The Innovative Medicines Initiative

Collaboration between Industry, Government Institutes, Universities and Regulatory Agencies in Europe

Prof Trevor M Jones CBE

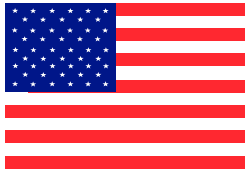
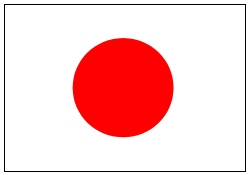
Barcelona Feb 14th 2012

Innovative Medicines Initiative

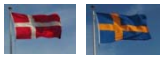
efpia
European Federation of Pharmaceutical Industries and Associations

Almirall
A lot to discover ESTEVE
MERCK SERONO
Pfizer
ucb
AMGEN
genzyme
MERCK SHARP & DOHME
Roche
AstraZeneca INTERNATIONAL
gsk GlaxoSmithKline
NOVARTIS
sanofi aventis
L'essentiel c'est la santé.
Johnson & Johnson
novo nordisk
BAYER Bayer
Lilly
ORION
SERVIER
Boehringer Ingelheim
sigma-tau
Fondazione Chiesi
Lundbeck
Pierre Fabre
SOLVAY
Wyeth

Competitive Environment in the World

	Innovative Medicines Initiative (EFPIA-European Commission)
	FDA Critical Path Initiative (NIH)
	Safe and Innovative Medicines (PhRMA)
	Biomarker Initiative (PhRMA)
	Critical Path Institute (University of Arizona)
	Center for Biomedical Innovation (MIT)
	Toxicogenomics Project (JPMA)
	Proteome Factory Consortium (JPMA)
	Large-scale Clinical Trial Network

Main National Initiatives in the EU

NAME	SPONSOR	FOCUS	BUDGET
Top Institute Pharma 	Public-Private Partnership: •Government •Industry •Academia	•Autoimmune diseases •Cardiovascular diseases •Neoplastic diseases •Infectious diseases •Brain diseases	€240 mn
BioWin 	Health Cluster of Wallonia (Government of Wallon)	Biomarkers for: Cancer, Inflammation & Brain diseases	€230 mn
Safety Biomarkers 	Department of Trade and Industry (UK Government)	Toxicology biomarkers	€11.7 mn
Canceropôles 	Hospitals and Research Institutions	Translational research in Cancer	€7.3 mn (Paris alone)
Medicon Valley 	Danish and Swedish Governments	Diabetes, Inflammation, Neuroscience & Cancer	Not indicated
Medicamentos Innovadores 	Public-Private Partnership between Government, Industry & Academia	Safety, Efficacy, KM & E&T	Not indicated

The need (imperative) to collaborate !!!!!!

- **Failure rate in Drug Development is too high !!!**
- **“Big Pharma” struggling to maintain ..and be productive with its very large R&D Budgets**
- **The complexity……(and the opportunities !!)..... of Drug Discovery now we have embarked on genomics/proteomics/epigenetics**

Failure in Drug Development
…….Attrition is a major problem

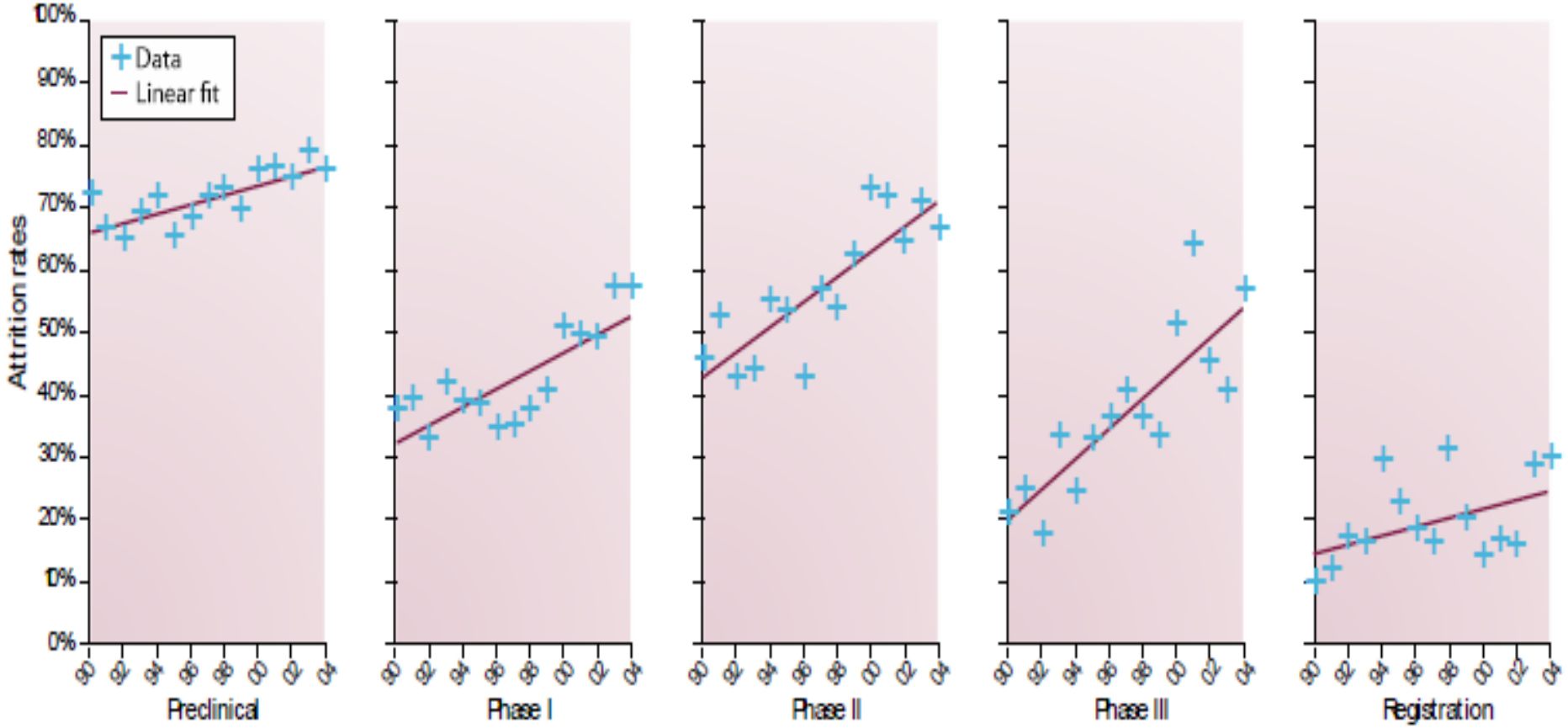
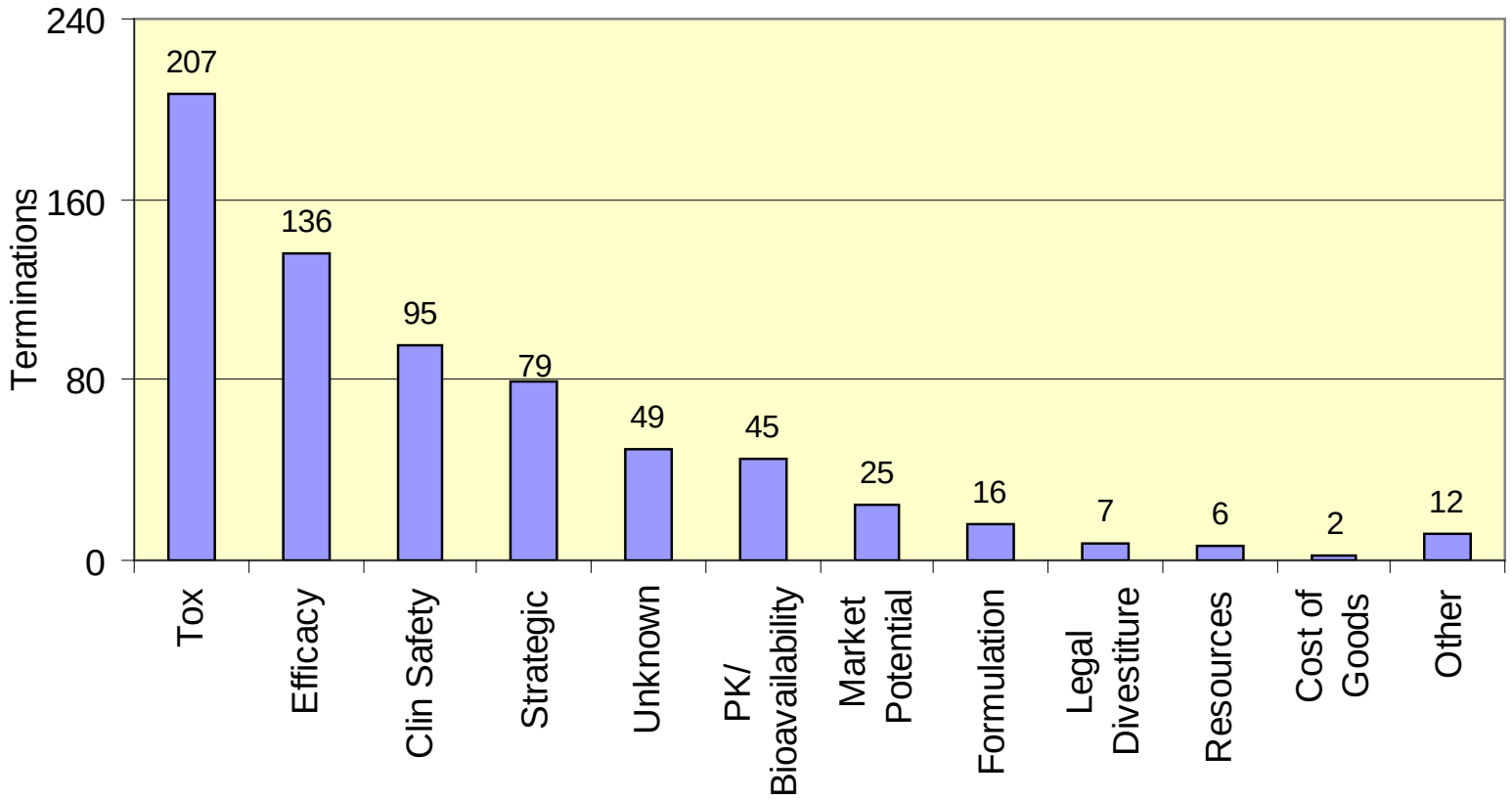


Figure 1 | **Trends in attrition rates of drug development projects.** Data are for projects started between 1990 and 2004 in the United States, Europe and Japan. Source: analysis of the Pharmaceutical Industry Database (BOX 1).

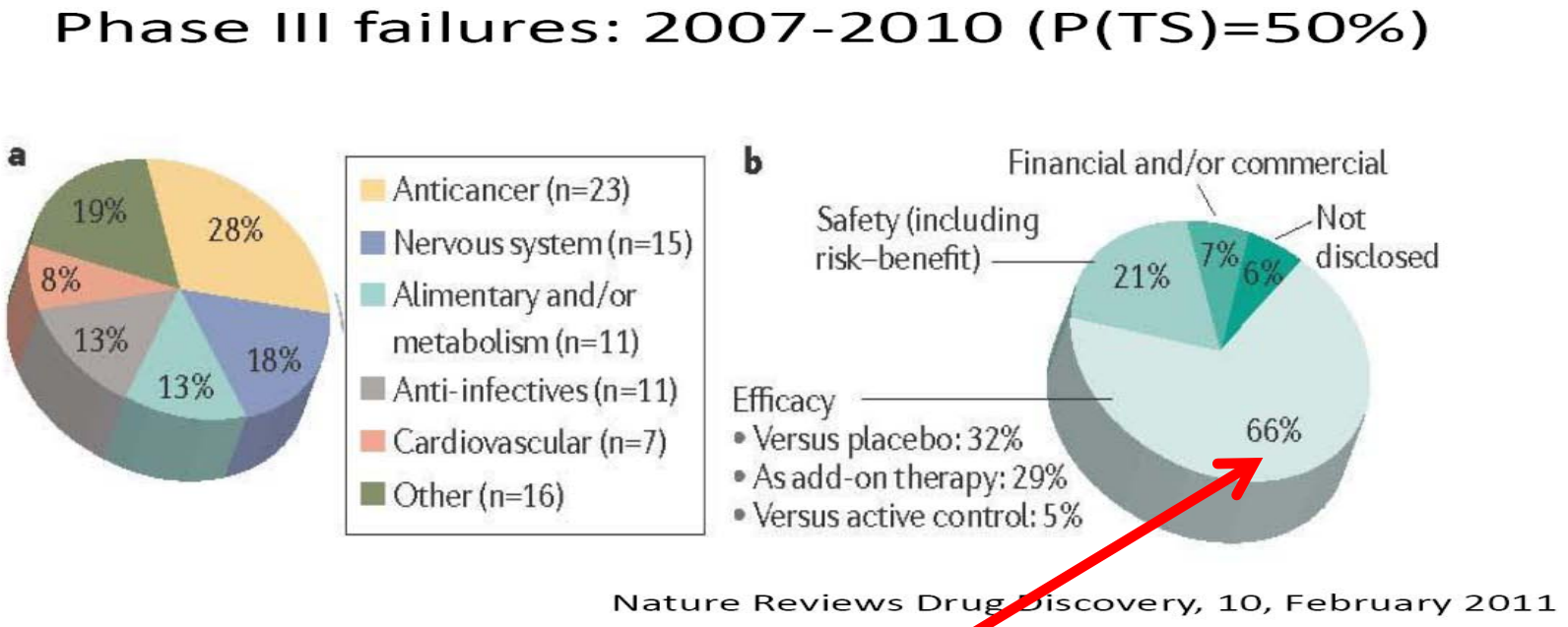
Source : Pammolli et al, Nature Reviews Drug Discovery June 2011

Primary reasons for attrition was "Safety"

2000-2004



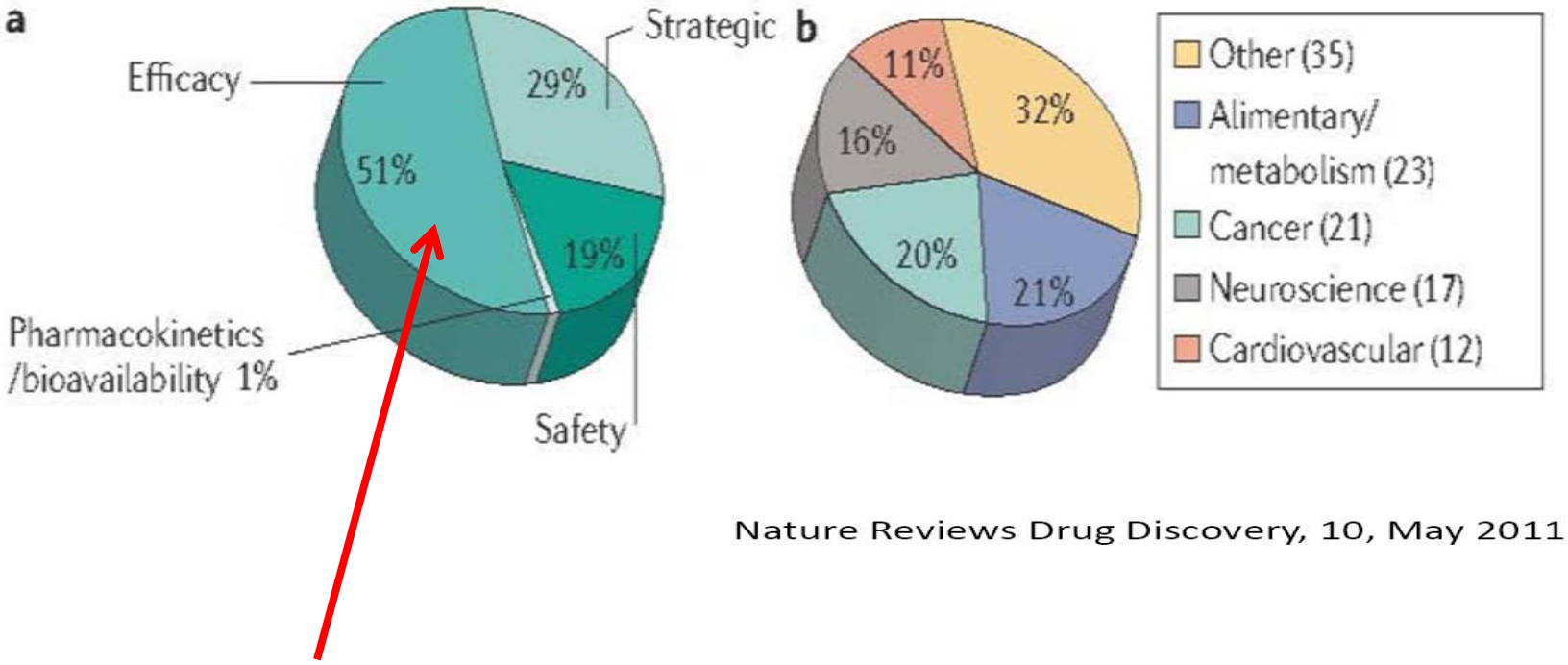
FAILURE...Phase III
Was Safety..but now the issue is EFFICACY



WHY ?

..and at "Phase II"

Phase II failures: 2008-2010 (P(TS)=18%)

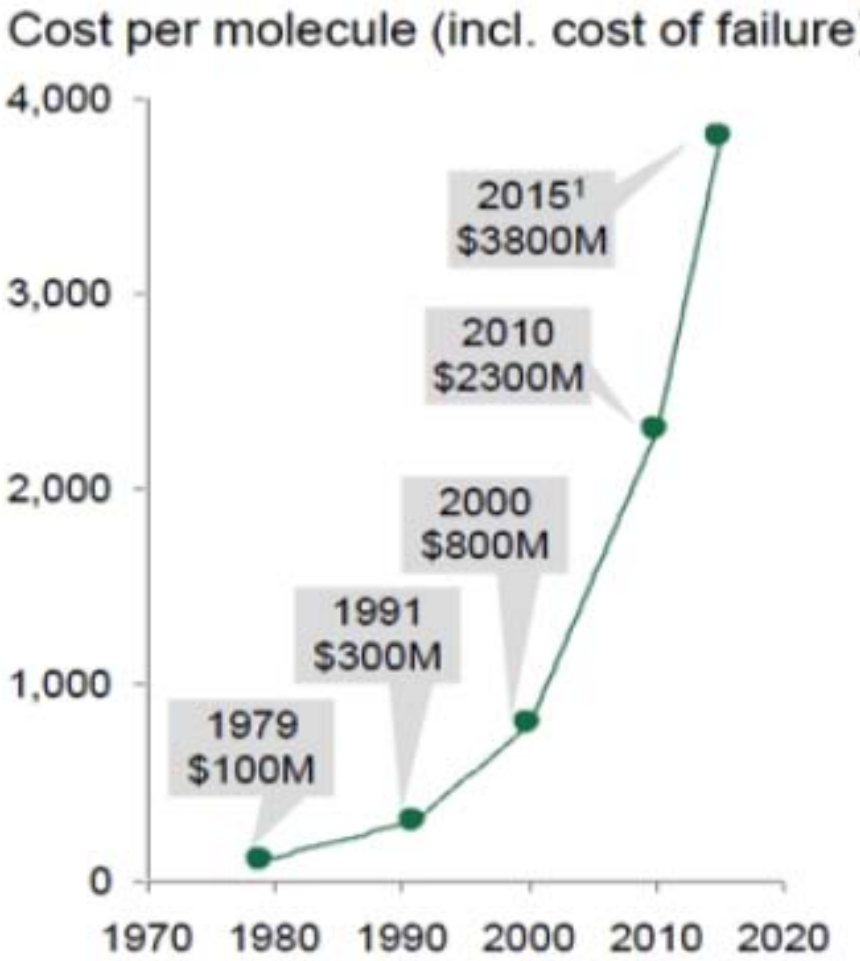


Nature Reviews Drug Discovery, 10, May 2011

It's all getting too expensive !!

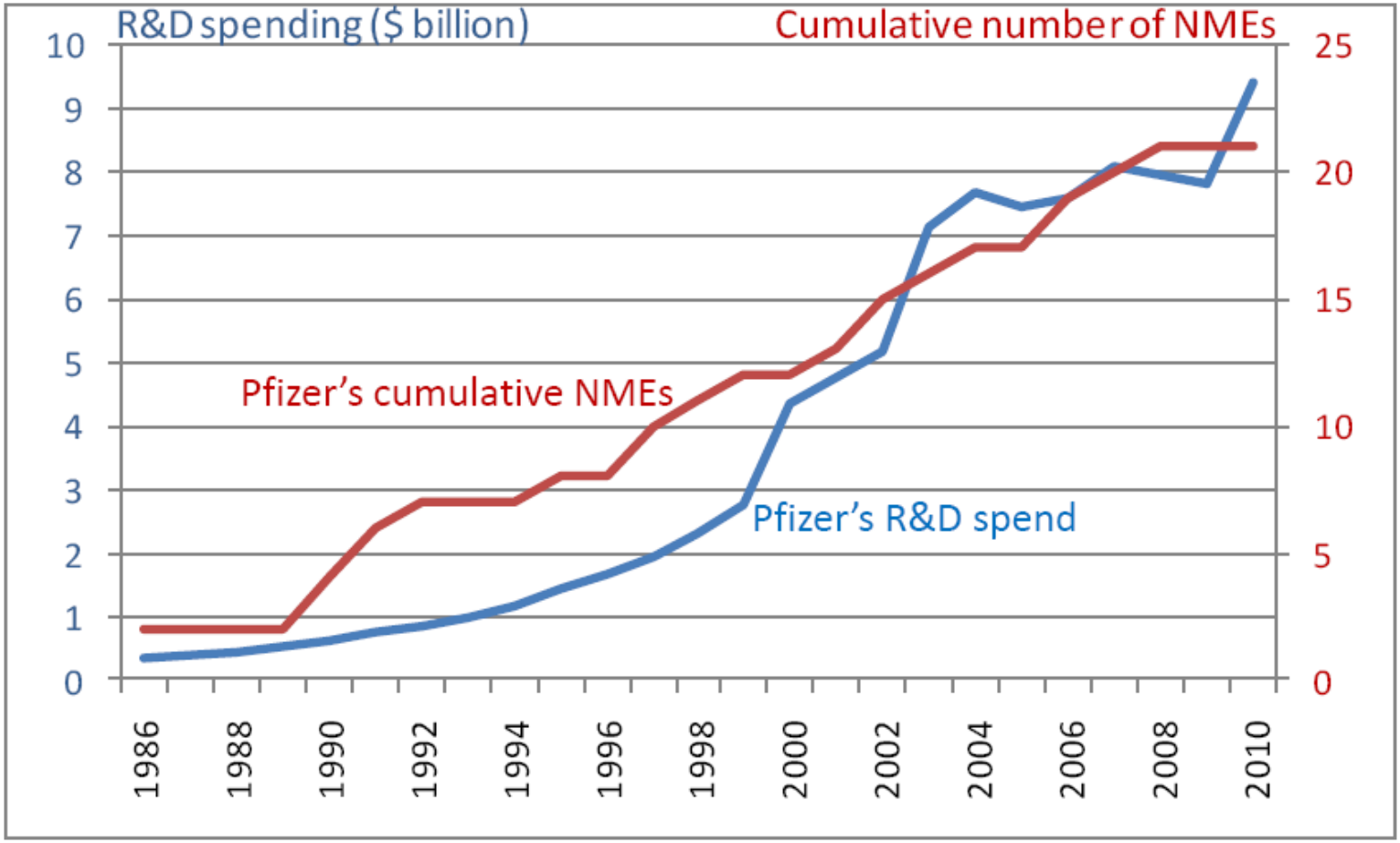
Estimates of the full cost of bringing a new molecular entity to market (US$ million, 2009 prices)

	2009
Hansen, 1979	179
Wiggins, 1987	204
DiMasi et al., 1991	406
OTA, 1993	562
Myers and Howe, 1997	598
DiMasi et al., 2003	928
Gilbert et al., 2003	1,967 (2000-02) 1,273 (1995-2000)
Adams and Branter, 2006	1,004
Adams and Branter, 2010	1,404
Paul et al., 2010	1,735
Mestre-Ferrandiz et al., 2011	1,369

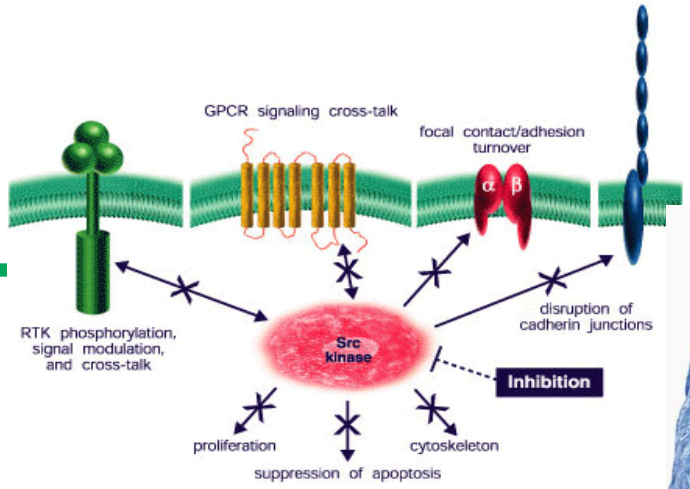


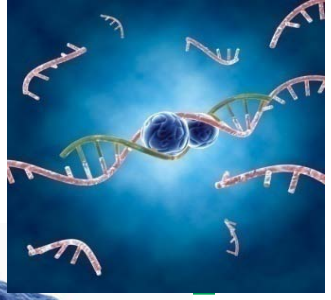
Source: Mestre-Ferrandiz J, Sussex J and Towse A. (2011) *Updating the cost of a new medicine*. Office of Health Economics – forthcoming & Source: The Boston Consulting Group, *Life Sciences R&D: Changing the innovation equation in India*, 2011

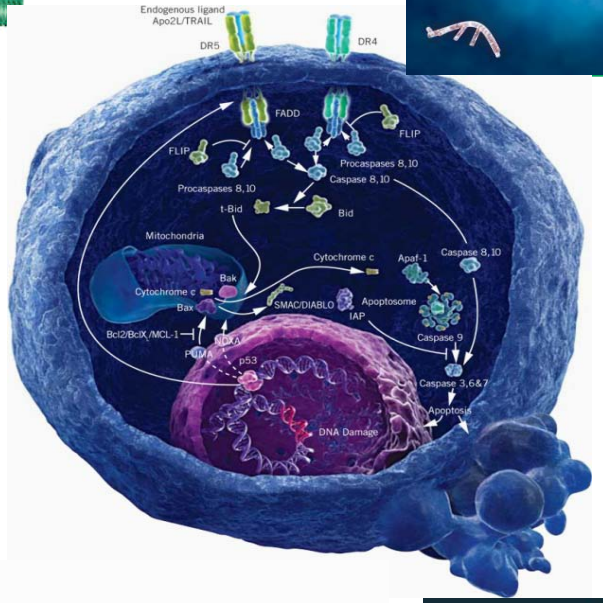
Innovation does not scale

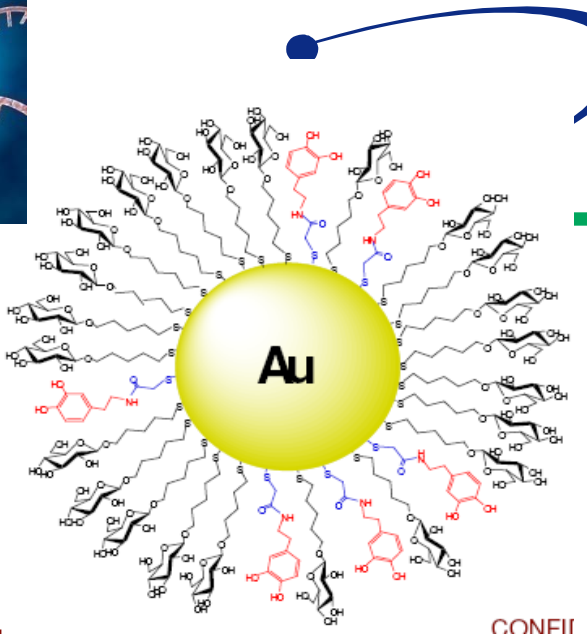


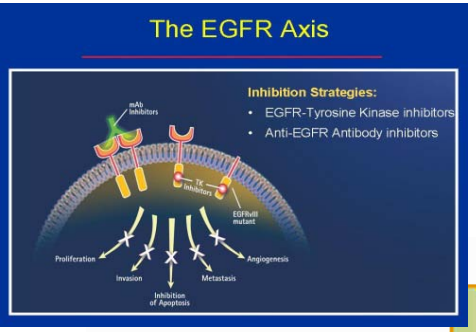
Pfizer's trebling of R&D spending since 1999 has had no detectable impact on its rate of NME production

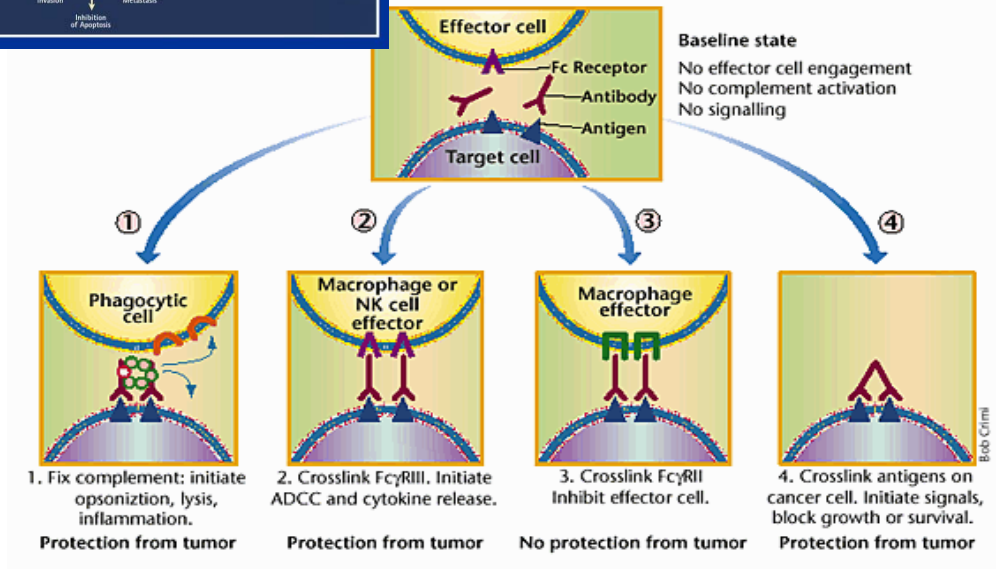

GPCR signaling cross-talk
focal contact/adhesion turnover
α
β
RTK phosphorylation, signal modulation, and cross-talk
Src kinase
disruption of cadherin junctions
Inhibition
proliferation
cytoskeleton
suppression of apoptosis

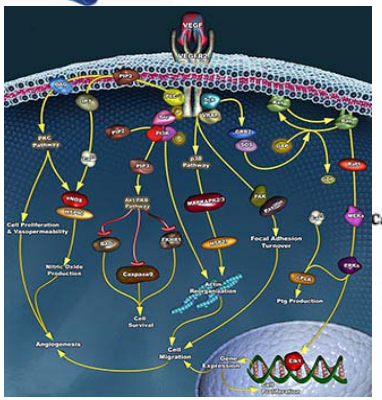


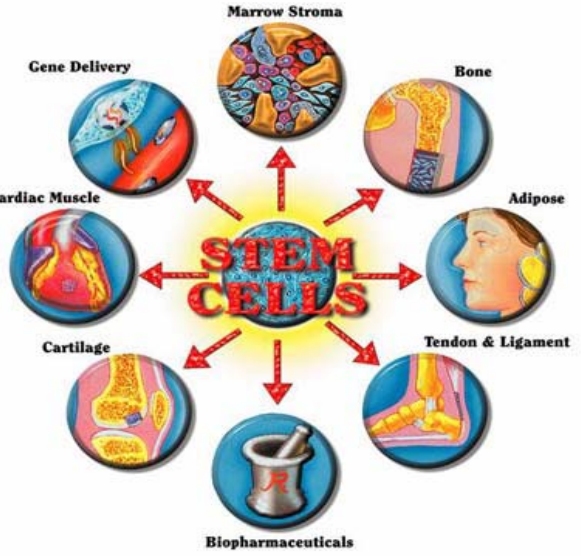

Endogenous ligand Apo2L/TRAIL
DR5
DR4
FADD
FLIP
Procaspases 8,10
Caspase 8,10
t-Bid
Bid
Mitochondria
Cytochrome c
Bak
Bax
Apaf-1
SMAC/DIABLO
Apoptosome
IAP
Caspase 9
Bcl2/BclX /MCL-1
p53
Caspase 3,6&7
Apoptosis
DNA Damage

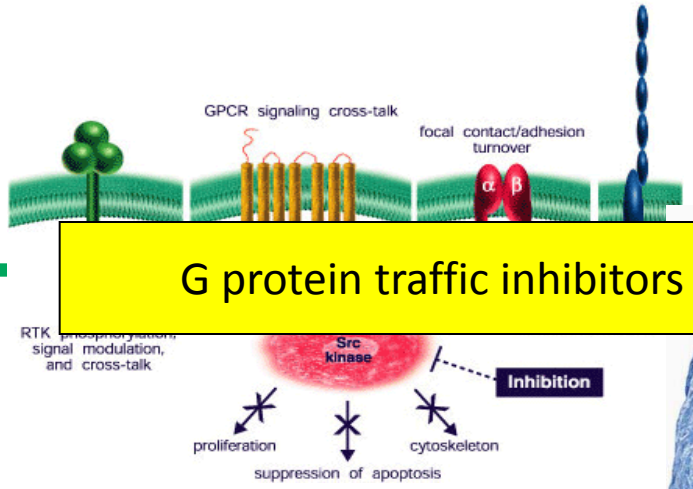

Au


The EGFR Axis
Inhibition Strategies:
• EGFR-Tyrosine Kinase inhibitors
• Anti-EGFR Antibody inhibitors
mAb Inhibitors
TK Inhibitors
EGFRvIII mutant
Proliferation
Angiogenesis
Invasion
Metastasis
Inhibition of Apoptosis

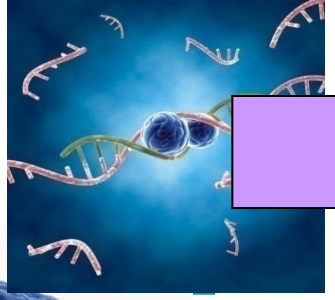

Effector cell
Fc Receptor
Antibody
Antigen
Target cell
Baseline state
No effector cell engagement
No complement activation
No signalling
①
②
③
④
Phagocytic cell
Macrophage or NK cell effector
Macrophage effector
1. Fix complement: initiate opsoniztion, lysis, inflammation.
Protection from tumor
2. Crosslink FcγRIII. Initiate ADCC and cytokine release.
Protection from tumor
3. Crosslink FcγRII Inhibit effector cell.
No protection from tumor
4. Crosslink antigens on cancer cell. Initiate signals, block growth or survival.
Protection from tumor
Bob Crimi



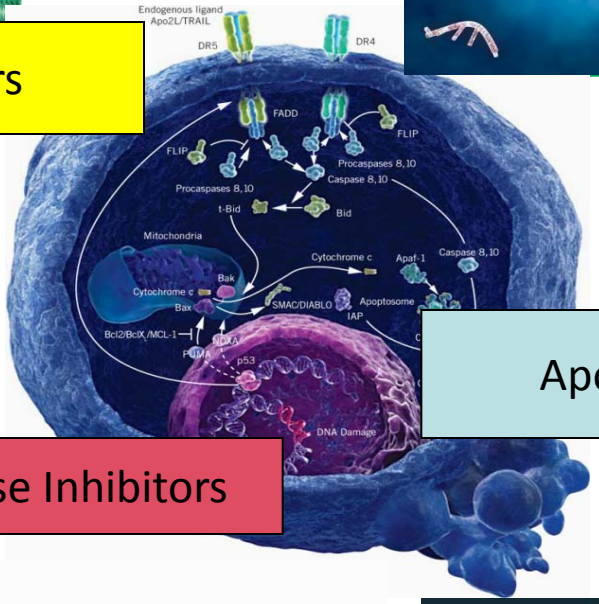

Marrow Stroma
Gene Delivery
Bone
Cardiac Muscle
Adipose
STEM CELLS
Cartilage
Tendon & Ligament
Biopharmaceuticals



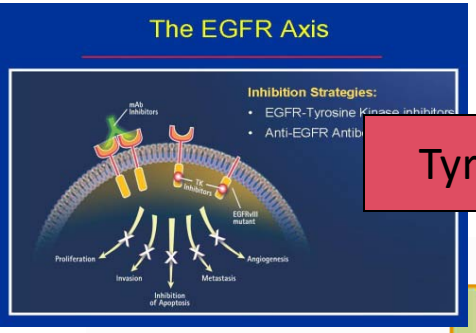
G protein traffic inhibitors



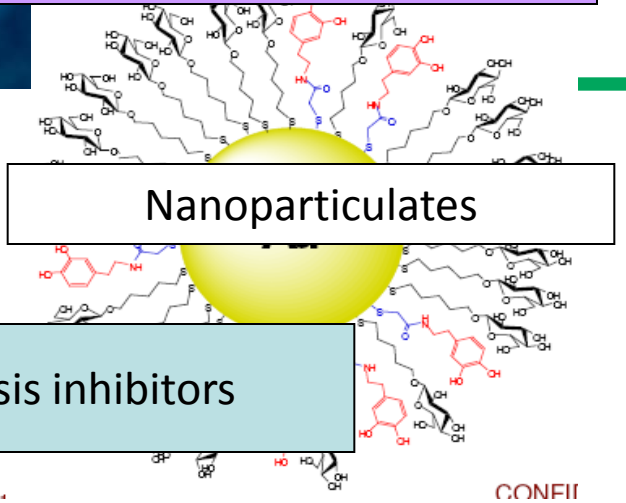
Single strand RNA



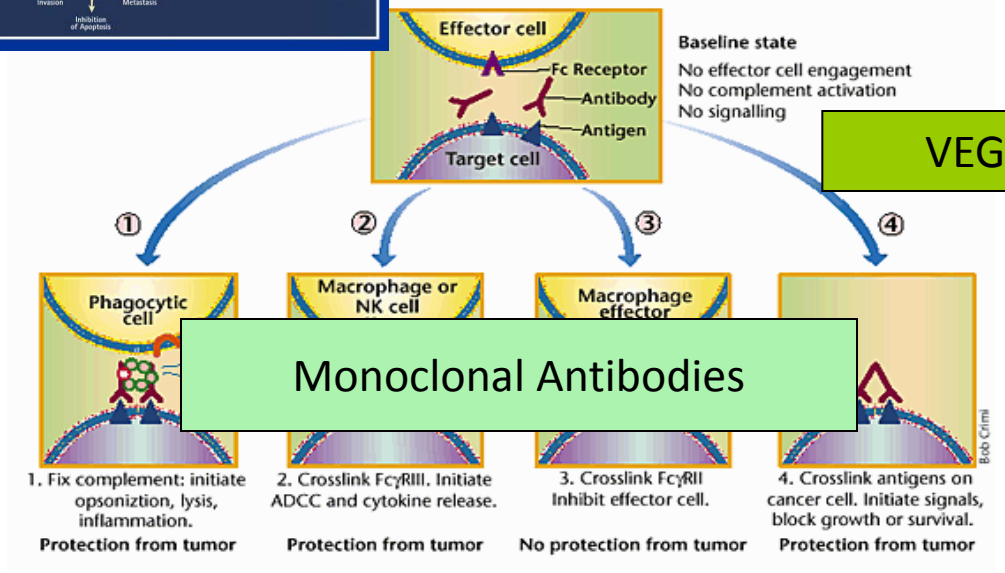
Apoptosis inhibitors



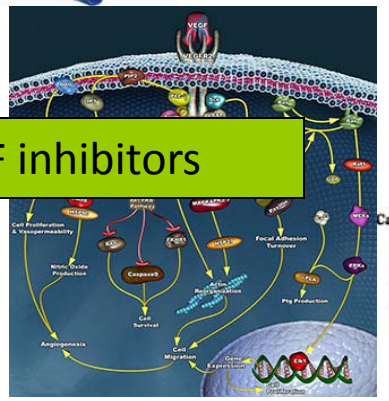
Tyrosine Kinase Inhibitors



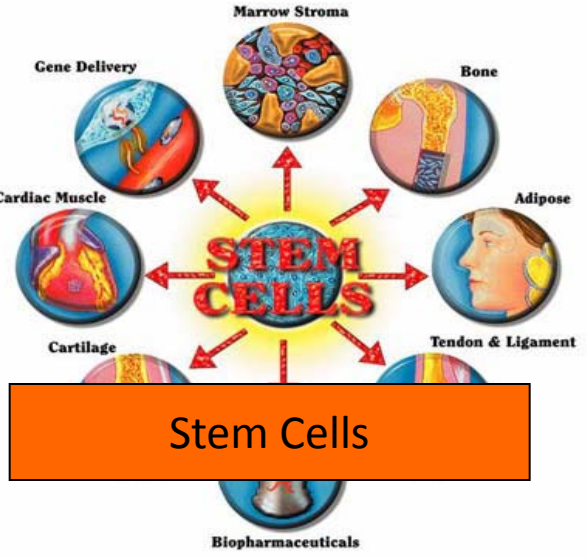
Nanoparticulates



Monoclonal Antibodies



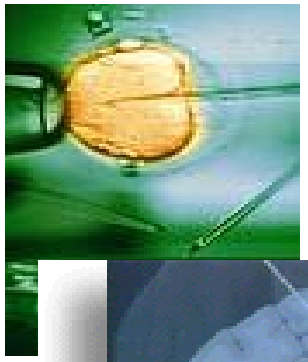
VEGF inhibitors

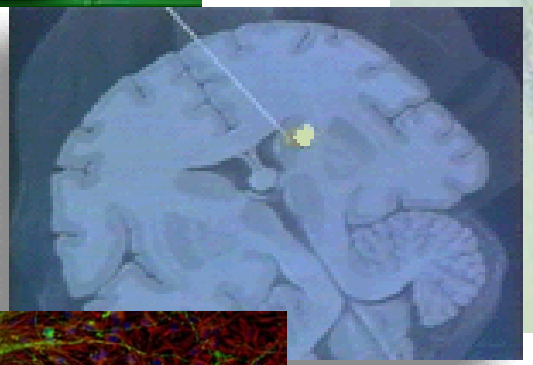


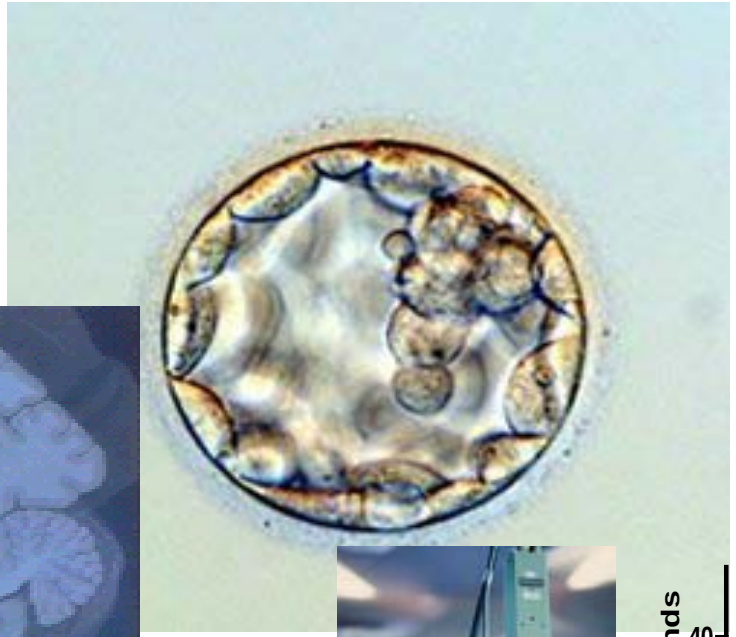
Stem Cells

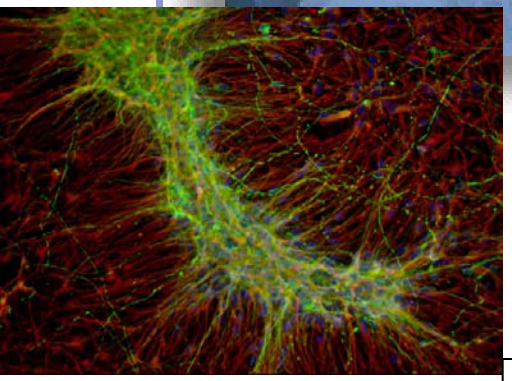
..entirely new technologies are emerging

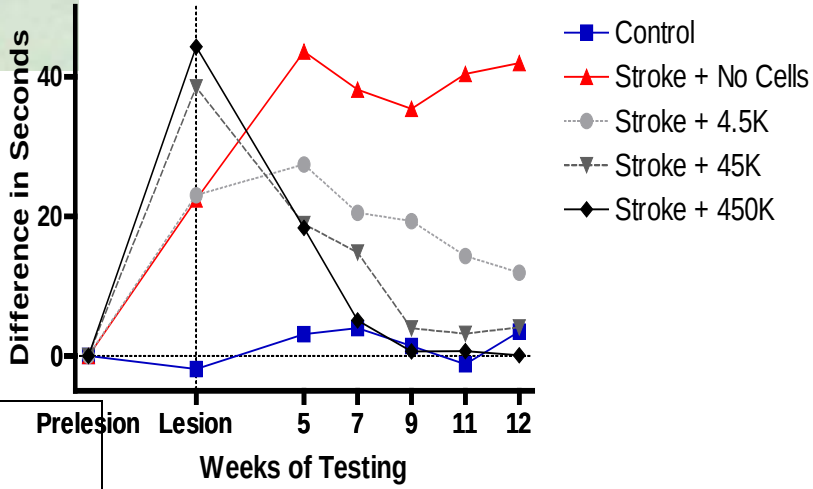
e.g Stem cells









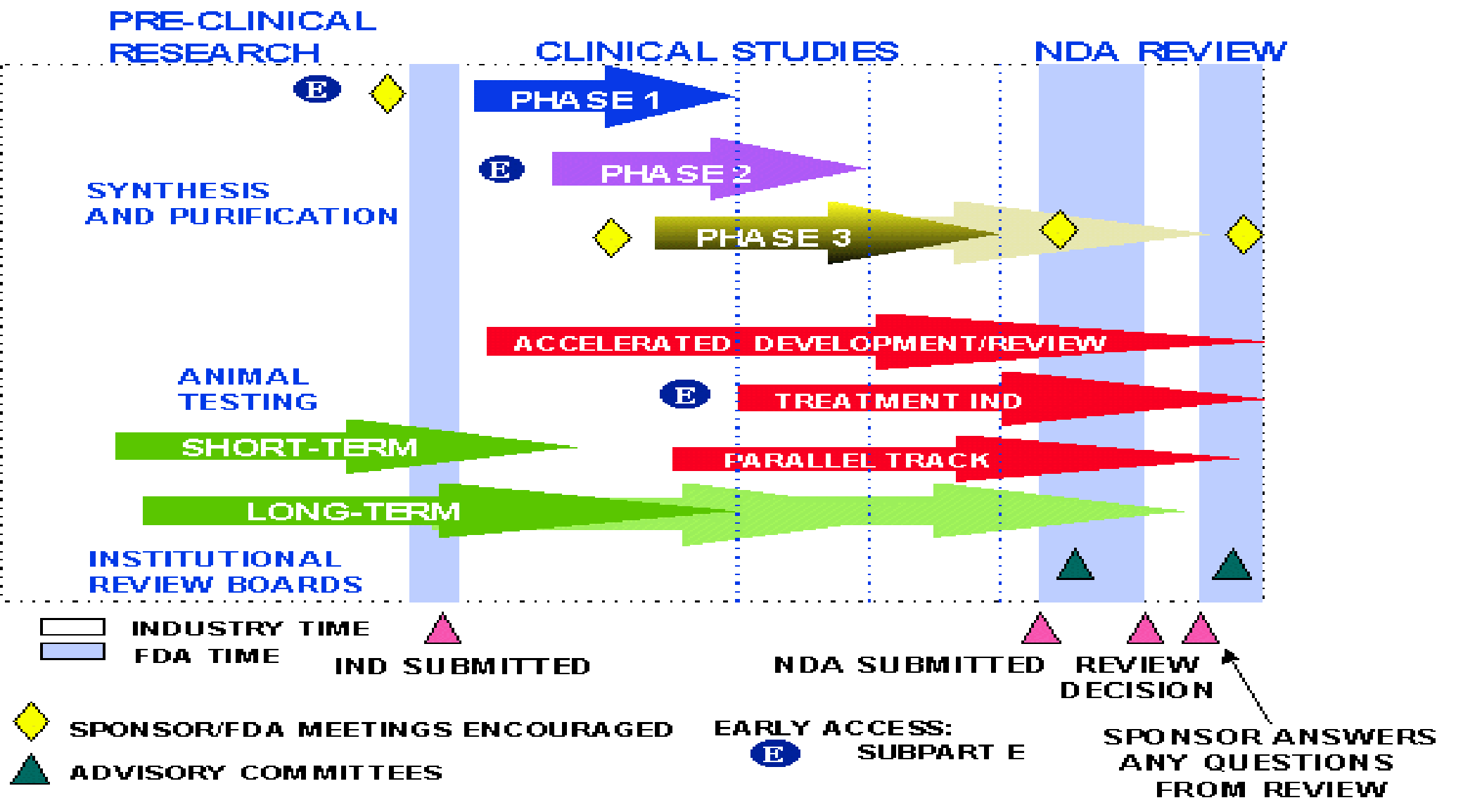


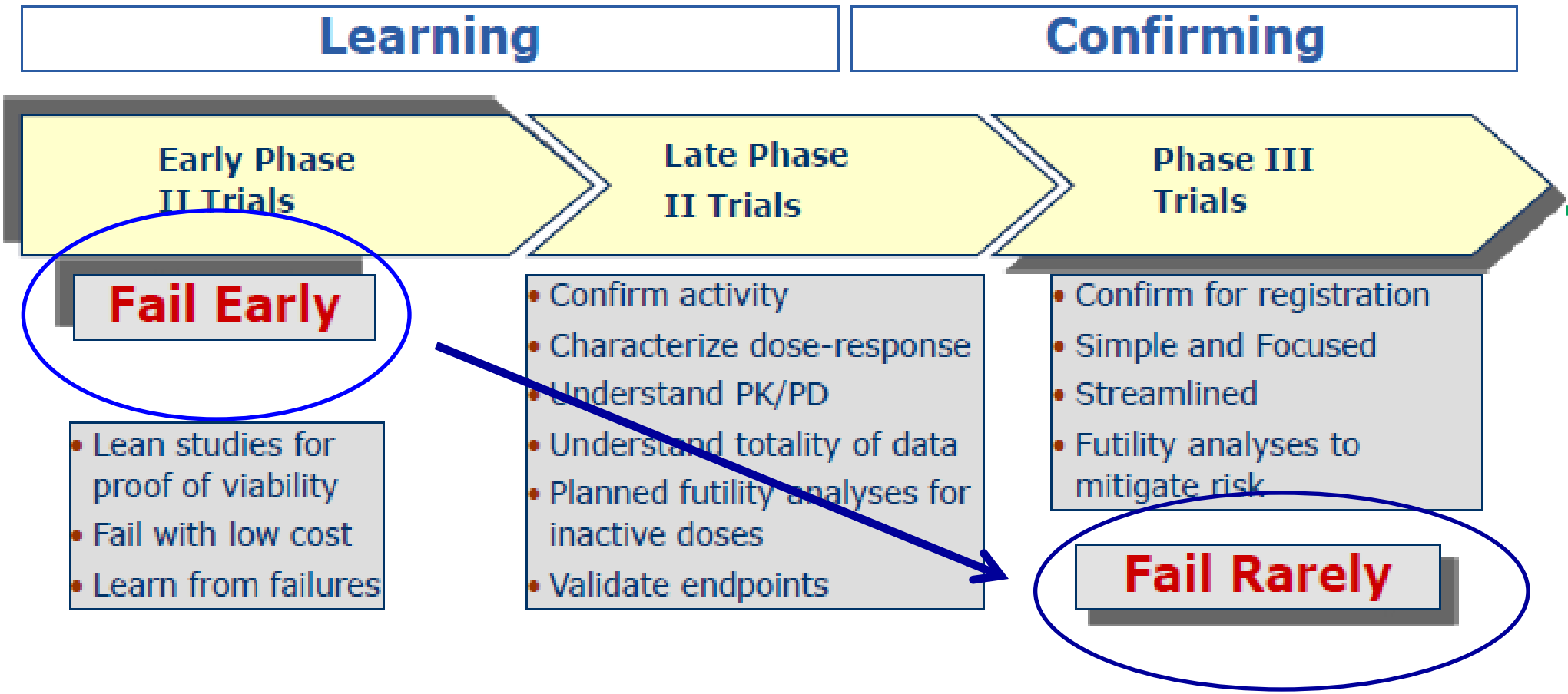
ReNeuron

pioneering stem cell therapeutics

Big Pharma
.....New Models for R&D

Changes in how we do R&D





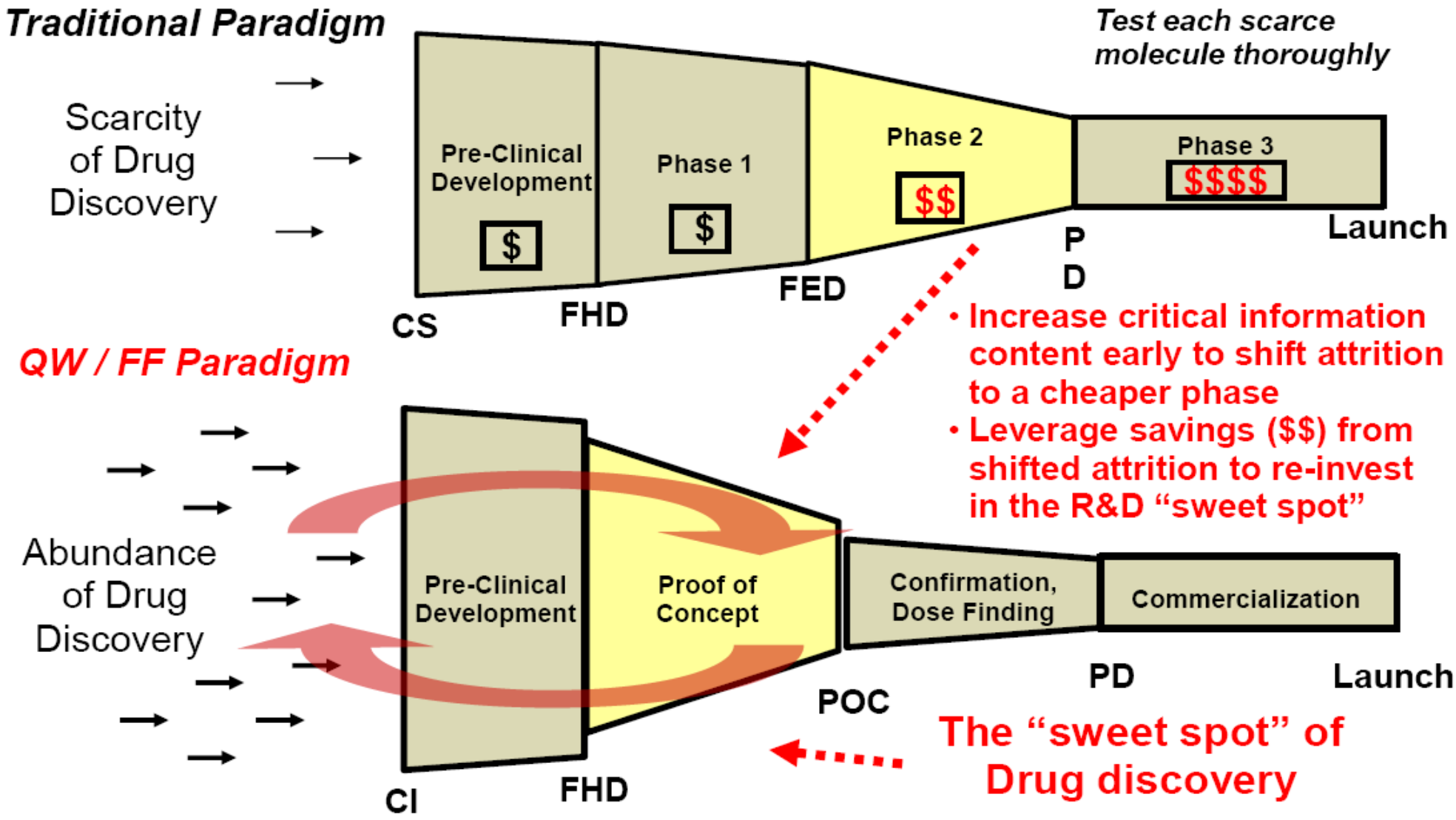
Precedented mechanisms:

- Potential to learn using prior data + modelling, can speed up programs without adding risk

Unprecedented mechanisms:

- Learning will usually require clinical studies; otherwise proceed to Phase III with quantified risk (High Ph III Failure)

Focus on R&D "Sweet Spot"



“Collaboration !!!”

- **Evergrowing “partnerships” between BigPharma and SME’s (Biotechs)**
- **OUTSOURCING ..e.g.**

  -Screening

  -Specialised Analytical Techniques

  -Safety Pharmacology

  -Toxicology

  -Human Pharmacology

  -Regulatory

  -Clinical Trials

  -Formulation (Galenic /Bio/Drug Delivery) etc etc etc

Biotech .....SPAIN !!

C A Walsh Pharm Market Europe Jan 2012 page 59

- Fastest growing business sector
- Turnover exceeds Euro 30,000
- 1,095 active Companies (2009 *) largest in Europe 2nd largest in OECD
- 239% increase in number of companies 200-2008
- strong "spin-off" culture ...10% from public institutions

SPAIN.....Science Base

- 35% publicly funded research is biomedicine
- Cost-effective clinical testing (30%<USA)
- 80 technology parks
- 9th in world scientific paper publication league
- New initiative (HIA) to define strategy for biomed research

Biotech .....SPAIN !!

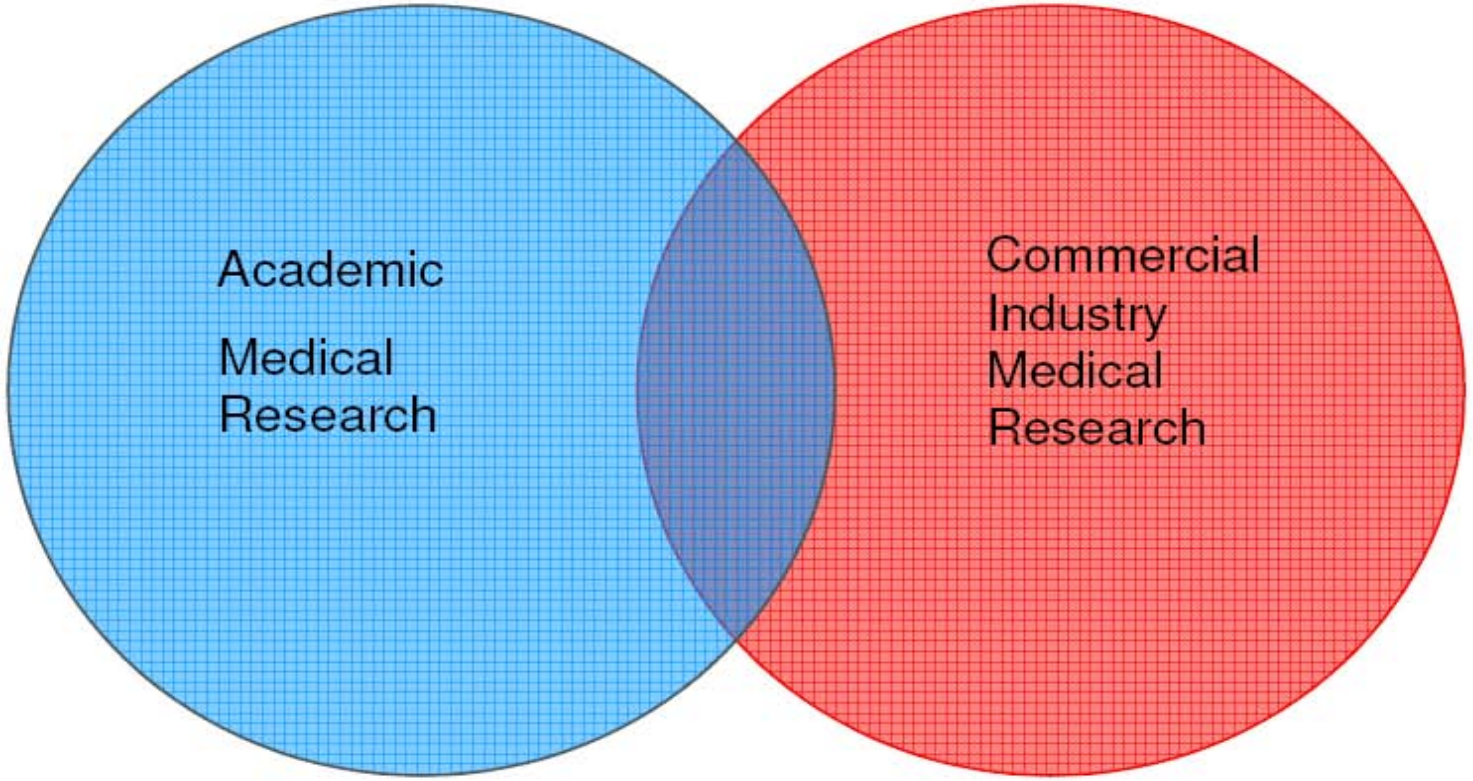
- **“In a bleak economic environment ,the biotech industry is fast replacing other ,failing,sectors as a good investment bet “**

C A Walsh Pharm Market Europe Jan 2012 page 59

The "Gap" in translational R&D

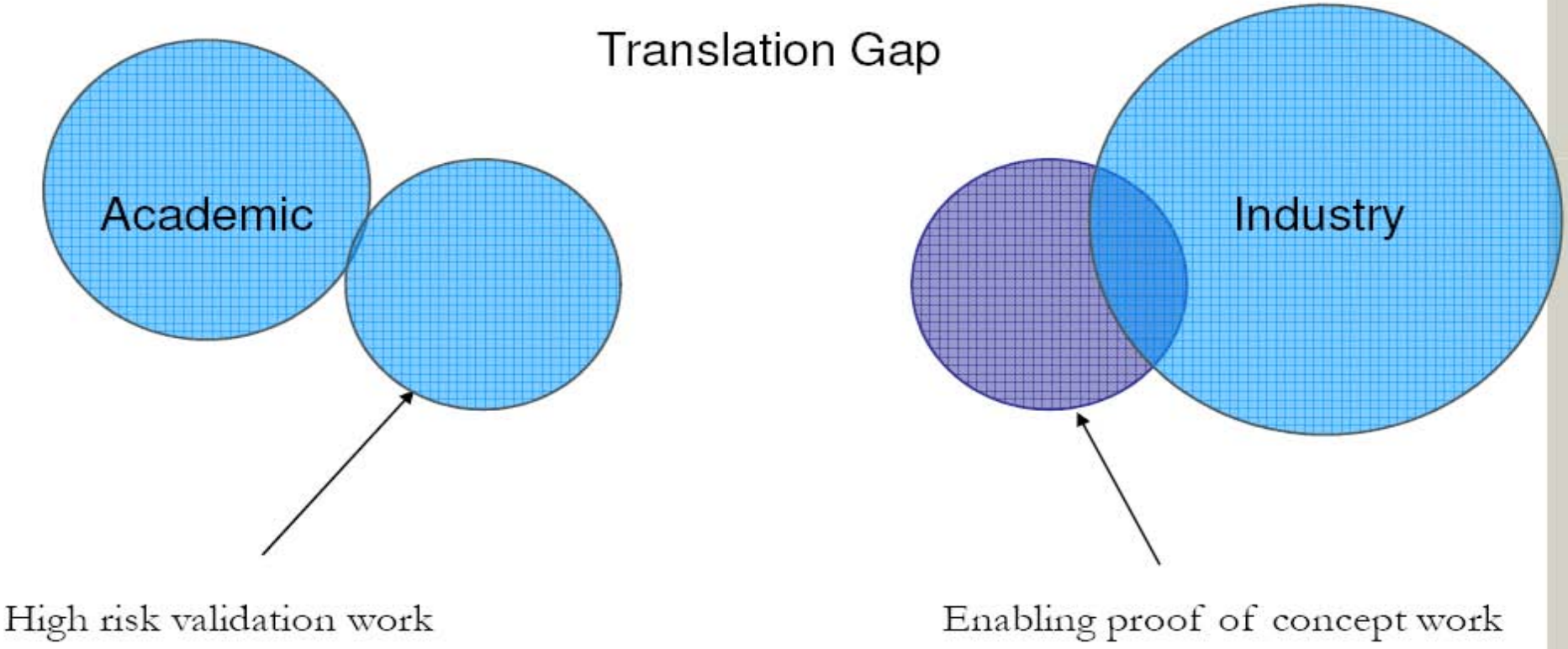
MRC T

Previous Situation 1990-2005

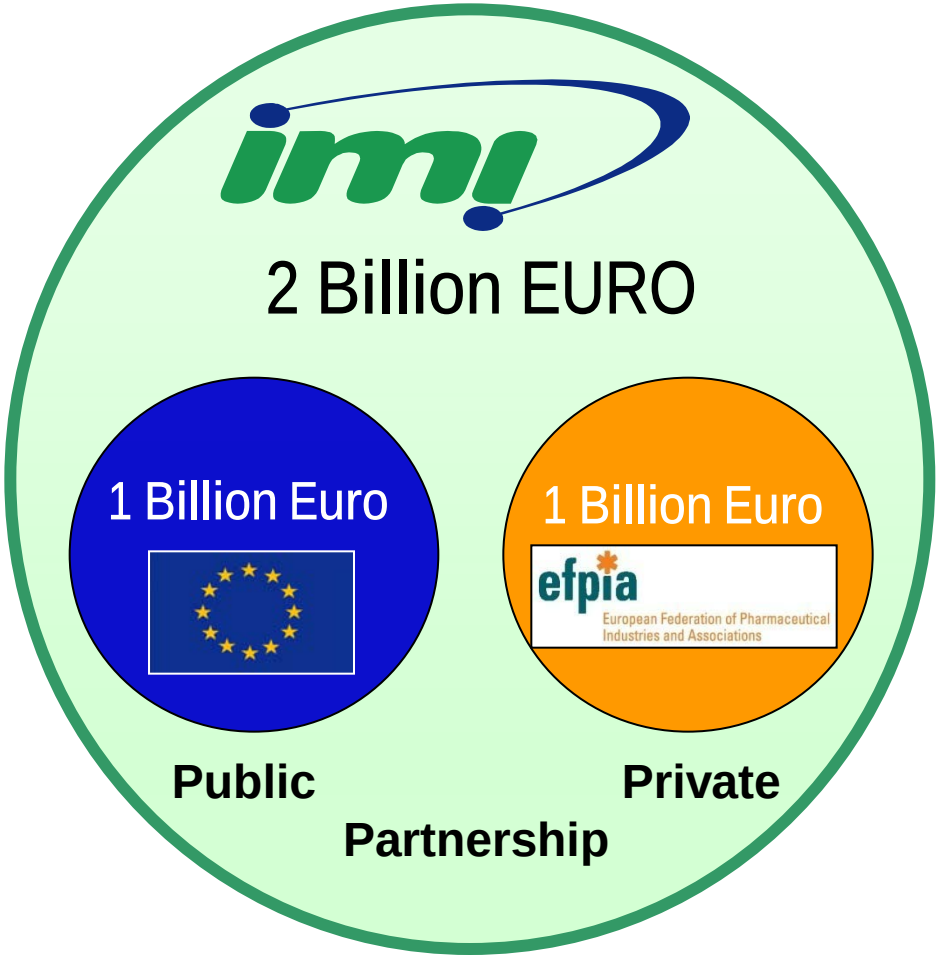


The "Gap" in translational R&D

CURRENT



Hence.....
Innovative Medicines Initiative



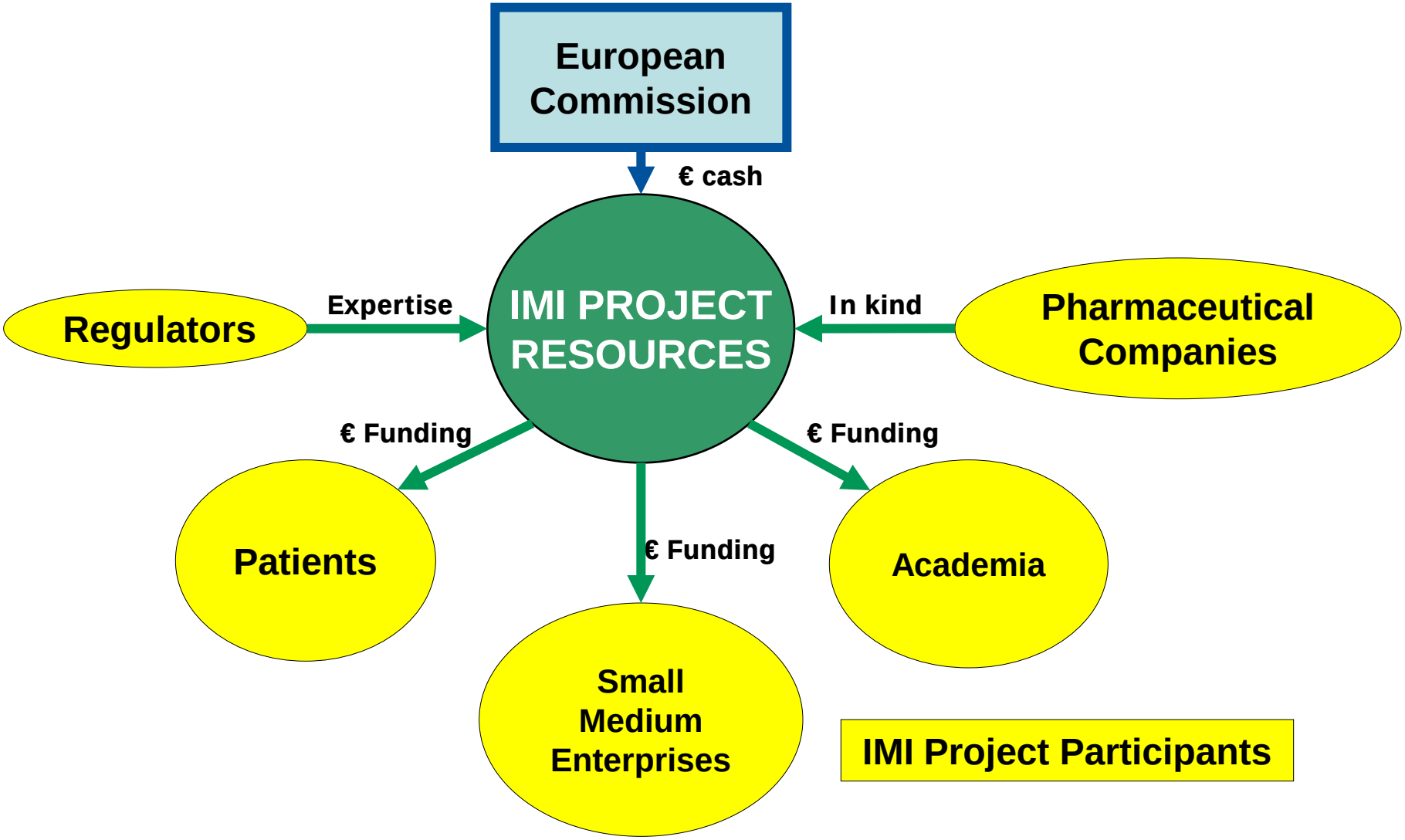
Biggest public-private partnership in the area of medicine

Innovative collaboration established between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA) as a Joint Technology Initiative under FP7

Aims at promoting medical innovation in Europe and addressing the bottlenecks in the R&D process

Public funding goes exclusively to academia, SMEs, patient organisations and Regulatory Authorities

Project Participants & their Contribution

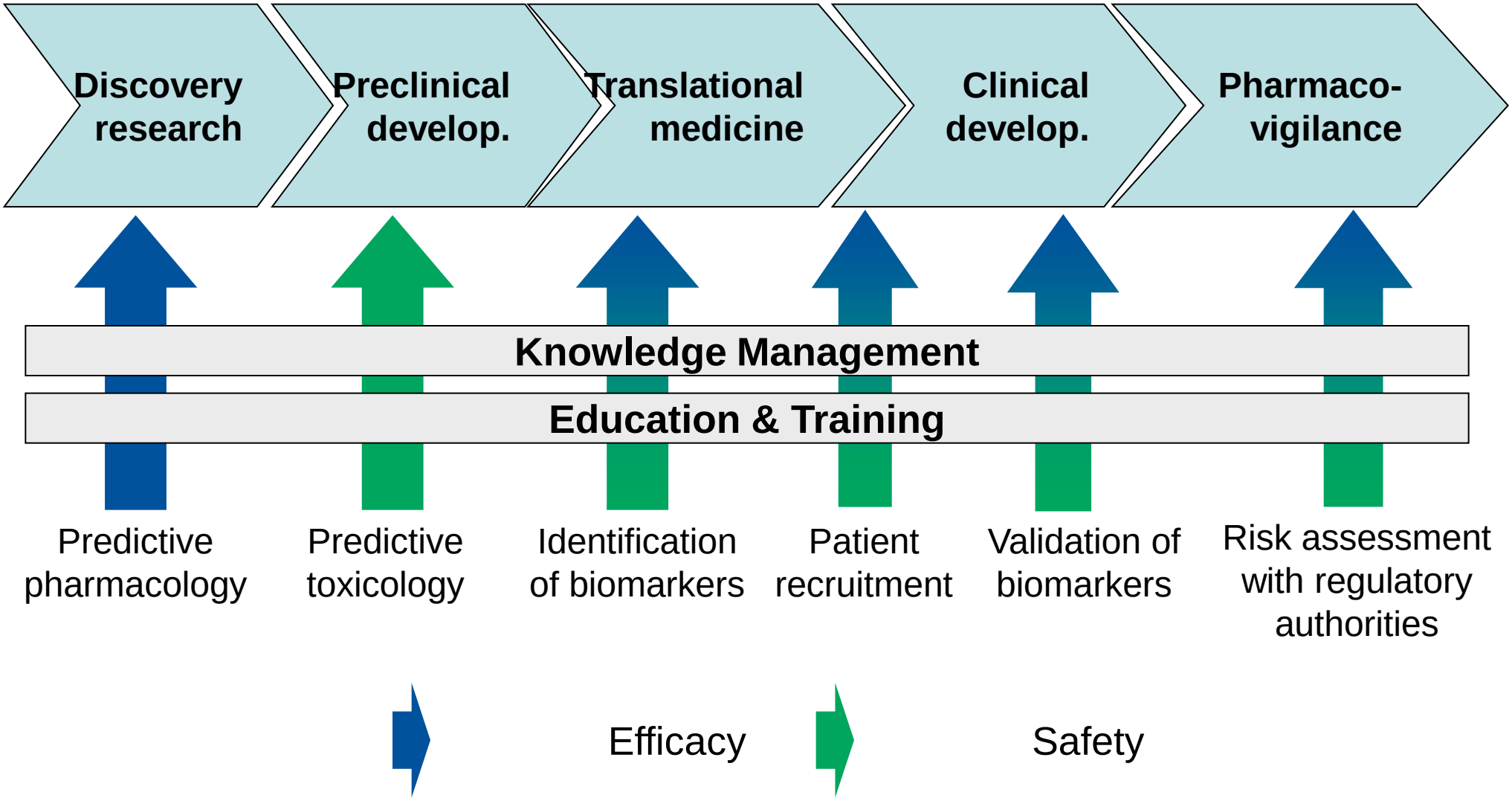


Eligibility for IMI JU funding

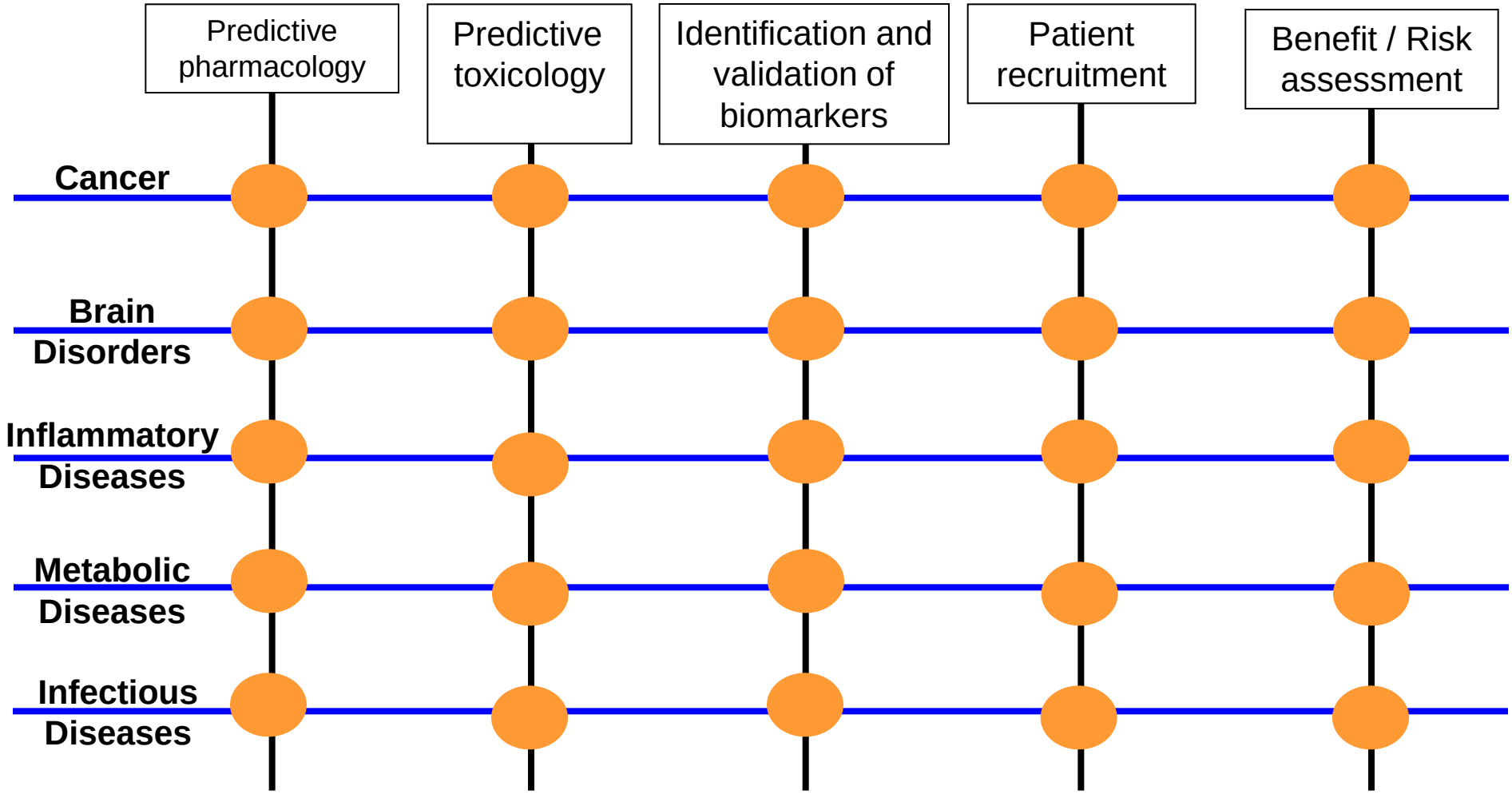
- Eligible **for funding**
- – Academia
- – SMEs (EU definition)
- – Patient Organisations
- – Non-profit research organisations
- – Intergovernmental organisations

- Non-Eligible **for funding**
- – EFPIA companies (in-kind contribution)
- – Companies not falling within the EU definition of SMEs
- – Others

IMI established to address the bottlenecks in R&D



IMI Historical Focusing on 5 Disease Areas



Main long term benefits for the Industry

- Faster approval through better collaboration with the regulatory authorities
- Less post marketing withdrawals through better pharmacovigilance tools
- Less patients needed in pivotal trials through optimized trial design
- Validation of new assessment methods such as biomarkers
- More skilled professionals available to the industry

⇨More cost-efficient R&D

We had established that such collaboration CAN work !!

The PredTox Consortium

PredTox ..part of the InnoMed project

Integrated project funded by the European Commissions' Sixth Framework Programme (FP6)

- 16 Companies, 14 Universities and 8 SMEs from across Europe
- Started in October 2005 for 3 years
- Total budget of €18 mio
- European Commission contribution of €12 mio.

PredTox

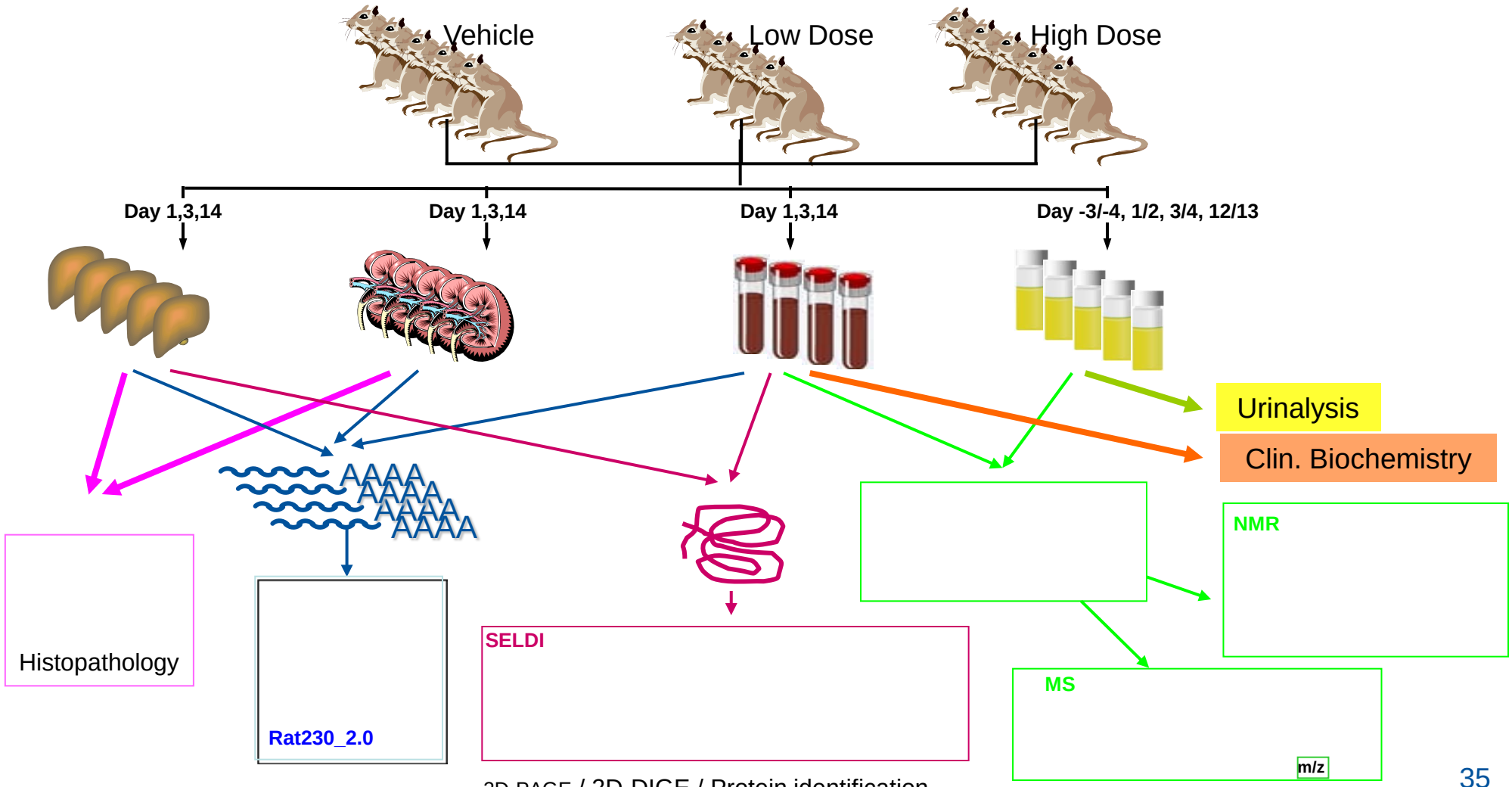
- **14 drugs that failed in Development due to preclinical liver or kidney toxicity were subjected to newer *in vivo / in vitro* screens and compared with 2 reference "known" toxic compounds …Gentamycin and Troglitazone**
- **Each of the 16 compounds were dosed at 2 level and at 3 time points**
- **The results were reviewed by 3 expert groups……..**

  -Liver Hypertrophy

  -Bile Duct Damage

  -Nephrotoxicity

The PredTox Study Design and Investigations
14 investigational + 2 reference compounds



PredTox….. Summary

Identification of new liver / kidney biomarkers appears to be realistic

- **Several distinct congruent biomarkers emerged notably**

  -Urinary Increases in phenylacetyl glycine
  -Decreases in trigonalline
  -Unconjugated bile acids in urine and serum
  -mRNA (tissue) specific markers .
  -kidney glycine, amidotransferase and protein 3PTD

- **The results will be published once the collaborating groups have determined the patentability of the data !!**

www.innomed-predtox.com

First (208) and Second(2009) calls

IMI Safety Pillar

1. Improve Predictivity of Immunogenicity
2. Non-genotoxic Carcinogenesis
3. Expert Systems for in silico Toxicity Prediction
4. Improved Predictivity of non-clinical Safety Evaluation
5. Qualification of Translational Safety Biomarkers
6. Strengthening the Monitoring of Benefit/Risk

IMI Efficacy Pillar

7. Islet Cell Research
8. Surrogate Markers for Vascular Endpoints
9. Pain Research
10. New Tools for the Development of Novel Therapies in Psychiatric Disorders
11. Neurodegenerative Disorders
12. Understanding Severe Asthma
13. COPD Patient Reported Outcomes

IMI Education & Training Pillar

14. European Medicines Research Training Network
15. Safety Sciences for Medicines Training Programme
16. Pharmaceutical Medicine Training Programme
17. Integrated Medicines Development Programme
18. Pharmacovigilance Training Programme

1. Oncology – Target Validation 4

2. Oncology - Molecular Biomarkers 10

3. Oncology: Imaging Biomarkers 16

4. Infectious Diseases - Diagnostic Tools 24

5. Inflammation – Aberrant Adaptive Immunity 29

6. Inflammation – Translational Research 34

IMI Knowledge Management Pillar 41

7. Knowledge Management – Drug/Disease Modelling 41

8. Knowledge Management – Open Pharmacological Space 51

9. Knowledge Management – Electronic Health Records (EHR) 57

Third Call (2010)

1. IMPROVING THE EARLY PREDICTION OF DRUG INDUCED LIVER INJURY IN MAN 7
2. IMMUNOGENICITY: ASSESSING THE CLINICAL RELEVANCE AND RISK MINIMIZATION OF ANTIBODIES TO BIOPHARMACEUTICALS 13
3. IMMUNOSAFETY OF VACCINES – NEW BIOMARKERS ASSOCIATED WITH ADVERSE EVENTS (EARLY INFLAMMATION, AUTOIMMUNE DISEASES AND ALLERGY) 19
4. IMPROVING THE PRECLINICAL MODELS AND TOOLS FOR TUBERCULOSIS MEDICINES RESEARCH 24
5. TRANSLATIONAL ENDPOINTS IN AUTISM 28
6. DEVELOPMENT OF PERSONALIZED MEDICINE APPROACHES IN DIABETES 33
7. FOSTERING PATIENT AWARENESS ON PHARMACEUTICAL INNOVATION. 38

Forth Call (2011)

EU MEDICAL INFORMATION SYSTEM

1. A EUROPEAN MEDICAL INFORMATION FRAMEWORK (EMIF) OF PATIENT-LEVEL DATA TO SUPPORT A WIDE RANGE OF MEDICAL RESEARCH 6
2. ETRIKS: EUROPEAN TRANSLATIONAL INFORMATION & KNOWLEDGE MANAGEMENT SERVICES 20

CHEMISTRY, MANUFACTURING AND CONTROL

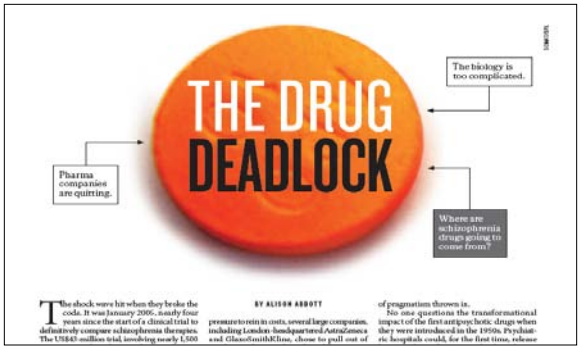
3. DELIVERY AND TARGETING MECHANISMS FOR BIOLOGICAL MACROMOLECULES 30
4. IN VIVO PREDICTIVE BIOPHARMACEUTICS TOOLS FOR ORAL DRUG DELIVERY 36
5. SUSTAINABLE CHEMISTRY – DELIVERING MEDICINES FOR THE 21ST CENTURY 44

TECHNOLOGY AND MOLECULAR DISEASE UNDERSTANDING

6. HUMAN INDUCED PLURIPOTENT STEM (HIPS) CELLS FOR DRUG DISCOVERY AND SAFETY ASSESSMENT 54
7. UNDERSTANDING AND OPTIMISING BINDING KINETICS IN DRUG DISCOVERY 65

NEWMEDS

- *Develops biomarkers and tools and models to allow better targeted treatments for* ***schizophrenia and depression***



Nature, 11 November 2010

19 Partners

- 9 EFPIA companies
- 7 Public organisations
- 3 SMEs

First achievements

- ✓ Has assembled the largest known repository of antipsychotic clinical trial data
- ✓ The database contains information on 23,401 patients from 67 industry sponsored studies
- ✓ Bringing together data from public projects and 3 companies on the genetics and clinical response in 1800 well characterized patients with depression

U-BIOPRED

- *By comparing data from several hundred people, the team will* ***characterise different kinds of severe asthma, paving the way towards a new classification of asthma and personalised treatments for patients***

38 Partners

- 9 EFPIA companies
- 23 Academic institutions
- 3 Patients' organisations
- 3 SMEs
- 1 non-SME company

First achievements

✓ Consensus statement on the definition of severe refractory asthma

Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI)

Elisabeth H Bel,[1] Ana Sousa,[2] Louise Fleming,[3] Andrew Bush,[4] K Fan Chung,[5] Jennifer Versnel,[6] Ariane H Wagener,[1] Scott S Wagers,[7] Peter J Sterk,[1] Chris H Compton,[8] on behalf of the members of the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome (U-BIOPRED) Consortium, Consensus Generation[9]

ABSTRACT

Patients with severe refractory asthma pose a major healthcare problem. Over the last decade it has become increasingly clear that, for the development of new targeted therapies, there is an urgent need for further characterisation and classification of these patients. The

DIAGNOSIS AND DEFINITION OF SEVERE ASTHMA OVER THE LAST 15 YEARS

Various documents proposing different clinical definitions of 'severe asthma' in adults and children have been published over the last 15 years by international task forces, workshops, networks and

Thorax (2010)

eTOX

- *Builds a large searchable database containing* ***drug toxicity-related data*** *extracted from relevant pharmaceutical* ***pre-clinical legacy reports***
- *Develops innovative methodological strategies and novel software tools to better* ***predict*** **in silico** ***the toxicological profiles of new molecular entities*** *in early stages of the drug development pipeline, using its database background*

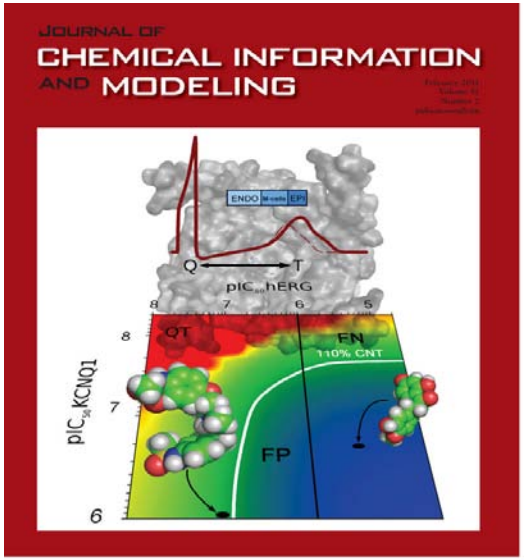
25 Partners

- 13 EFPIA companies
- 8 Public organisations
- 4 SMEs

First achievements

✓ An innovative multi-scale modelling strategy for the prediction of cardiotoxicity has been developed, successfully tested and published

J. Chem. Inf. Model. 2011, 51:483-92



SAFE-T

- *Addresses the current lack of sensitive and specific clinical tests to* ***diagnose and monitor drug-induced injury to the kidney, liver and vascular tissues*** *in man, which is a major hurdle in drug development*

20 Partners

- 11 EFPIA companies
- 5 Academic institutions
- 4 SMEs

A generic operational strategy to qualify translational safety biomarkers

Katja Matheis[1], David Laurie[2], Christiane Andriamandroso[3], Nadir Arber[4], Lina Badimon[5], Xavier Benain[6], Kaïdre Bendjama[7], Isabelle Clavier[6], Peter Colman[8], Hüseyin Firat[7], Jens Goepfert[9], Steve Hall[8], Thomas Joos[10], Sarah Kraus[4], Axel Kretschmer[11], Michael Merz[2], Teresa Padro[5], Hannes Planatscher[9], Annamaria Rossi[8], Nicole Schneiderhan-Marra[9], Ina Schuppe-Koistinen[12], Peter Thomann[7], Jean-Marc Vidal[13] and Béatrice Molac[7]

[1] Boehringer-Ingelheim Pharma GmbH & Co. KG, Biberach, Germany
[2] Novartis Pharma AG, Basel, Switzerland
[3] Interface Europe, Brussels, Belgium
[4] Tel-Aviv (Souraski) Medical Center, Tel-Aviv, Israel
[5] Barcelona Cardiovascular Research Center (ICCC-CISC), Barcelona, Spain
[6] Sanofi-Aventis, Paris, France
[7] Firalis SAS, 35 rue du Fort, 68330 Huningue, France
[8] Pfizer Ltd, Sandwich, UK
[9] Natural and Medical Sciences Institute, Reutlingen, Germany
[10] Experimental & Diagnostic Immunology GmbH, Reutlingen, Germany
[11] Bayer Schering Pharma AG, Leverkusen, Germany
[12] AstraZeneca R&D, Södertälje, Sweden
[13] EMA, London, UK

Drug Discov. Today, 2011, 16: 600-608

First achievements

- ✓ 153 potential biomarker candidates for drug-induced injury of the kidney, liver and vascular system have been evaluated and are currently undergoing clinical evaluation.
- ✓ The strategy adopted has been agreed with the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA).

IMI Education & Training projects

- ✓ First course in Nov. 2010 on drug discovery development
- ✓ Certificate and Master courses in pharmacovigilance and pharmacoepidemiology in Sept. 2011
- ✓ EU syllabus on pharmaceutical medicine
- ✓ Database on over 700 master courses, 110 professional development courses, 380 learning tools

Call 5 topic (2012)

European lead factory:

Building a joint European compound library and screening centre for drug discovery

Info Day on the 5th Call on Monday 27 February

European lead factory:

- the **new project** will:
  - **produce** a **unique collection of compounds**, composed of chemicals from companies and public organisations, that will **be accessible to public and private partners**
  - a **centre** to screen the unique collection
  - **develop novel tools** to **improve screening procedures** and pick up interesting molecules
  - **deliver 'qualified hits'** or tool compounds (substances that have the **potential of becoming new medicines**) that can be **investigated further**
  - create a **unique platform** to foster **collaboration** and exchange between industry and academia **and accelerate the development of new leads**
  - result in a **broad knowledge base** to delineate successful strategies for library design

… “so far …so good”

…….but what do we do next ??

The Innovative Medicines Initiative

- Much of the original SRA have been addressed by IMI Calls 1-3
- Science has moved on since 2005
- The industry is changing – both where we operate, how we do research and what we can share
- The need for appropriate collaboration to tackle major challenges remains a priority!

And not only challenges for industry !

Innovative Medicines Initiative

Challenge for the future of Europe

Today's health challenges – tomorrow's socio-economic burdens:

not only from increasing **healthcare costs**, but also from **loss of productivity** and **impact on the social sector**.

Key healthcare challenges

- Growing elderly population
- Diseases caused by change in lifestyle
- Neglected diseases in developing world ??

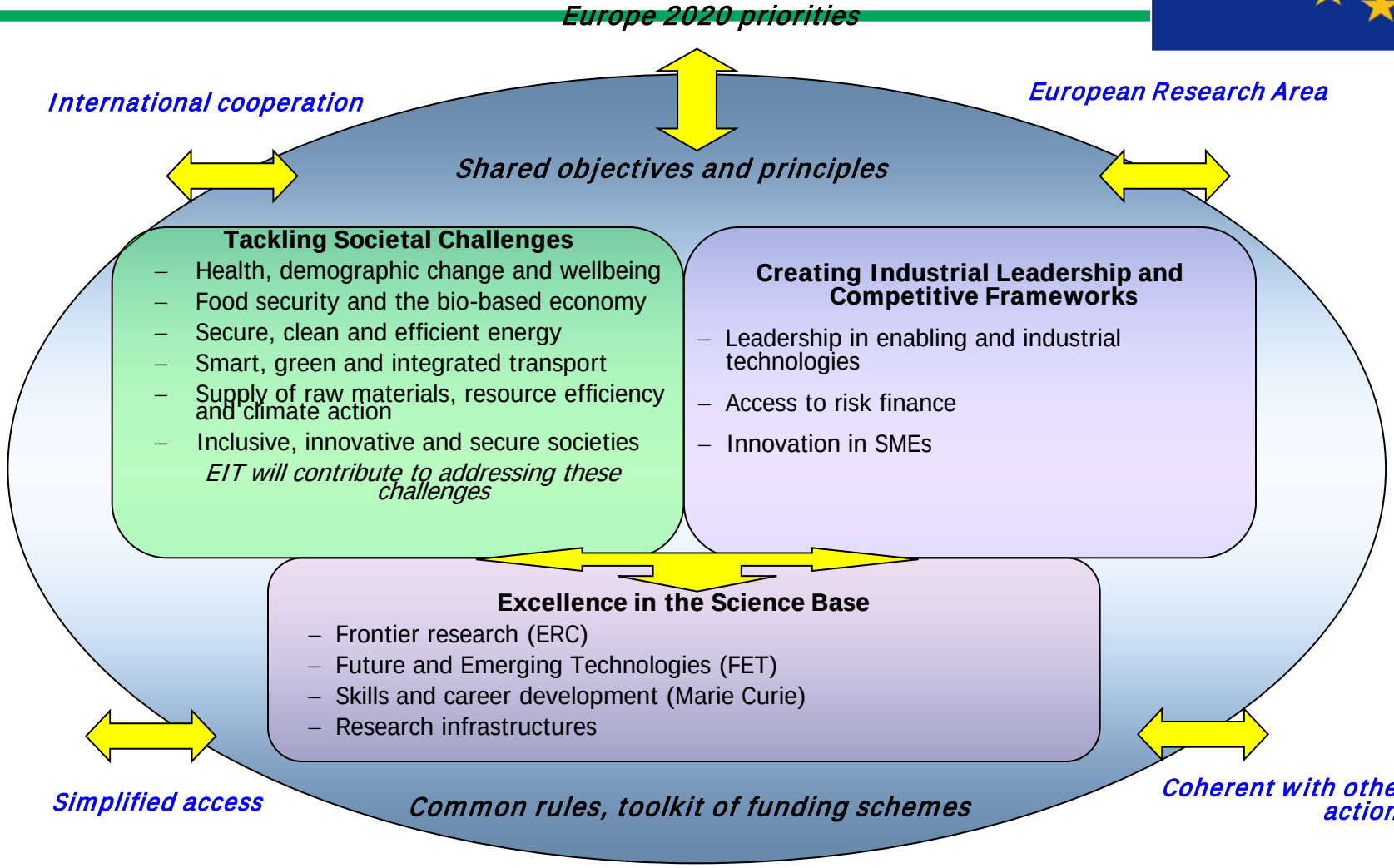
Policy objectives

- Europe needs cutting edge research and innovation
- Essential to ensure competitiveness, growth and jobs
- Vital to tackle pressing societal challenges (climate change, energy security, health & demographic change,…)
- 3% of GDP to be invested in R&D: headline target of Europe 2020
- But: Europe's performance lags behind USA and JP, BRIC countries rapidly catching up

➔ Coordinated action needed at EU level

➔ EU Budget can make the difference!

Horizon 2020
–Objectives and structure



Horizon 2020:
Industry opportunity

Horizon 2020 is a unique opportunity for industry to propose a new forward looking frame for a Public Private Partnership in the Healthcare area.

…an Industry view

1. We don't have sufficient understand of the diseases and therefore don't have **targets** and **biomarkers** for developing new drugs.

1. Methodologies for evaluating treatment effects in several key disease areas are not well developed.

3. Incentives for doing research and developing new treatments in key diseases do not match the risks (economically and standard attrition).

Development towards more personalized medicine with the current incentive structures will only increase the challenges.

So……what is needed to meet the healthcare burden ?????

1. Better understanding of diseases
   - The underlying biology
   - Link between diseases and environment/ lifestyle factors

2. Development of new and better treatments paradigms in disease areas of importance to society (key diseases)

3. Prevention of diseases

A clear priority ?
Tackling resistance to antibiotics:

Building partnerships to progress the discovery and development of novel antibiotic drugs to treat the most urgent infections

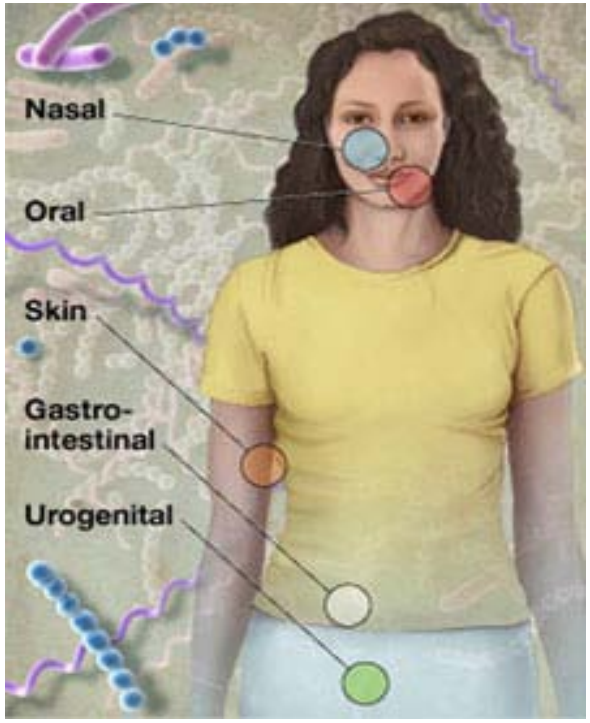
Tackling resistance to antibiotics: NewDrugs4BadBugs (ND4BB)

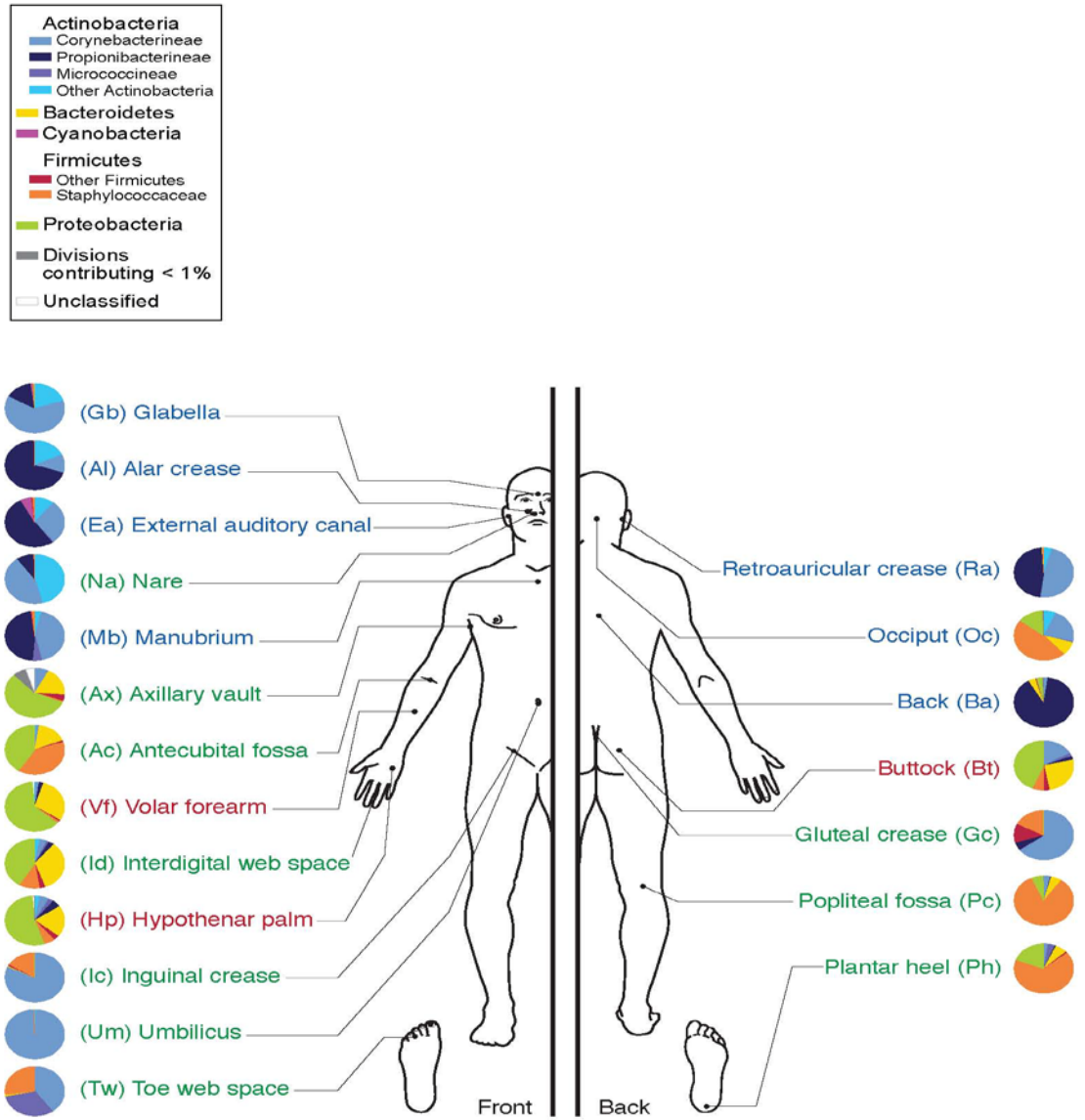
- Antimicrobial resistance (AMR) is now a major global public health threat.
- Despite the recognized need for new antimicrobials, only two new classes of antibiotics have been brought to market in the last 30 years, and many companies have left the area.

Key barriers to the development and delivery of effective antibiotics are:

- Discovery and development of novel antibacterial agents is a very difficult scientific challenge
- Substantial regulatory challenges to the introduction of novel antibacterial agents…"DELTA 10" RULE
- Antibiotics have a low return on investment (ROI) relative to other medicines.

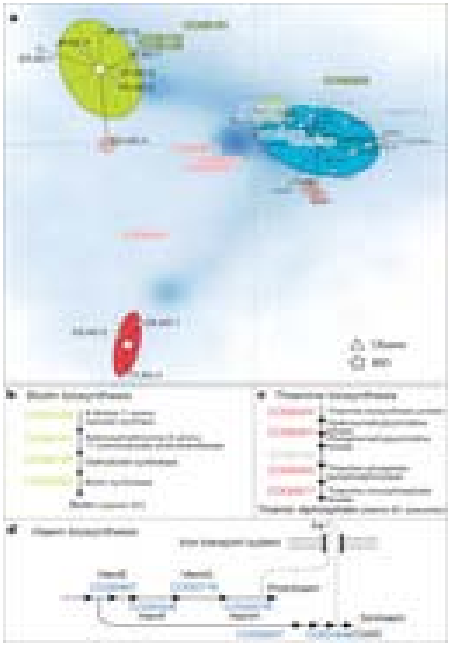
Human Microbiome





The International Human Microbiome Consortium

Enterotypes



By combining 22 newly sequenced faecal metagenomes of individuals from four countries with previously published data sets, here we identify three robust clusters (referred to as enterotypes hereafter) that are not nation or continent specific

Nature **473**,174–18 (12 May 2011)

Tackling resistance to antibiotics: NewDrugs4BadBugs (ND4BB)

- Collaborative R&D on diagnostic devices and drugs, sharing, evolution of regulatory insight.
- Focus on antibacterial agents targeting drug-resistant priority pathogens
- (Gram-negative pathogens (e.g. Enterobacteriaceae, *Acinetobacter, Pseudomonas*), *Clostridium difficile,* methicillin-resistant *Staphylococcus aureus* (MRSA)).
- Encompass all aspects from the discovery of novel mechanism antibiotics to Phase 2/3 clinical trials.
- Bayesian trial designs and PK/PD modeling.

Tackling resistance to antibiotics: NewDrugs4BadBugs (ND4BB)

- Optimization of novel ‘leads’ into development candidates.

- Knowledge sharing e.g. details of failed compounds, protocols of clinical trials and regulatory feedback.

- Seeks to integrate new measures that will enhance the efficiency of antibiotic clinical trials...e.g.

➢ studies to test and validate diagnostics

➢ creation of an antibiotic clinical trial network

➢ Bayesian trial designs and PK/PD modeling.

➢ creation of global surveillance programs

2020 Areas of Focus

- **Understanding and classification of diseases**
- **Target validation**
- **Safety of compounds**
- **Methodologies to evaluate treatment effects**

Understanding and classification of diseases

- better definition of diseases based on molecular disease understanding (the taxonomy of human disease*)and thereby drug mechanism of action to support clinical trial design to increase probability of success

- identify predictive markers of susceptibility and disease progression to support clinical trial design

- define better tools for basic and non-clinical research

- identification of new targets

(*Ismail Kola and John Bell, Nat Rev Drug Discov 2011 vol. 10 (9) pp. 641-642)

Cancer

- 3142 Gene Mutations in HUMAN cancers
- 286 are Tumour suppressor genes*
- 33 are Oncogenes

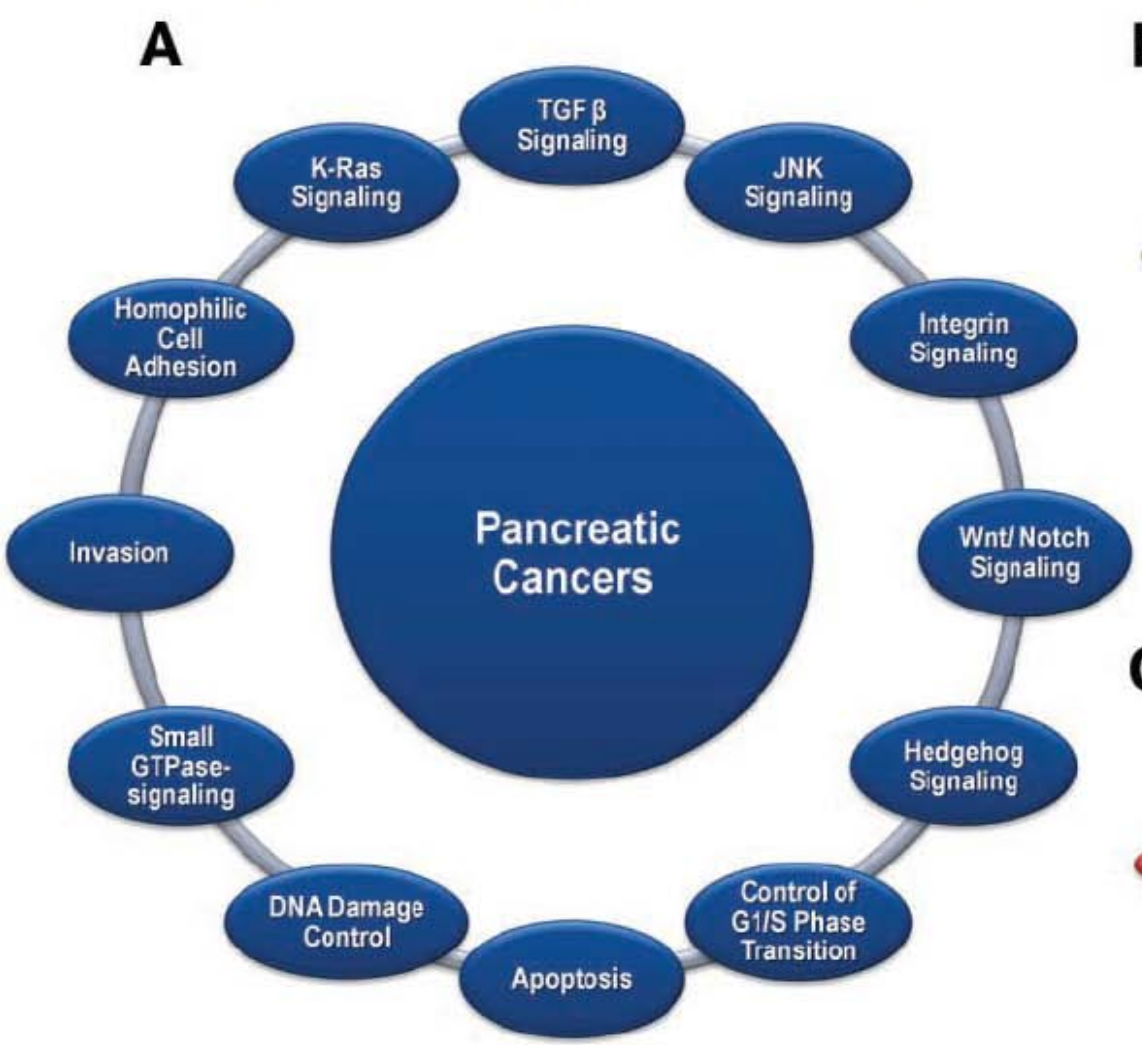
*90% of the drivers are oncogenes ..virtually all are components of 12 core pathways

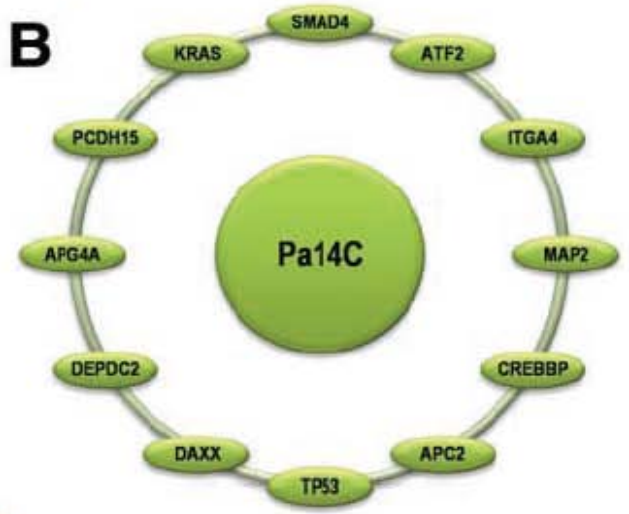
---

- In parallel a range of **Cancer Exomes** is now being defined

"Cancer"

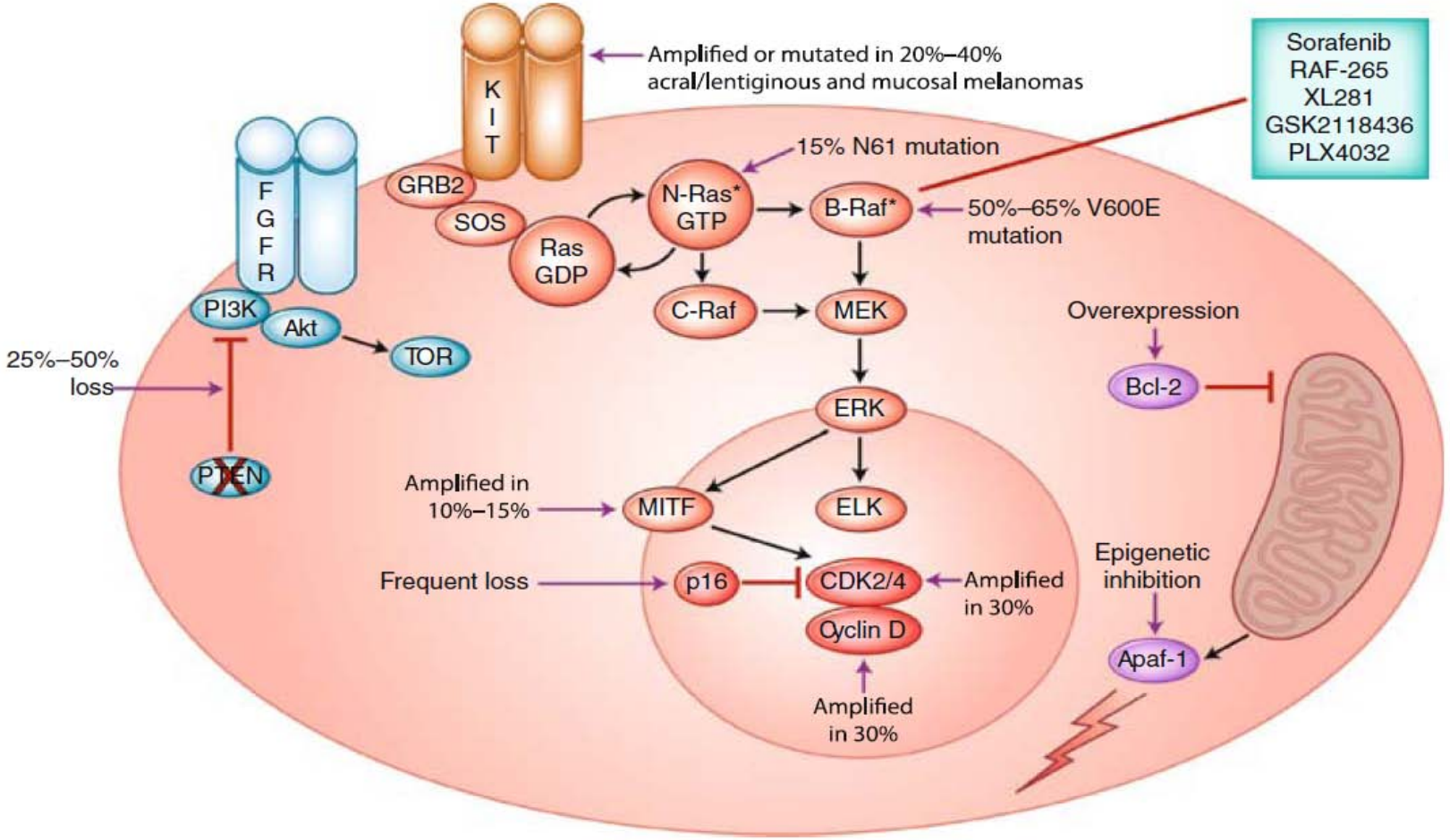
Signalling pathways and processes





Jones S *et al*. Science 321, 1801 (2008)

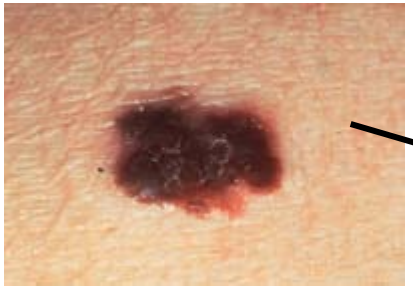
Genetic lesions in melanoma: targeting BRAF gain of function mutation



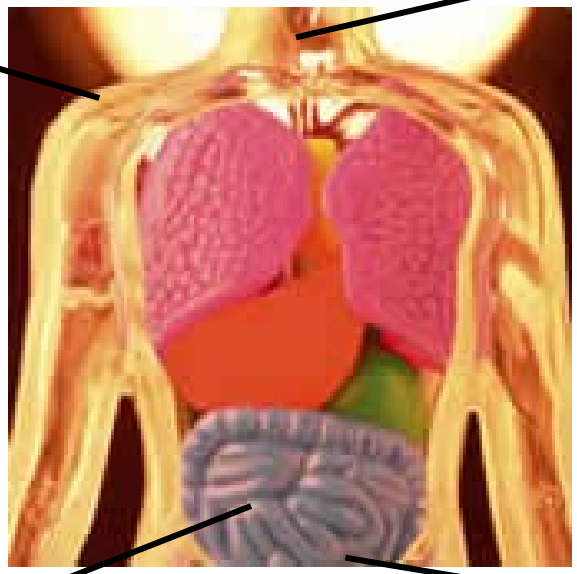
Shepherd C. Curr Oncol Rep 2010, 12 p146

Prevalence of B-Raf mutations in solid tumors

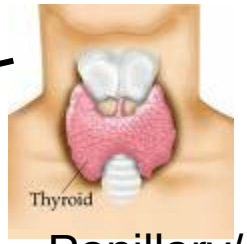
Metastatic Melanoma



B-Raf 68%



Metastatic Thyroid

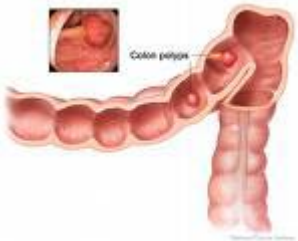


Papillary/Anaplastic

B-Raf

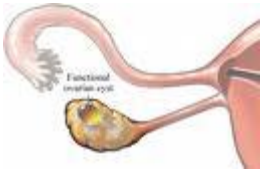
- Papillary 69%
- Anaplastic 83%

Metastatic Colon



B-Raf 4-16%

Metastatic Serous Low Grade Ovarian

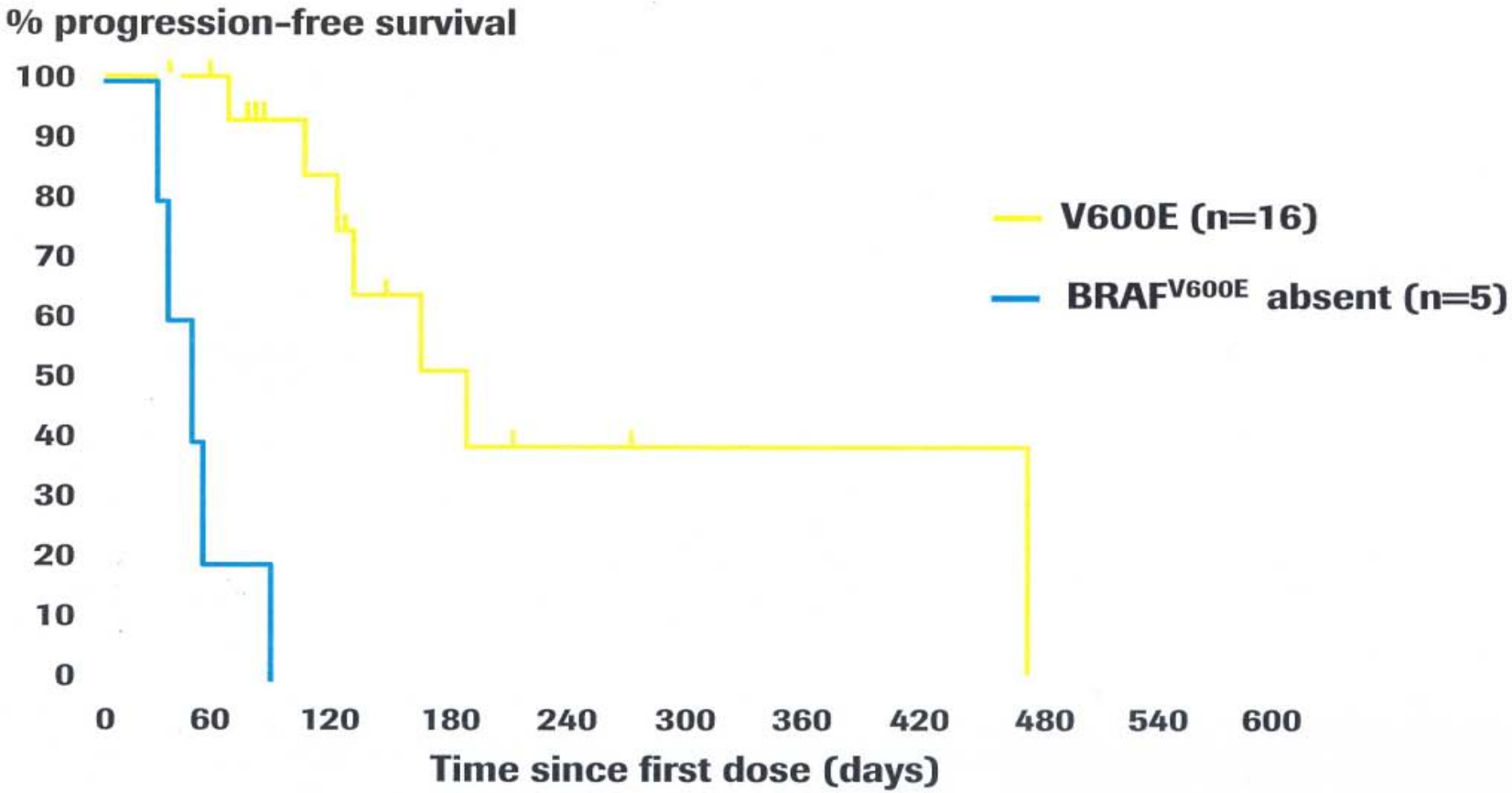


B-Raf 68%

(ACS 2006)

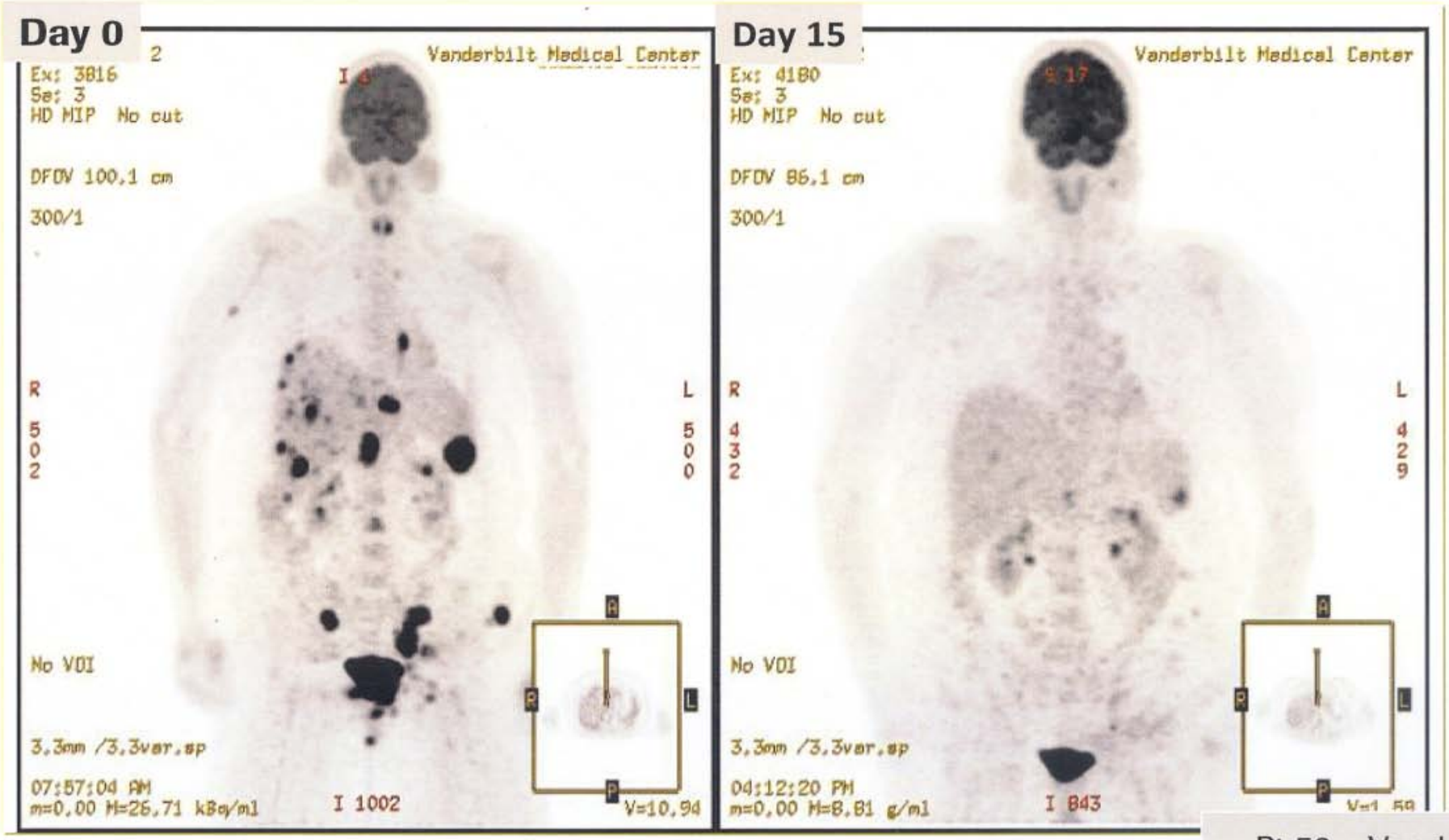
PLX4032 in metastatic melanoma patients

Mutated BRAF vs non- mutated BRAF patients



Data as of 5.13.09

Metastatic melanoma patient with BRAF mutation



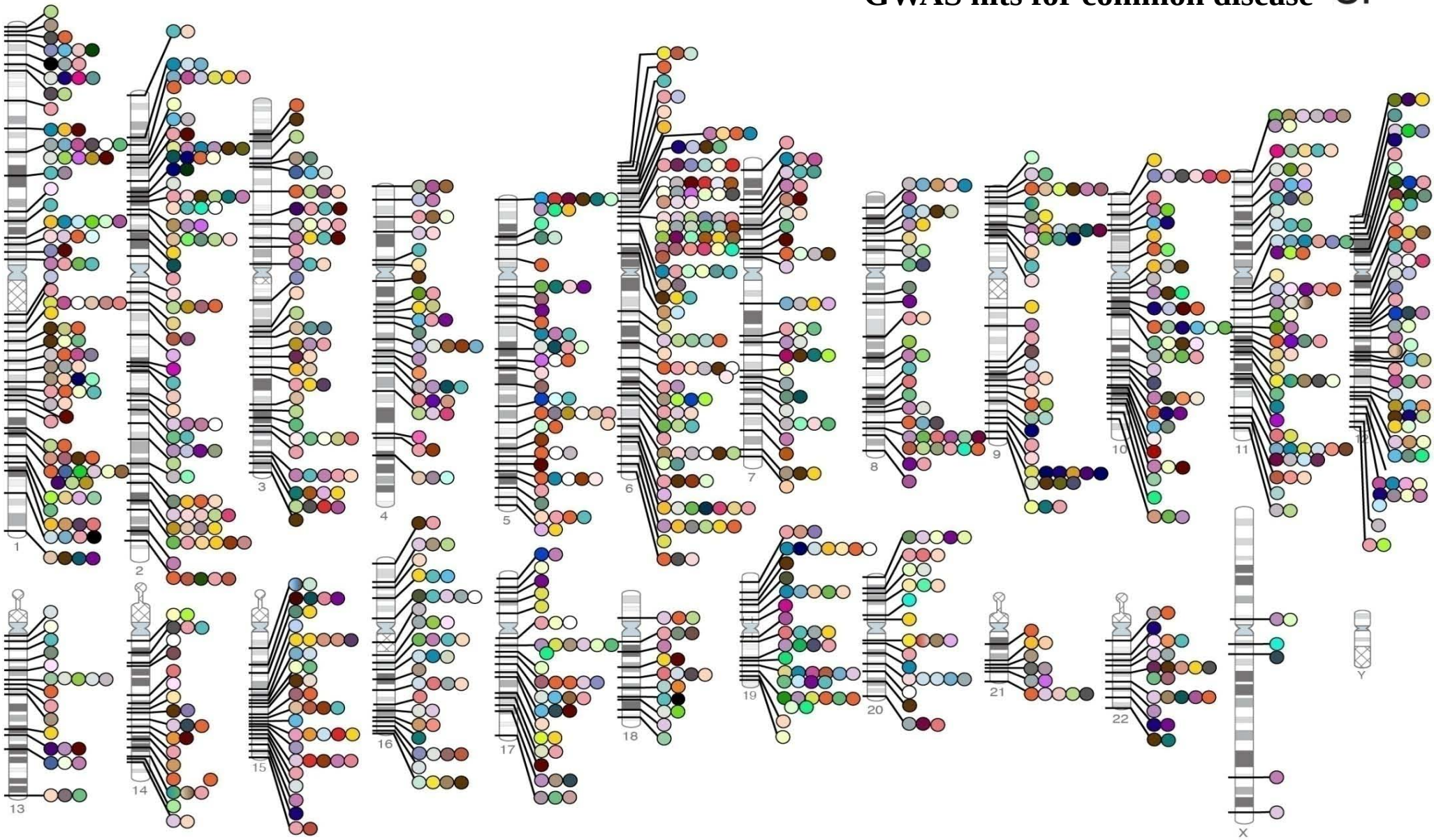
Pt 56 – Vanderbilt

Target validation

With the availability of sequencing data, genome wide association studies (GWAS) as well as metabolomic, epigenomic, metagenomic studies, a large number of possible targets have already or will soon be identified but will these be of therapeutic benefit in patients ???

We need to characterise the biology of novel genes/proteins in a more systemic way to understand the role of a given target in the context of the physiology and of the pathology

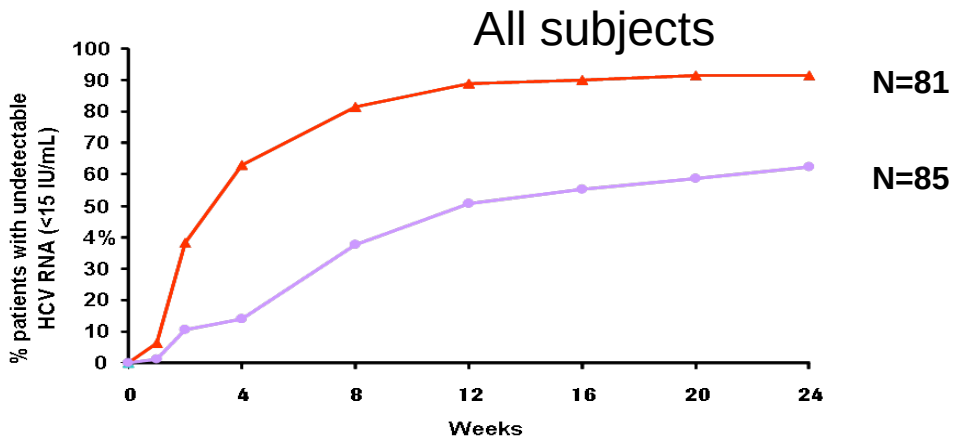
GWAS hits for common disease er

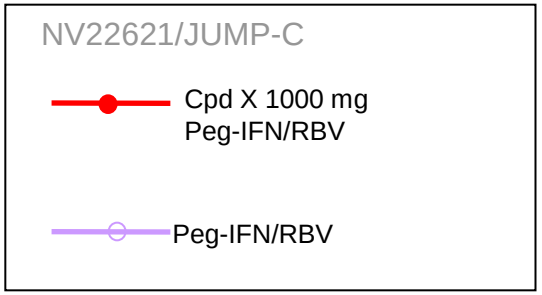


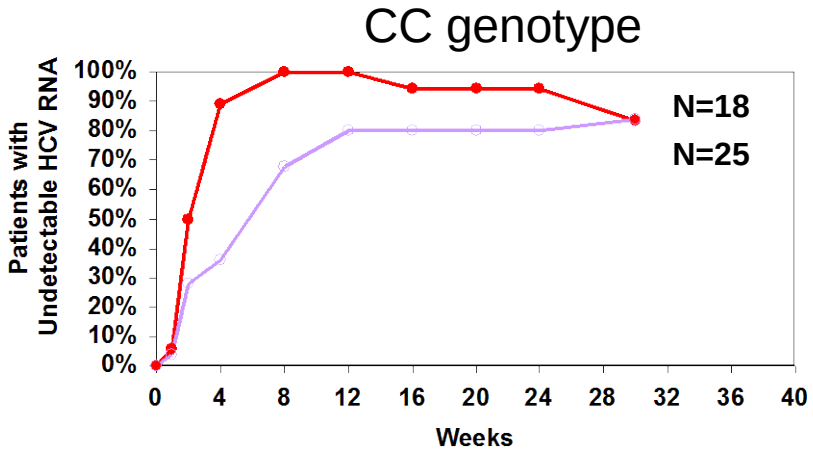
Example From Genetics: HCV viral response over time

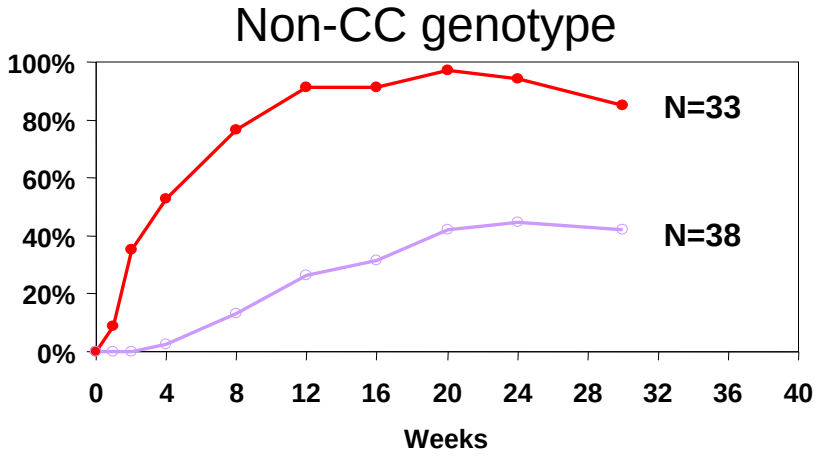
Differential response by IL28B genotype

IL28B is a genetic polymorphism identified by genome-wide association studies (GWAS) to be associated with treatment response in HCV patients









Safety of compounds

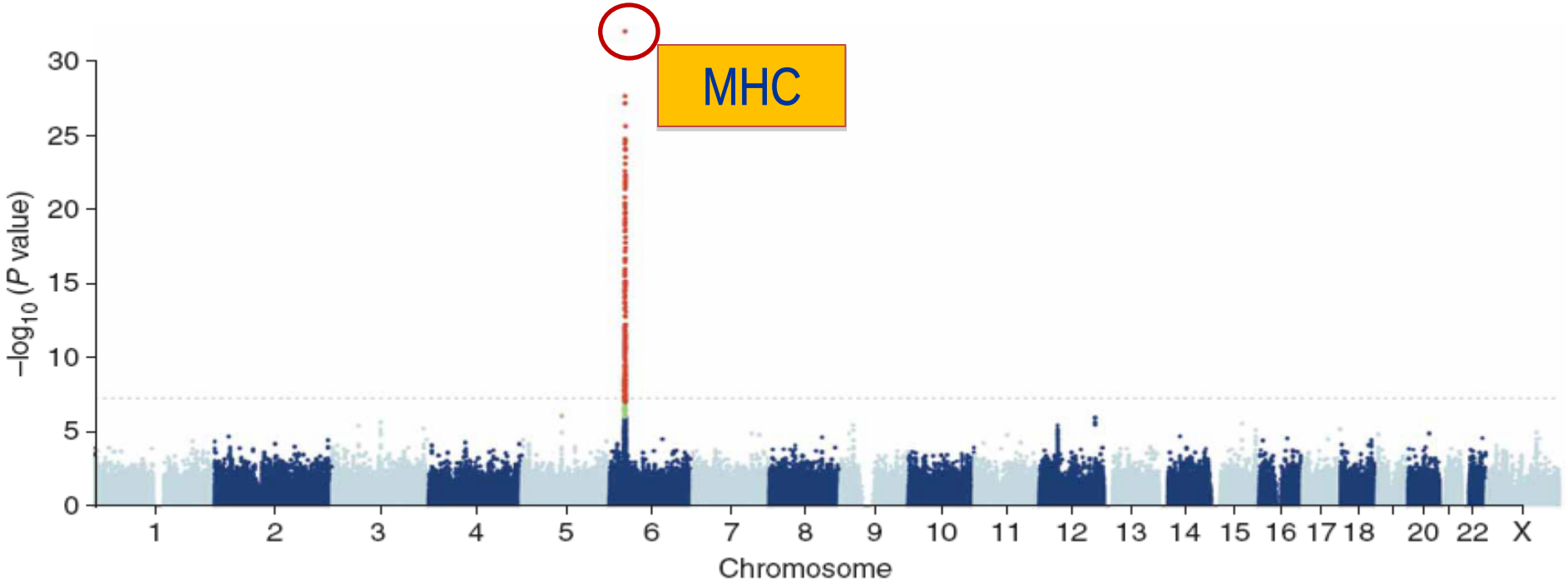
- New innovative tools, methods for the prediction of safety of clinical candidate **and** for clinical assessment of effects of new drugs
- Clinical guidelines for assessment of effects of new drugs
- Increasing networking and knowledge **sharing** between companies
- Better methods for understanding differences between patients in clinical trials and patients in “real” life
- Alternative strategies to studies in animals should be identified, validated and used.
- Use of system models and strategies combining technology, biology, computational methods with information retrieved from historical compounds tested in preclinical models or in patients The use of strategies such as ‘induced pluripotent stem cells’, computational prediction of adverse effects, virtual screenings.

International Serious Adverse Event Consortium (iAES)

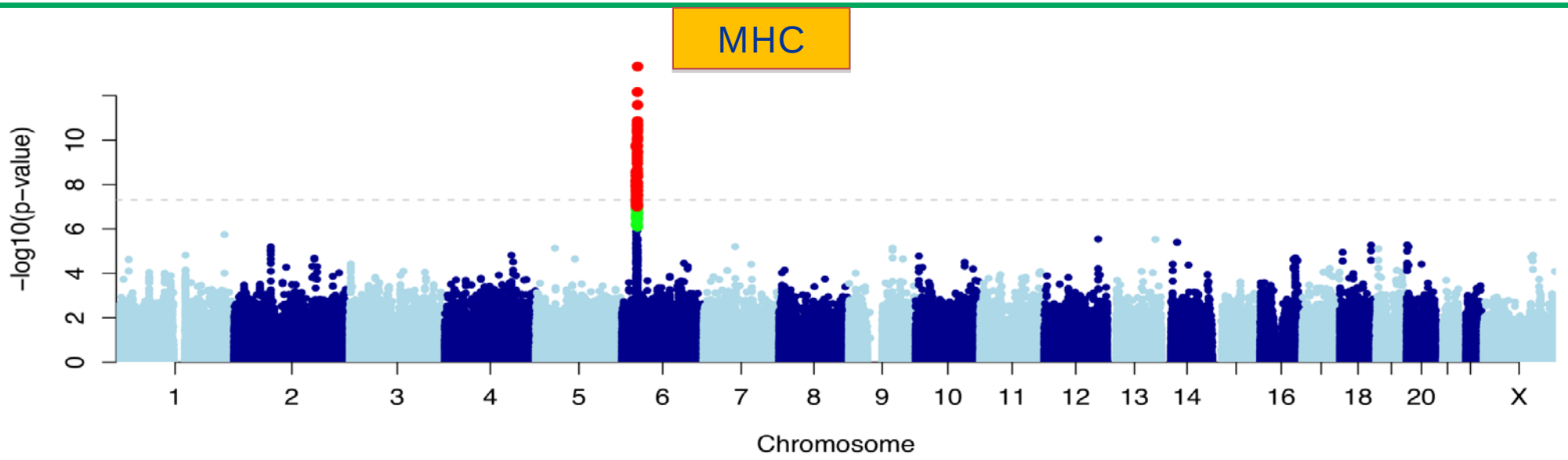
nature genetics

*HLA-B*5701* genotype is a major determinant of drug-induced liver injury due to flucloxacillin

Ann K Daly[1], Peter T Donaldson[1], Pallav Bhatnagar[1], Yufeng Shen[2], Itsik Pe'er[2], Aris Floratos[2], Mark J Daly[3], David B Goldstein[4], Sally John[5], Matthew R Nelson[6], Julia Graham[1], B Kevin Park[7], John F Dillon[8], William Bernal[9], Heather J Cordell[1], Munir Pirmohamed[7], Guruprasad P Aithal[10,11] & Christopher P Day[1,11], for the DILIGEN study[12] and International SAE Consortium[12]



Augmentin GWAS results
201 cases, 532 POPRES controls



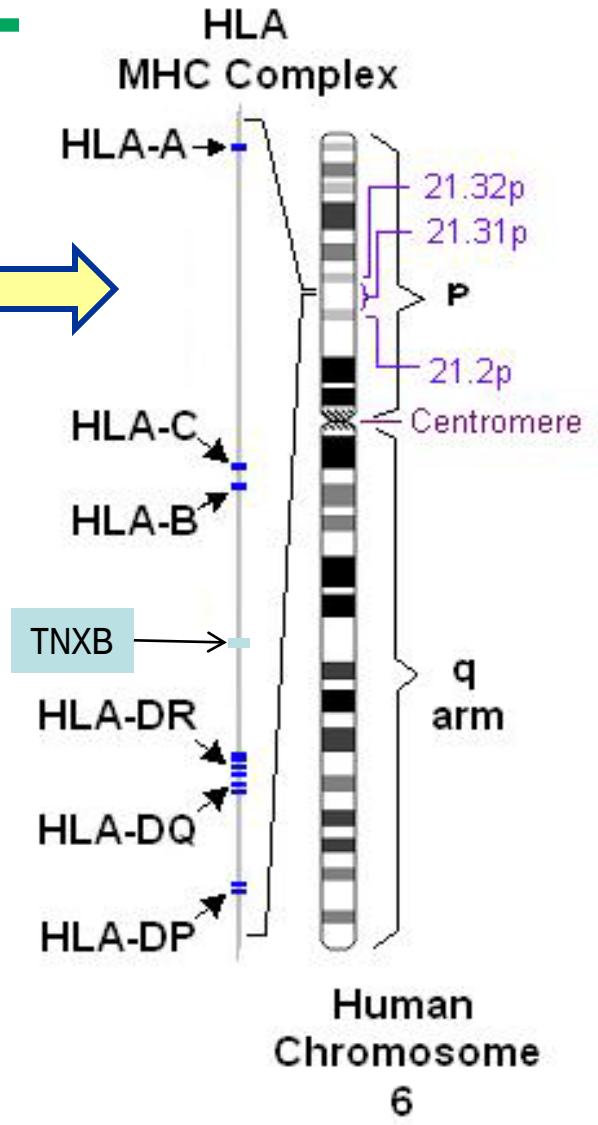
- **DR2** association is confirmed, however…
  - ***DQB1*0602*** has a larger effect in Spanish than nw-EU
  - ***DQB1*0402*** is strongly associated only in nw-Eu and perhaps stronger in hepatocellular cases
- **rs2523822** (class I) is a novel association, significant in both sub-populations

Importance of MHC variants in SAEs

***Emerging* Sample Set:**

- **HLA-DRB1*1501** → DILI with Augmentin & Lumiracoxib
- **HLA-DRB1*0701** → DILI with GSK Oncology drug & Ximelagatran
- **HLA-B*5701** → DILI & AHSS Flucloxacillin & Abacavir

Genetic Risk Alleles for SAEs/ADRs

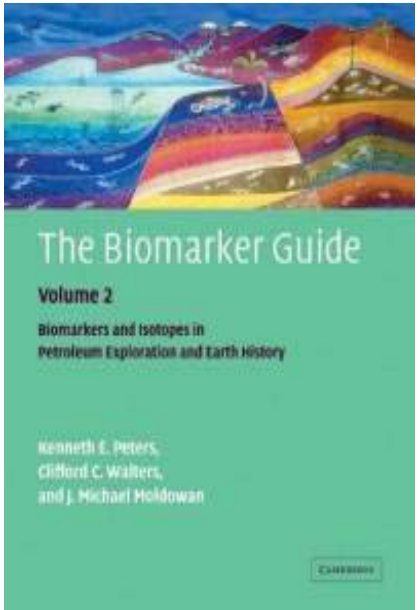


Common Risk Alleles are Beginning to Emerge

Drug	Reaction Details	Prev	Risk Allele	Freq.	Rel Risk	PPV	1 - NPV
Ximelagatran	DILI	0.08	*HLA-DRB1*0701*	0.08	4	0.22	0.055
Augmentin	DILI	<0.001	*HLA-DRB1*1501 A*0201/B*1801*	0.15	4	5.7e-4	5.7e-5
Isoniazid	DILI	0.15	*CYP2E1*1 & 2*	0.13	7	0.59	0.084
Lapatinib		0.09	*HLA-DQA1*0201 (HLA-DRB1*0701)*	0.08	9	0.17	0.03
Lumiracoxib	DILI	0.013	*HLA-DRB1*1501*	0.15	13	0.039	0.0030
Ticlopidine		<0.001	*HLA-A*3303*	0.07	36	1.2e-3	3.5e-5
Tranilast		0.12	*UGT1A1*28*	0.30	48	0.23	0.0048
Flucloxacillin	DILI	<0.001	*HLA-B*5701*	0.04	81	0.0022	2.8e-5
Irinotecan	Neutropenia	0.20	*UGT1A1*28*	0.30	28	0.36	0.013
Mercaptopurine	Neutropenia	0.12	*TPMT*2/3A/3B/3C*	0.05	9.0	0.77	0.086
Abacavir	Hypersensitivity	0.04	*HLA-B*5701*	0.04	>1000	0.50	5.0e-4
Carbamazepine	SJS/TEN -Taiwan	0.003	*HLA-B*1502*	0.04	>1000	0.038	3.8e-5

Methodologies to evaluate treatment effects

- To develop new and innovative medicines, novel methodologies for evaluating treatment effects are essential.
- Existing methodologies such as imaging and other biomarkers are not well enough developed or validated to reduce risk and ensure better and faster development of new treatments ……..especially where disease modification and prevention is the target.



What Else ??????????????

USA and EU (+elsewhere) collaboration

Sharing Data

- Tox (Preclin and Clinical)
- Placebo (Clinical)
- Patient Stratification by diseases
- JV's for Developing Drugs /Comparators
- Combination Drugs
- "Repurposing" Drugs

New Science

- Next generation sequencing.Tissue typing

Regulatory "Efficiency"

- "Flagging" issues … e.g. class effects
- Standardization of "Ethics/IRBs"
- "Comparative **Therapeutic** Efficacy"
- Improved co-ordination of HTA demands (EU ..and USA)
- "Conditional" / "Staggered" Approval

.....we have so much to do
……..let's see how much we can do together !

Back Up Slides

Ownership: basic principles

- **Background** remains the exclusive property of each participant
- **Foreground** (project results) are owned by the generator(s)
- Possibility to **freely license, assign or otherwise dispose** of its ownership rights provided access rights to other partners are respected
- Possible **transfer** of ownership

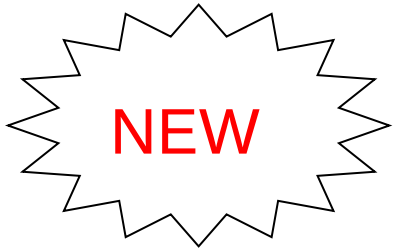
Funding rules

- **Direct costs** (personnel, consumables, equipment,…)
- **Indirect costs** = **overheads**

  Flat rate of 20% of direct eligible costs

  or

  actual indirect costs



- **Funding rates**
  - Research activities
    - 75% of total eligible costs
  - Other activities, including management and training
    - 100% of total eligible costs