COMMENTARY

Anti-tumor necrosis factor patent expiration and the risks of biocopies in clinical practice

Morton Scheinberg[1*] and Gilberto Castañeda-Hernández[2]

Abstract

Biosimilars that were not compared in clinical trials with the compound innovator are not true biosimilars (biocopies) and are associated with risks that the clinical rheumatologist should be aware of before generalized use. This article comments on various aspects surrounding the use of such biocopies in clinical rheumatology.

similar reduction having occurred with the use of biosimilars for erythropoietin [5-7].

The European Medicine Agency (EMA) has already approved the first biosimilar version of infliximab from Celltrion (Incheon, Korea) and Hospira (Lake Forest, IL, USA) for rheumatoid arthritis, paving the road for less expensive medications when they finally reach the market in 2015. Also important was the EMA recommendation for approval of the infliximab biosimilar for ankylosing spondylitis, psoriatic arthritis, psoriasis, and, surprisingly,

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Therapy for Hepatitis C — The Costs of Success

Jay H. Hoofnagle, M.D., and Averell H. Sherker, M.D.

NEJM 2014, 370:16

The NEW ENGLAND JOURNAL of MEDICINE

Revisiting the Rosiglitazone Story — Lessons Learned

Clifford J. Rosen, M.D.

In July 2007, 24 members of the Endocrinologic and Metabolic Drug Advisory Committee (EMDAC) and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration (FDA) held a joint meeting, which I chaired, and concluded that rosiglitazone, an insulin-sensitizing agent used in

of the joint advisory committee met for 20 hours over 2 days to further advise the FDA about rosiglitazone. Ultimately, the committee agreed that the drug posed significant cardiovascular risk. Twelve participants voted that it should be removed from the market, 10 (including me) voted for much stricter control over pre-

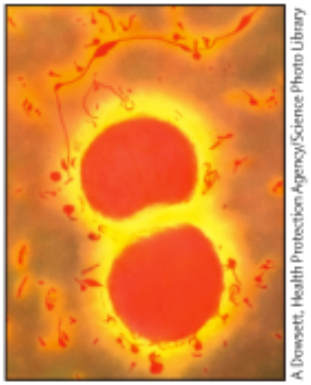
formin, the hazard ratio is lower, although it is still greater than 1. In comparison with the FDA's 2007 meta-analysis, the newer analyses showed higher odds ratios for major adverse cardiovascular events, myocardial infarction, and serious ischemic events in patients receiving rosiglitazone (see Table 1).[4] A similar level of

NEJM 2010, 363:09

The price of prevention: what now for immunisation against meningococcus B?

Meningococcal sepsis is one of the most dreaded bacterial infections: the death rate remains at about 5% and the effects for survivors include neurological damage, limb amputation, and widespread skin necrosis.[1] There is a compelling case for prevention of meningococcal disease by immunisation. On July 24, 2013, in an interim position statement,[2] the UK Joint Committee on Vaccination and Immunisation (JCVI) concluded that it cannot currently recommend a vaccines against all the major causes of non-neonatal acute bacterial meningitis.

A major responsibility of the JCVI, the advisory body to UK health departments on immunisation, is to assess the cost-effectiveness of vaccines. The JCVI concluded that routine immunisation using 4CMenB is highly unlikely to represent value for money at any vaccine price—ie, the costs of implementing the vaccine would be greater than those resulting from the impact of



A Dowsett, Health Protection Agency/Science Photo Library

The Lancet 2013, 382:369

The antiepileptics armamentarium

Focal seizures and most generalized seizure types

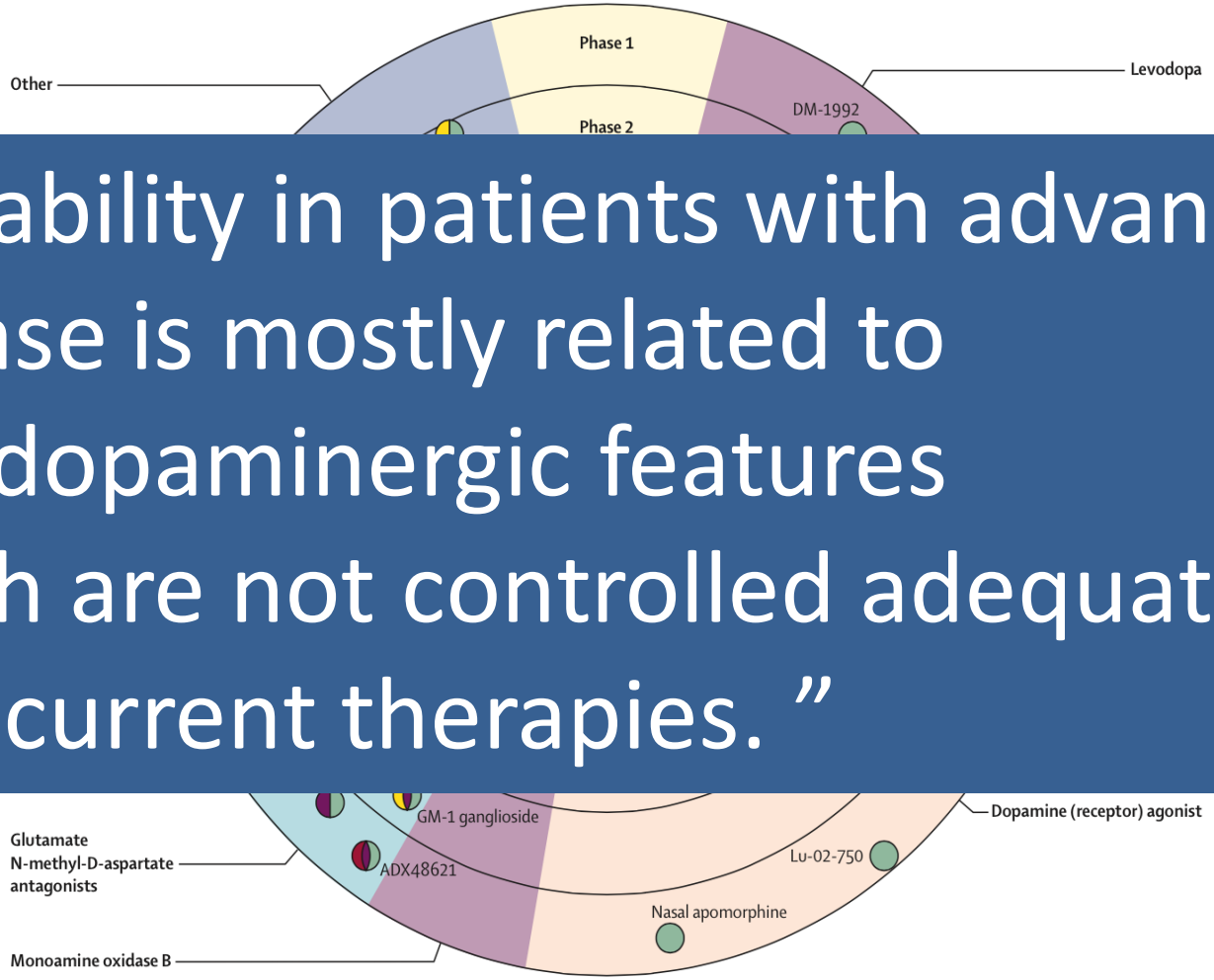
- Valproic acid
- Benzodiazepines
- Phenobarbital, primidone
- Lamotrigine

"Although the number of antiepileptic drugs has increased substantially, about a third of patients remain resistant to medical treatment."

- Carbamazepine, phenytoin, oxcarbazepine, eslicarbazepine, tiagabine
- Lacosamide, perampanel, retigabine
- Gabapentin, pregabalin
- Vigabatrin

Moshé et al, Lancet 2015, 385: 884-898

Existing and evolving treatments for Parkinson's disease



" Disability in patients with advanced disease is mostly related to non-dopaminergic features which are not controlled adequately with current therapies. ”

A. Shapira et al., Lancet 2014, 384:545-555

Immunotherapies for Multiple Sclerosis

- Glatimer acetate

" The relentless disability accumulation does not seem to be altered by immunosuppression.
We need different strategies to prevent lesions and disabilities ."

Kantanci O, Clin Pharmacol Ther 2014, 95:32-44

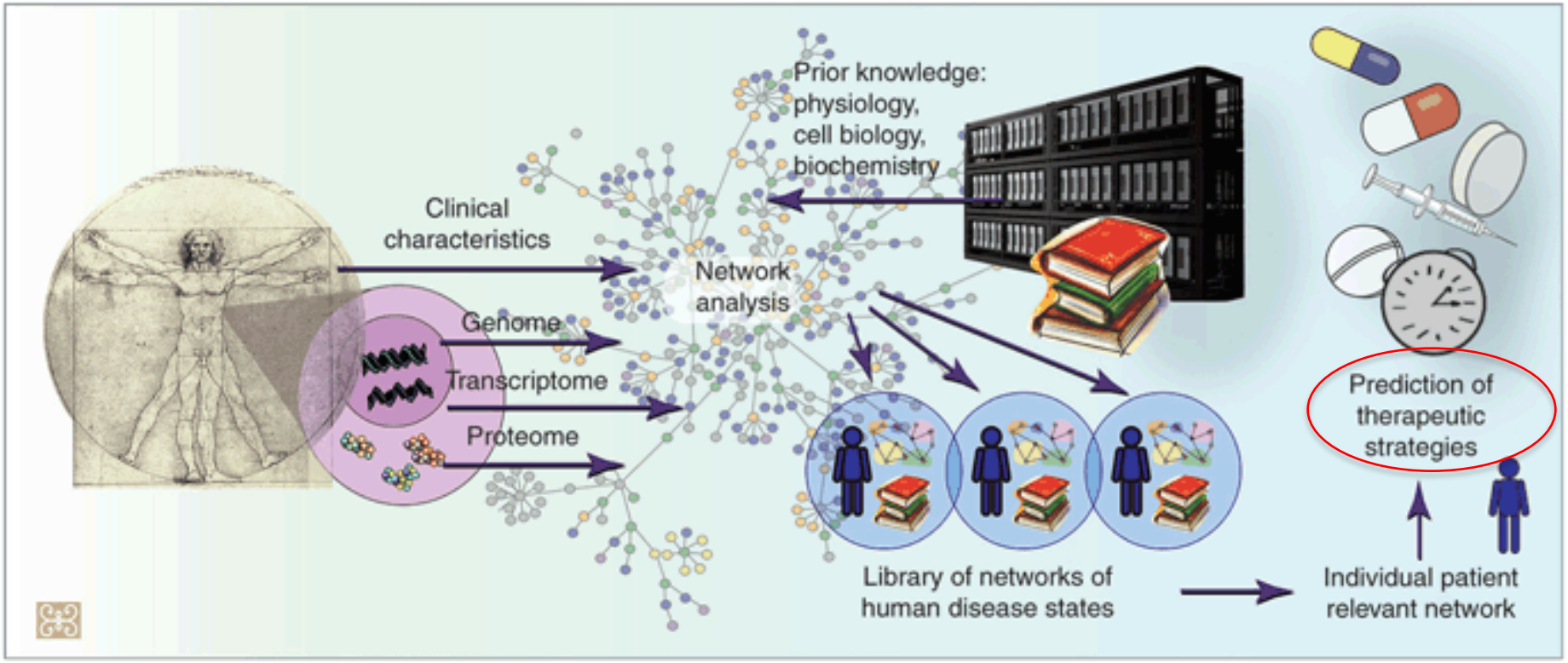
Diabetes:
A major public health challenge

Major Public Health Need	Distrust in past-research	Hurdles to drug development
Diabetes will affect 43 million Europeans in 2030 €89 million spent on 2011 on treating diabetes and its complications	Cardiovascular complications of rosiglitazone and benfluorex	Patients' heterogeneity Lack of reliable markers for disease activity and complications

Diabetes:
A major public health challenge

Major public health need	Recent failures	Hurdles to drug development
Diabetes will affect **43 million Europeans** in **2030** **€89 million** spent on 2011 on treating diabetes and its complications	Cardiovascular complications of rosiglitazone and benfluorex	▪ Patients' heterogeneity ▪ Lack of reliable markers for disease activity and complications

Information Flow in Translational Medicine

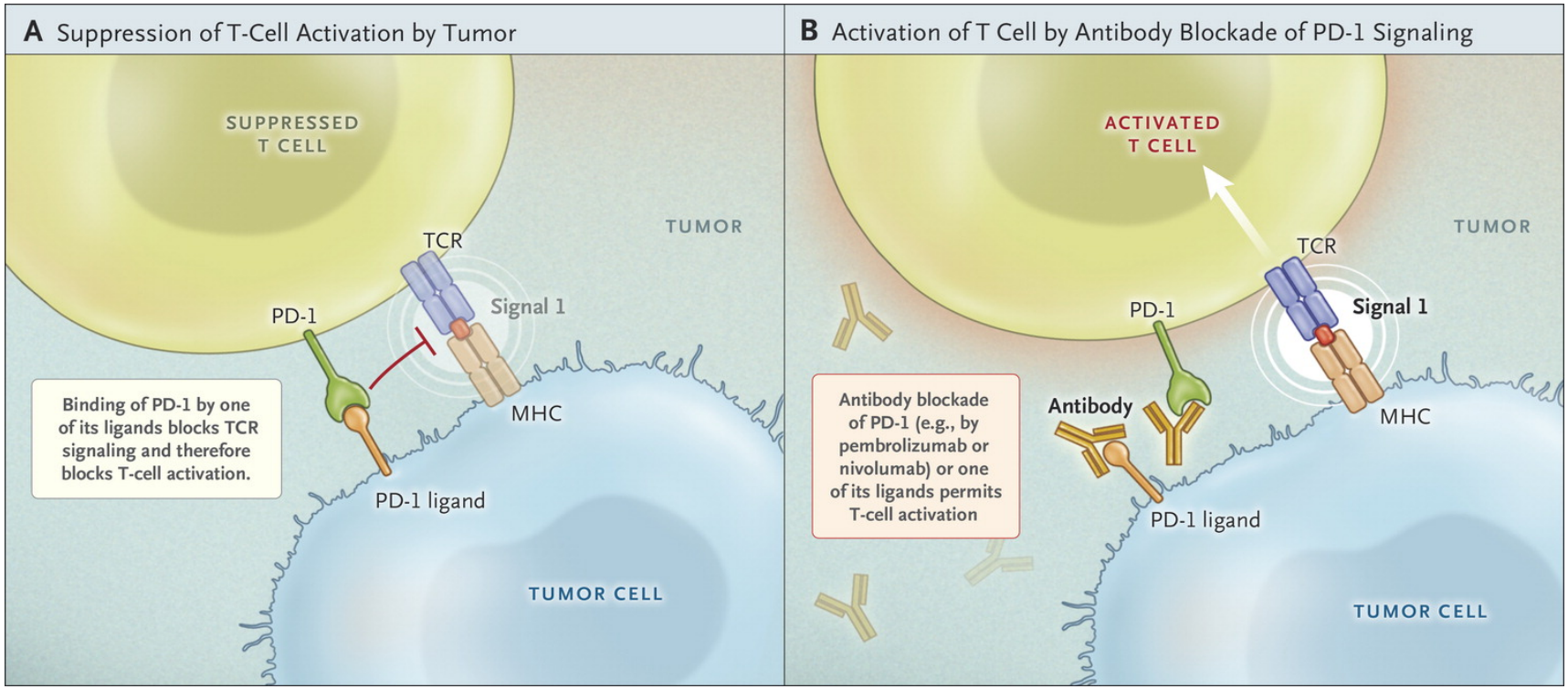


J. Hansen & R. Iyengar, Clin. Pharmacol. Therapeut. 93:117-28, 2013

“Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease“

- Sir William Osler

Latest Developments in Cancer Immunotherapy (1)



Ribas A. N Engl J Med 2015; 373:1490-1492

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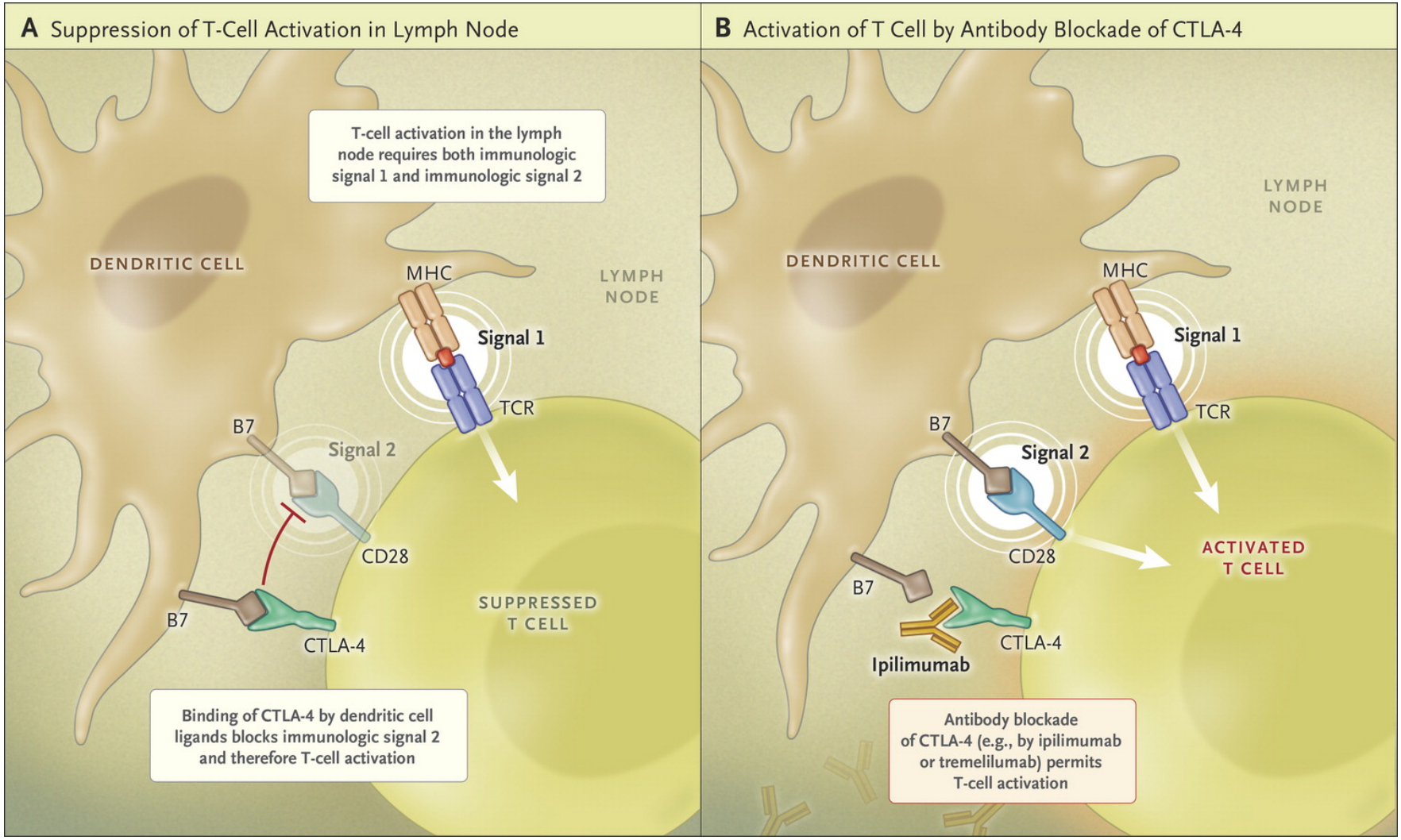
A Suppression of T-Cell Activation in Lymph Node
T-cell activation in the lymph node requires both immunologic signal 1 and immunologic signal 2
DENDRITIC CELL
LYMPH NODE
MHC
Signal 1
TCR
B7
Signal 2
CD28
B7
CTLA-4
SUPPRESSED T CELL
Binding of CTLA-4 by dendritic cell ligands blocks immunologic signal 2 and therefore T-cell activation
B Activation of T Cell by Antibody Blockade of CTLA-4
LYMPH NODE
DENDRITIC CELL
MHC
Signal 1
TCR
B7
Signal 2
CD28
ACTIVATED T CELL
B7
CTLA-4
Ipilimumab
Antibody blockade of CTLA-4 (e.g., by ipilimumab or tremelilumab) permits T-cell activation