The many ways of getting lost in Translational Medicine

Jornadas de Química terapéutica, Noviembre 2008, Carmona

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- Definition
- Considerations
- Scope
- Goals of TM in Drug discovery

Some examples of TM:

- 3 succesful ones (Hope so !)
- 1 lost in translation

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What is Translational Medicine ?

TM is the branch of biomedical research that aims to translate basic research findings to medical need (*bench to bedside*).

Is a **multidisciplinary** task that involves:

- Basic scientific research to discover the origins and mechanisms of disease
- Identification of and insight into specific biological events, biomarkers, or pathways of disease
- Use of such insights to systematically discover and develop new diagnostics and therapeutic methods and products
- Adoption of such new diagnostic and therapeutic approaches into the routine standard of care.

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A paradigm shift in the biomedical research enterprise

Patient-centered medicine

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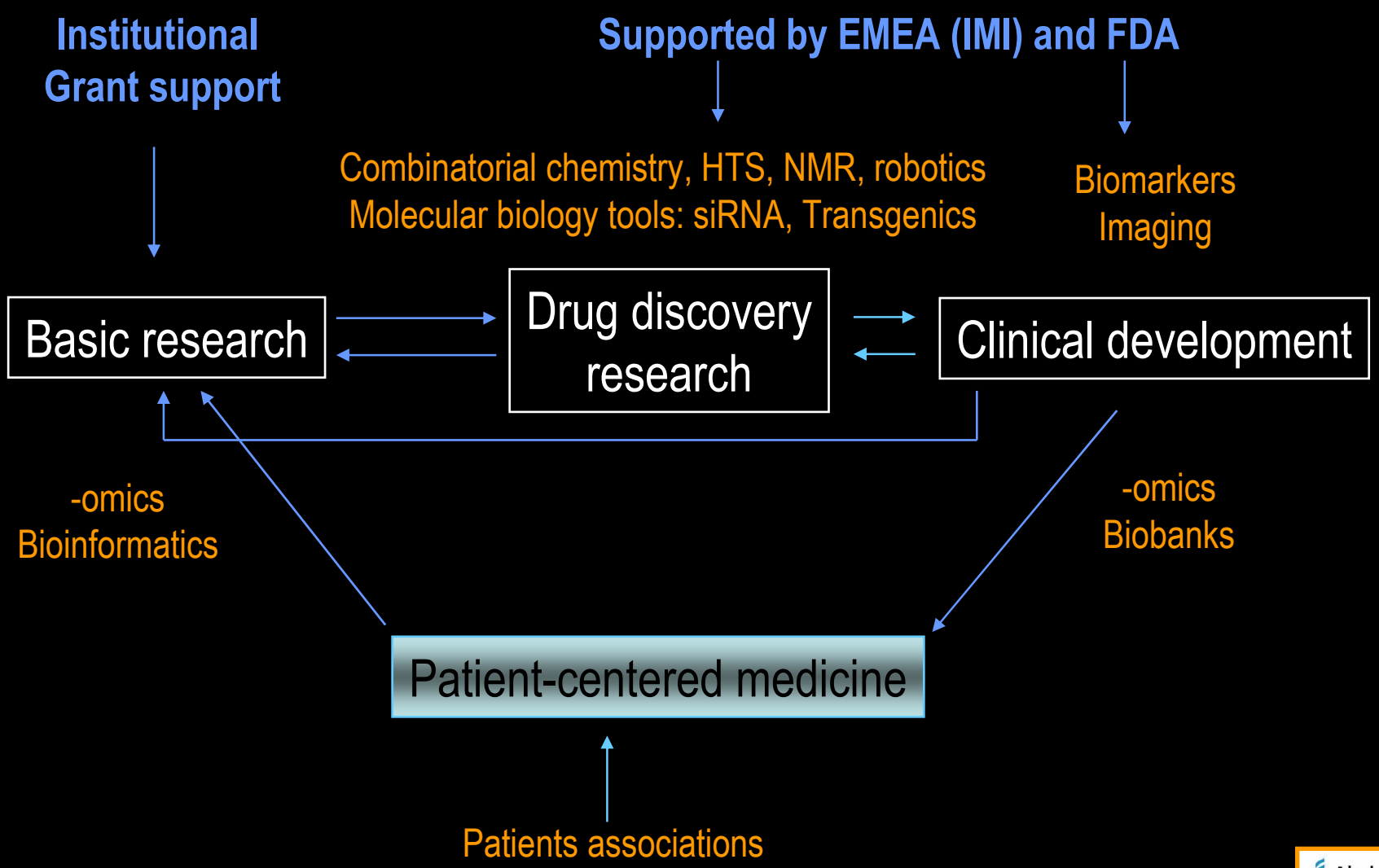
A paradigm shift in the biomedical research enterprise



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Translational Medicine in Drug discovery

Goals

- improve confidence in human drug targets
- increase confidence in drug candidates
- understand the therapeutic index in humans
- enhance cost-effective decision making in exploratory development
- increase Phase II success and reduce phase 3 attrition

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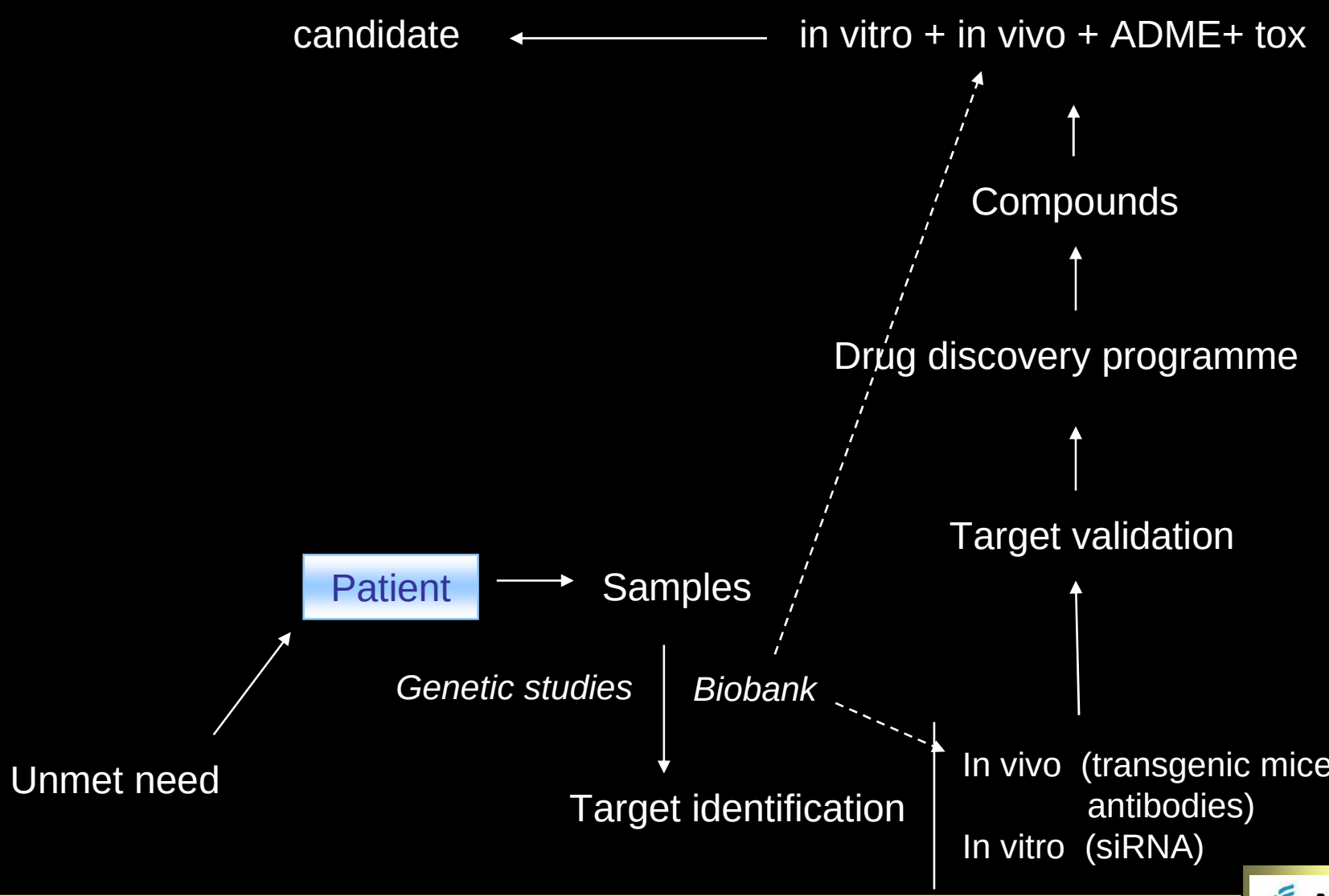
Translational Medicine scope



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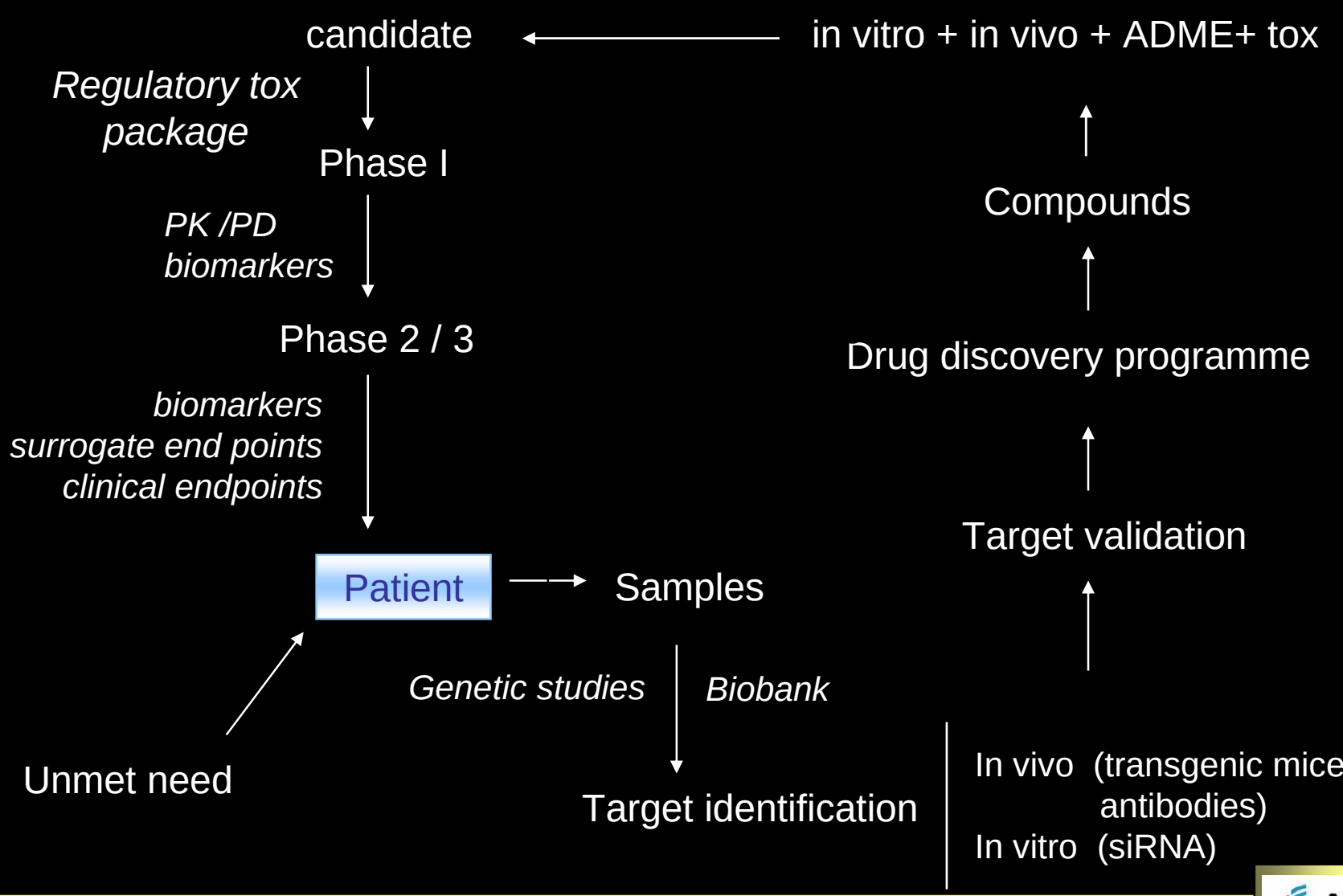
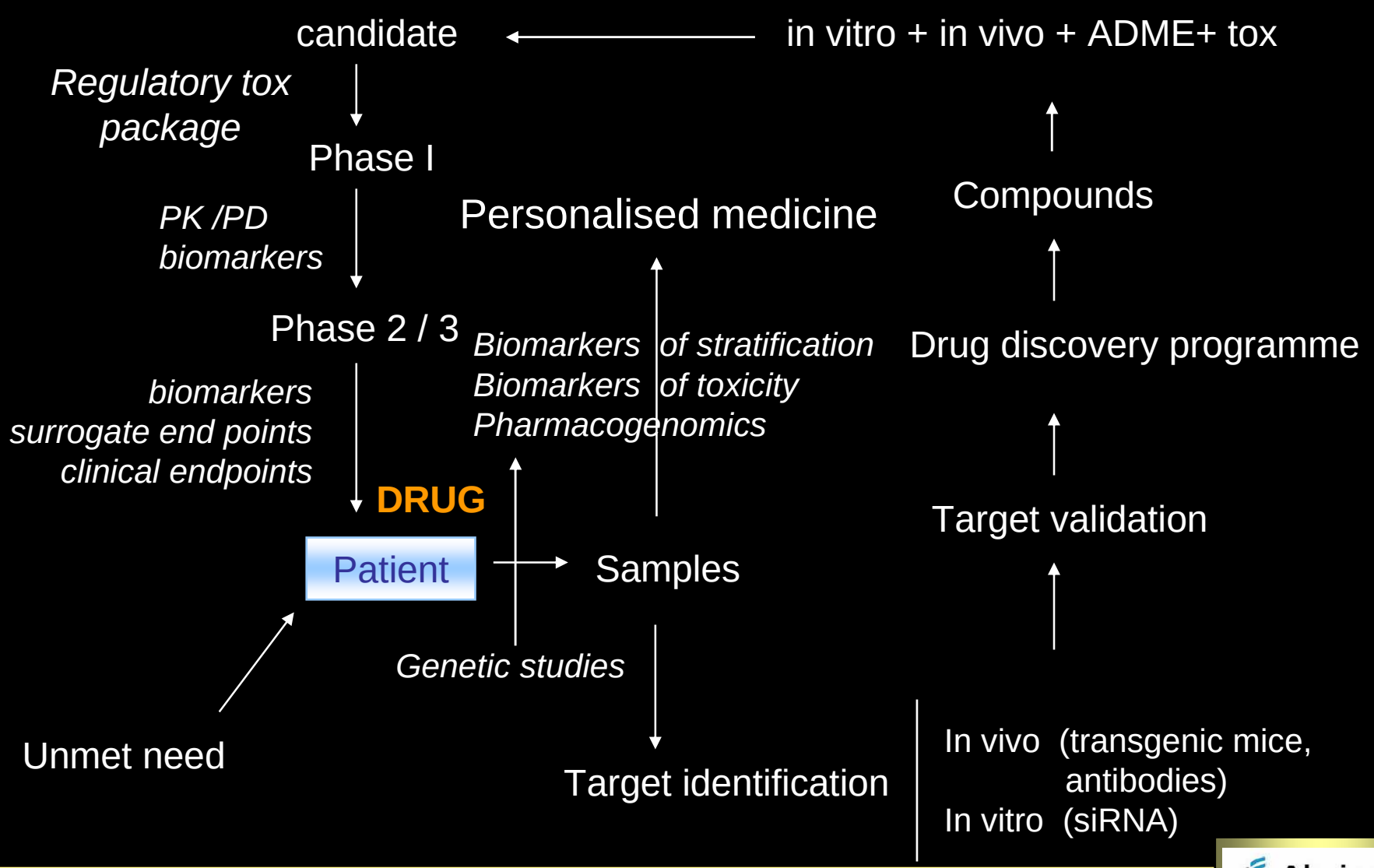
Translational Medicine scope



Translational Medicine scope



Translational Medicine in Drug discovery

Higher success in Biotechs than big pharmas.

Higher success in cancer than in other diseases:

Reasons ?

1.- Higher investment in basic research

2.- Sample availability (genetic studies,…)

3.- Less restrictions in the evaluation of new drugs (higher tolerance to toxicity, phase I in patients)

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Translational Medicine in Drug discovery

In autoimmune diseases (multiple sclerosis, lupus, rheumatoid arthritis), the only big success in the last decade has been the arrival of biological therapies (monoclonal antibodies, fusion proteins).

In terms of NCEs, the only approved compound has been:

- Arava® (antiproliferative) for RA. In the market since 1998.

The next one will probably be 11-12 years later !!

- Fingolimod : the first oral drug for MS (phase 3). To be launched in 2009- 2010.

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Translational Medicine

Some examples

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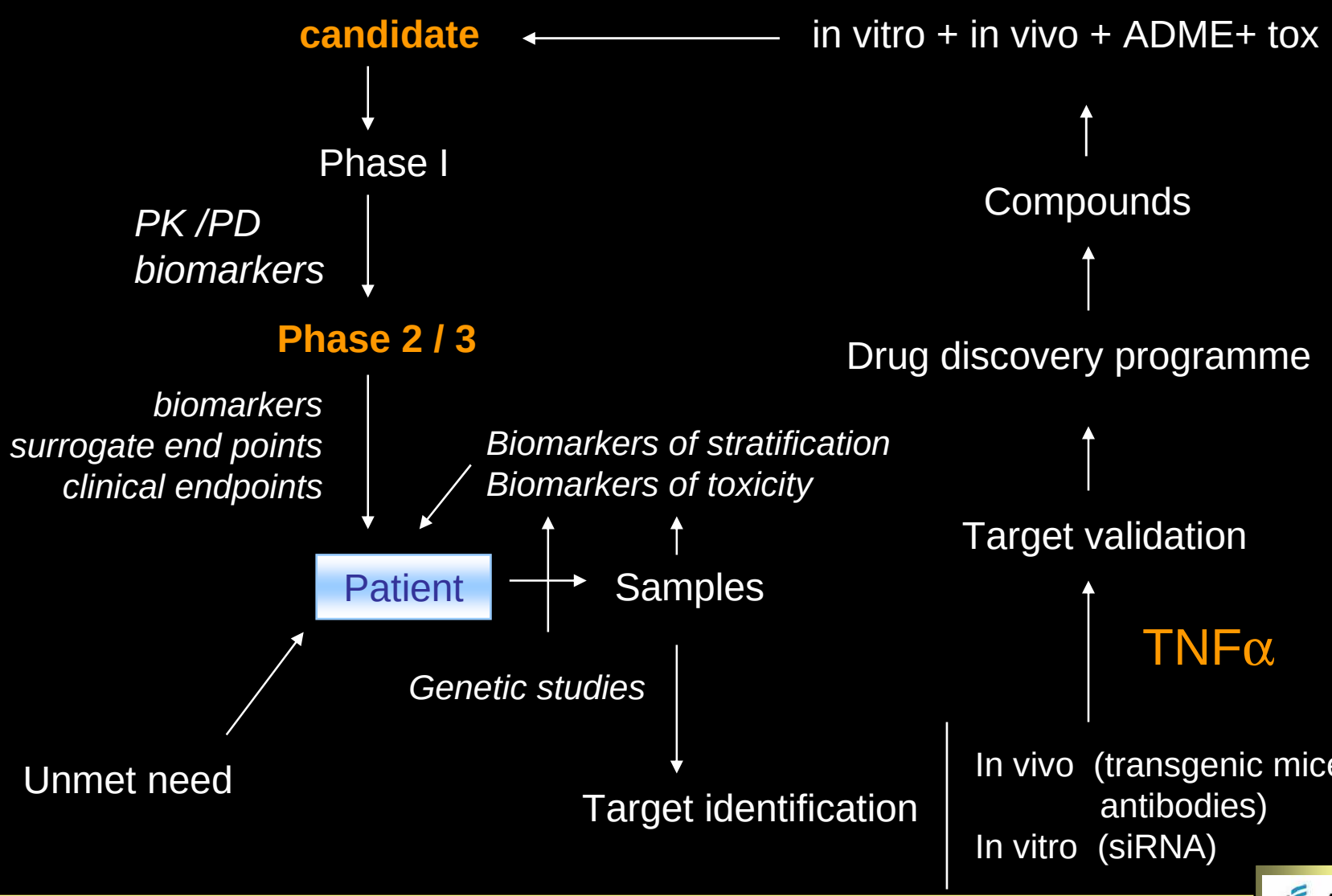
Example 1: the value of a model



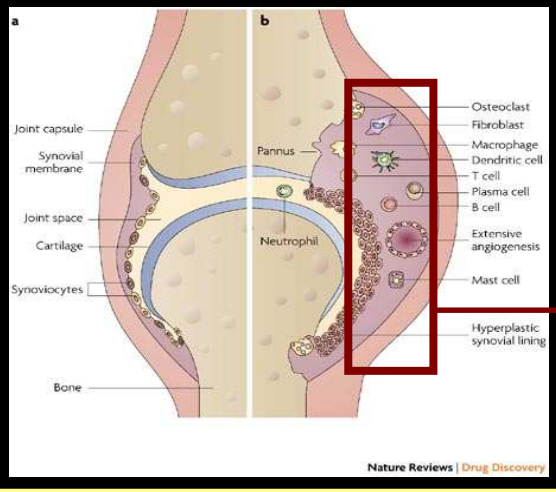
TNFα: the value of a model

FROM BENCH (1):

M. Feldmann: spontaneous release of cytokines from samples of synovium from RA patients. The samples reflected the complex interactions of all the cells present *in vivo*.

Antibodies against several cytokines were used to determine how the blockade of one of them impacted on the others..

An anti-TNF antibody caused a decrease in the production of multiple proinflammatory cytokines, such as IL-1, GM-CSF, IL-6 and IL-8.



TNF drives a cytokine cascade in RA

Cell culture → IL-1, TNFα, IL-6, IL-8, GM-CSF, VEGF

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TNFα: the value of a model

FROM BENCH (2)…

In mice with collagen-induced arthritis, treatment with an anti-TN antibody ameliorated inflammation and protect cartilage and bone.

George Kollias showed that transgenic mice overexpressing human TNF develop a destructive polyarthritis resembling human rheumatoid arthritis.

TNFα is a potential therapeutic target for RA

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TNFα

TO BEDSIDE

Dr. Jim Woody, chief scientist at Centocor , supported the suggestion of the scientists of performing a clinical trial using its chimeric TNF -specific monoclonal antibody (infliximab).

20 patients with therapy-resistant rheumatoid arthritis were treated with 20 mg/kg of the antibody. The dose was chosen by extrapolation from the experiments in mouse collagen-induced arthritis.

The trial was a sucess.

There are currently 4 different anti-TNF biologicals in the market for the treatment of RA, Crohn´s disease, and psoriasis.

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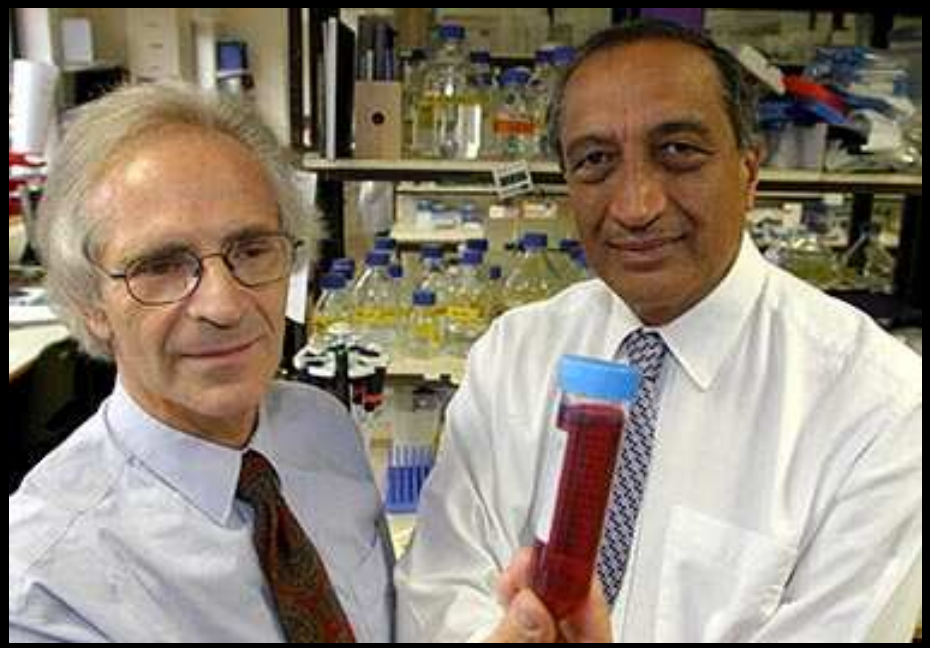
and the Lasker goes to…

Marc Feldmann Ravinder Maini



Crafoord prize 2000
Lasker award 2003

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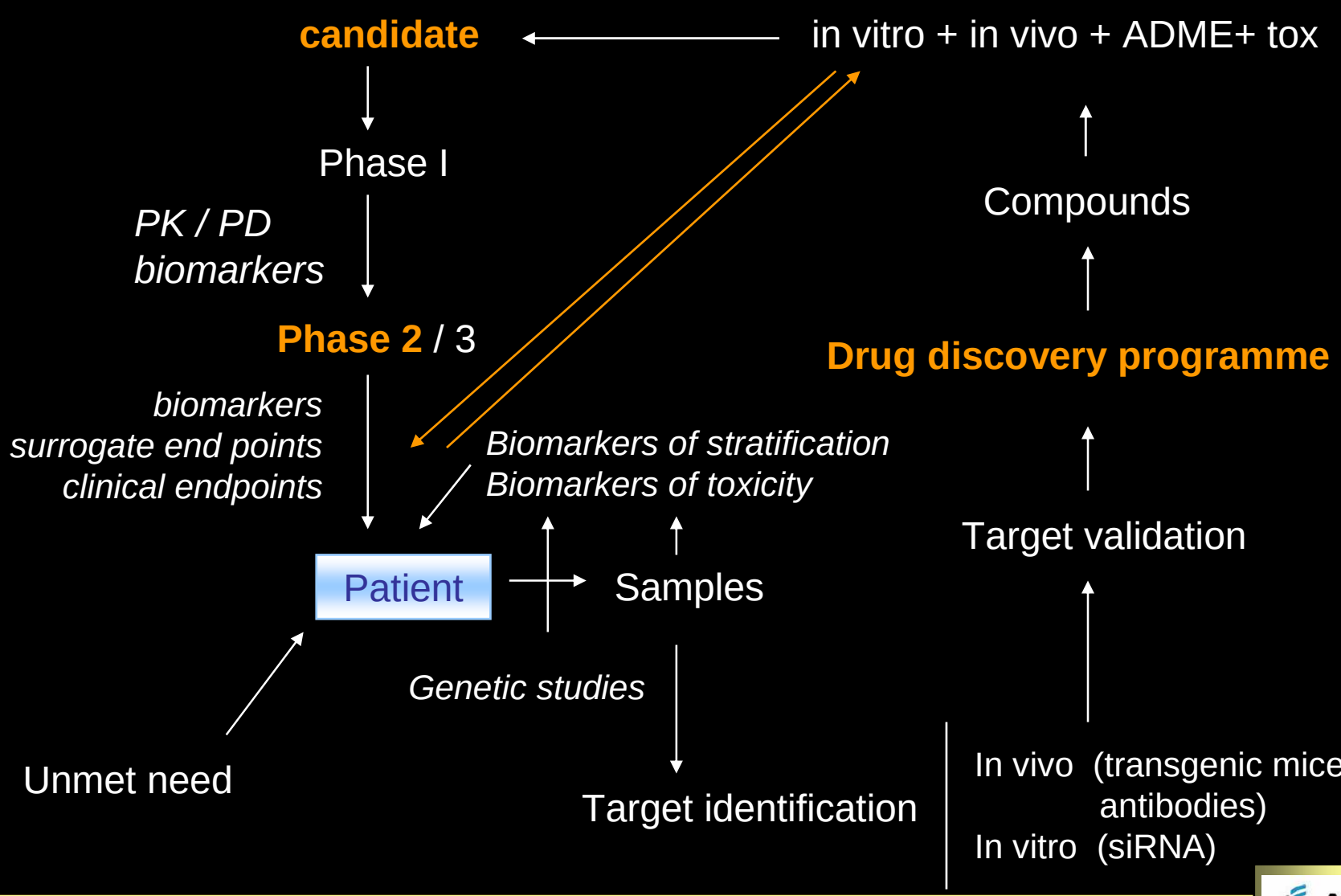
Example 2: bedside to bench to bedside



From bedside to bench and viceversa

Clinically validated targets : by definition, there is at least one reference compound with clinical data.

We want a best-in-class: the existing compound can be improved (efficacy, ADME, toxicity)

What are we going to improve ?

Careful analysis of human data available to finds possible points for improvement.

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From bedside to bench and viceversa

Diana terapéutica: PARADOR

PARADOR está validada clínicamente en artritis reumatoidea por el compuesto A.

El compuesto A es una prodroga inactiva que *in vivo* se convierte en B, inhibidor de la citada diana.

El compuesto tiene varios puntos susceptibles de mejora.

Hablaremos sólo de uno de ellos: hipertensión.

El compuesto provoca hipertensión en un 10% de los pacientes que toman el fármaco.

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From bedside to bench and viceversa

La hipertensión la podremos obviar con nuestros futuros compuestos si:

-La diana responsable no es PARADOR.

- El efecto se observa en animales (medible, aunque no sepamos el mecanismo).

- Identificamos el mecanismo (ensayo in vitro).

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From bedside to bench and viceversa

Sintetizamos la prodroga A y el fármaco activo B.

Los evaluamos en un modelo de hipertensión en rata. Dosis-respuesta.

Determinamos los niveles plasmáticos de A y B cuando administramos A, y de B cuando administramos B.

¿Qué pasó ?
Que vimos hipertensión sólo cuando administrábamos A

A: 10A + 70B Hipertensión
B: 70B, 150B no hipertensión

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From bedside to bench and viceversa

A: no inhibe PARADOR

Induce hipertensión a dosis que dá niveles elevados de B

B: inhibe PARADOR

No induce hipertensión

El responsable es la prodroga
La diana de la hipertensión NO es PARADOR

Refinamos el modelo de hipertensión para que nos oriente sobre el posible mecanismo: catecolaminas ?
Rata reserpinizada: perdemos el efecto.

¿¿Dianas posibles ??

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From bedside to bench and viceversa

Dianas posibles: 5
Screening de A y B en las dianas
Sólo A fue activa en una de las dianas
IC50: 1 μM

Programa de investigación: Inhibidores de PARADOR
Screening:
in vitro, tox, eficacia
Hipertensión en rata in vivo
No efecto sobre la diana in vitro

CANDIDATO en FASE 1

Continuará…

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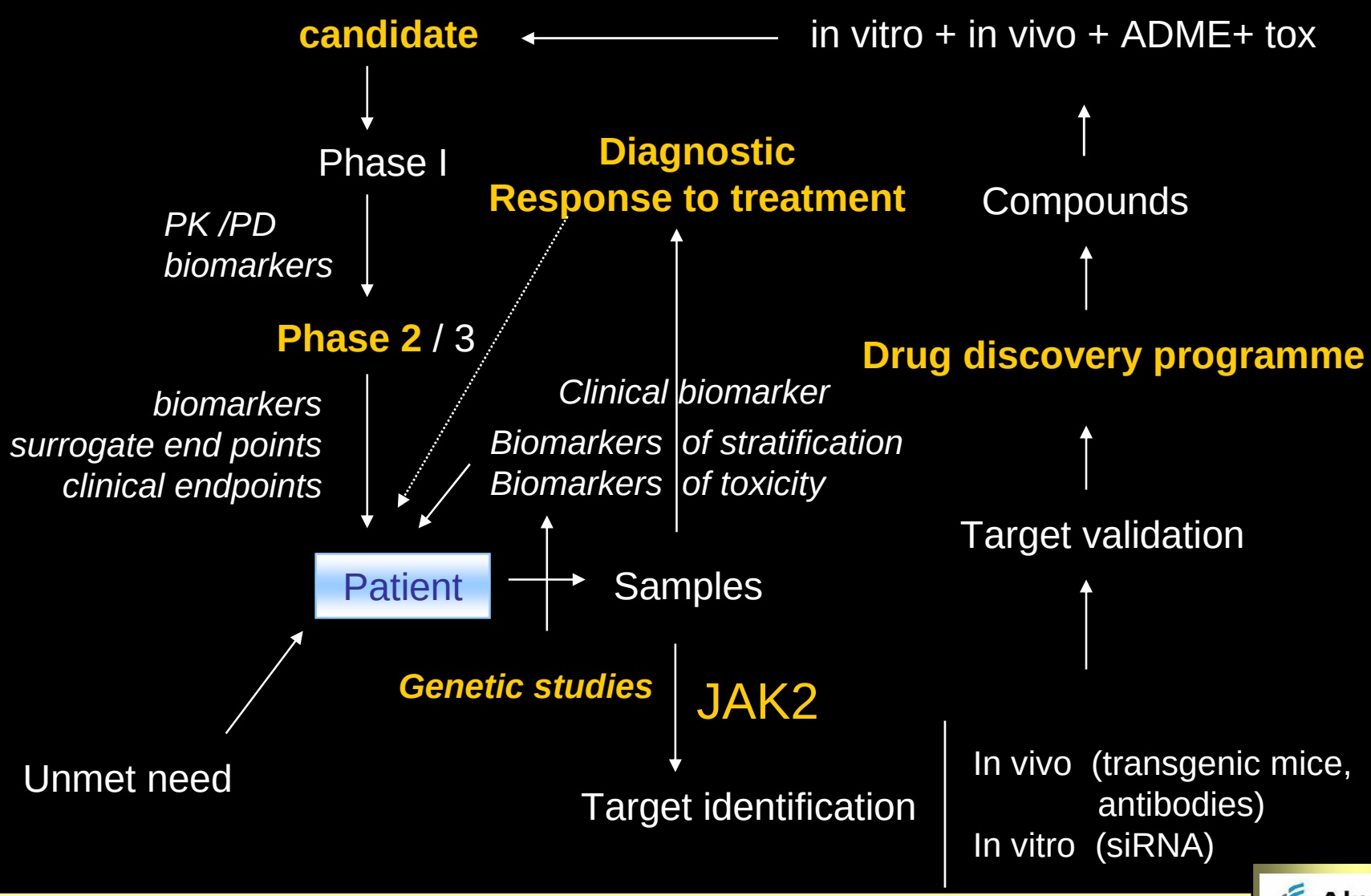
Example 3: from gene to treatment



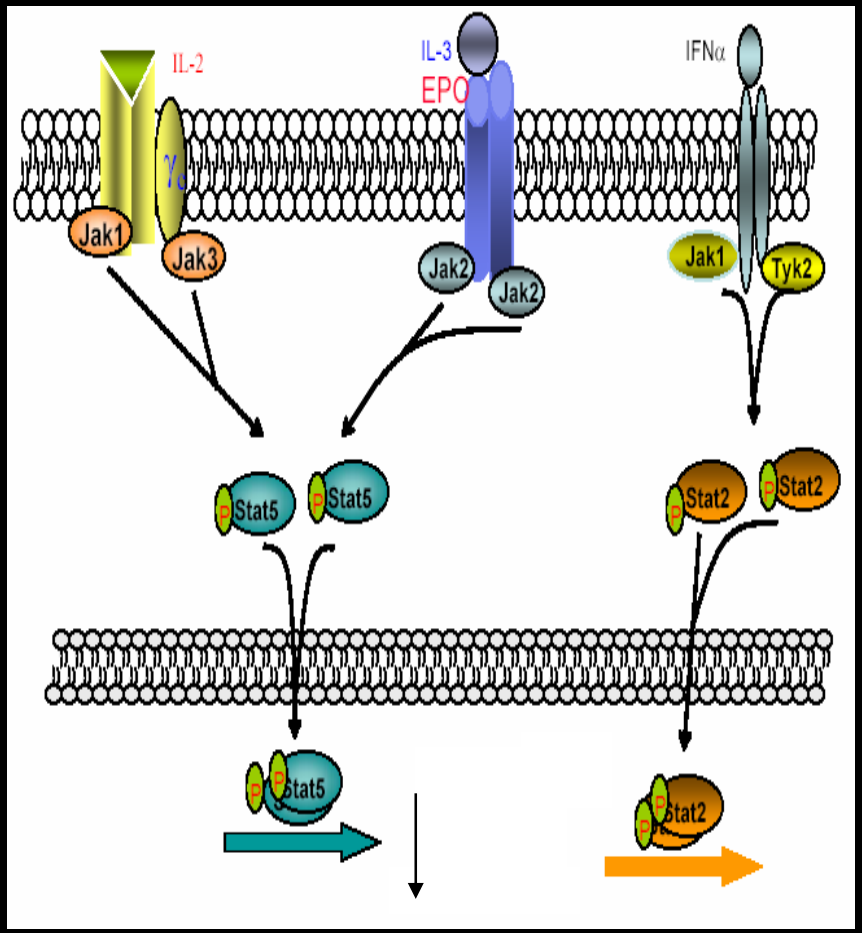
JAK2: not Just Another Kinase

JAK2 is a member of the JAK kinase family (JAK1, JAK2, JAK3 and Tyk2).

JAK2 is a cytoplasmic tyrosine kinase that mediates cell signaling downstream of several cytokine receptors.

The effectors of JAKs are transcription factors known as signal transducers and activators of transcription (Stat) proteins.

Cytokines responsible for hematopoiesis (EPO, thrombopoietin), signals via JAK2



Transcription of genes
involved in proliferation / survival

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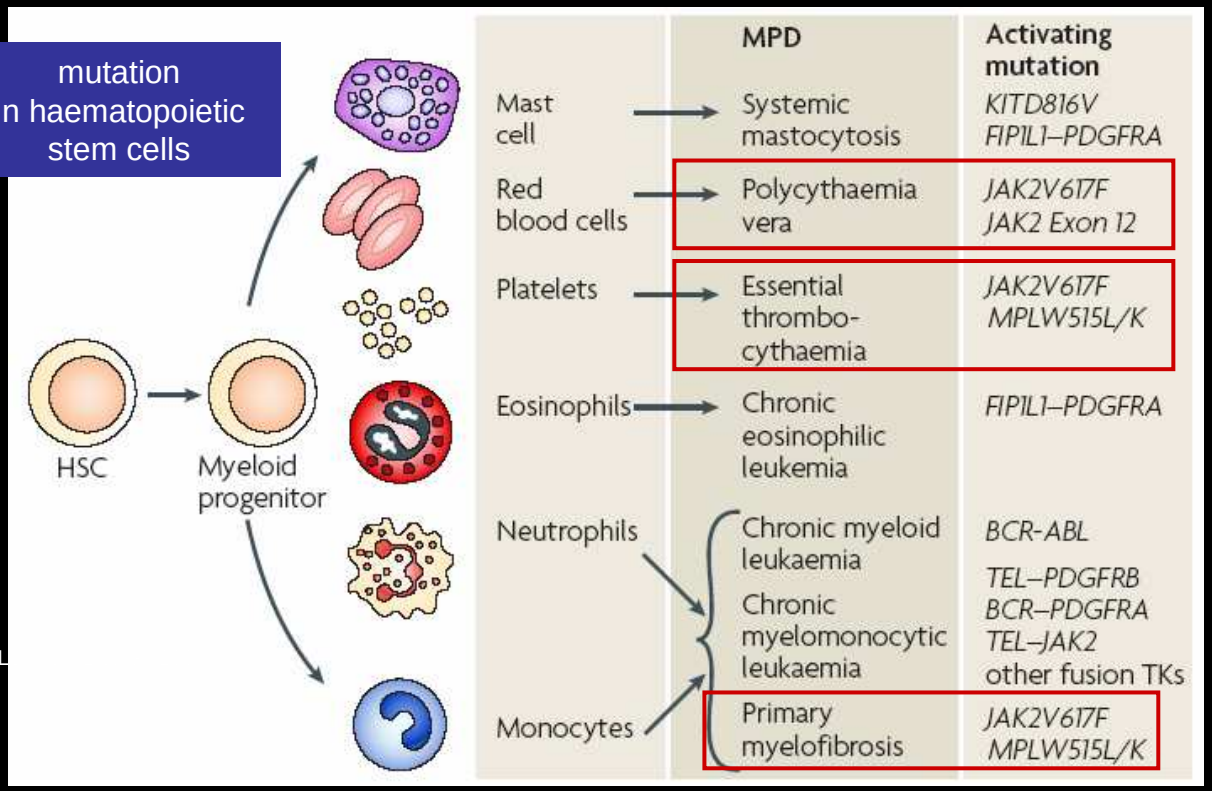
JAK2 and myeloproliferative diseases



JAK2 - V617F

PV: 81-99%
ET: 41-72%
PMF : 39-57%

Mutation in JH2 domain:
JAK2 constitutively phosphorylated
Gain of function phenotype.
The kinase is active in the absence of a cytokine.

Levine RL. 2007.Nature Rev Cancer. 7:673
Mata R. 2007. Cardiovasc Haematol Agent Med Chem. 5:198
Pardani A et al. 2007. Leukemia. 21:1658

MPDs are the primary indication for an anti-JAK2 therapy

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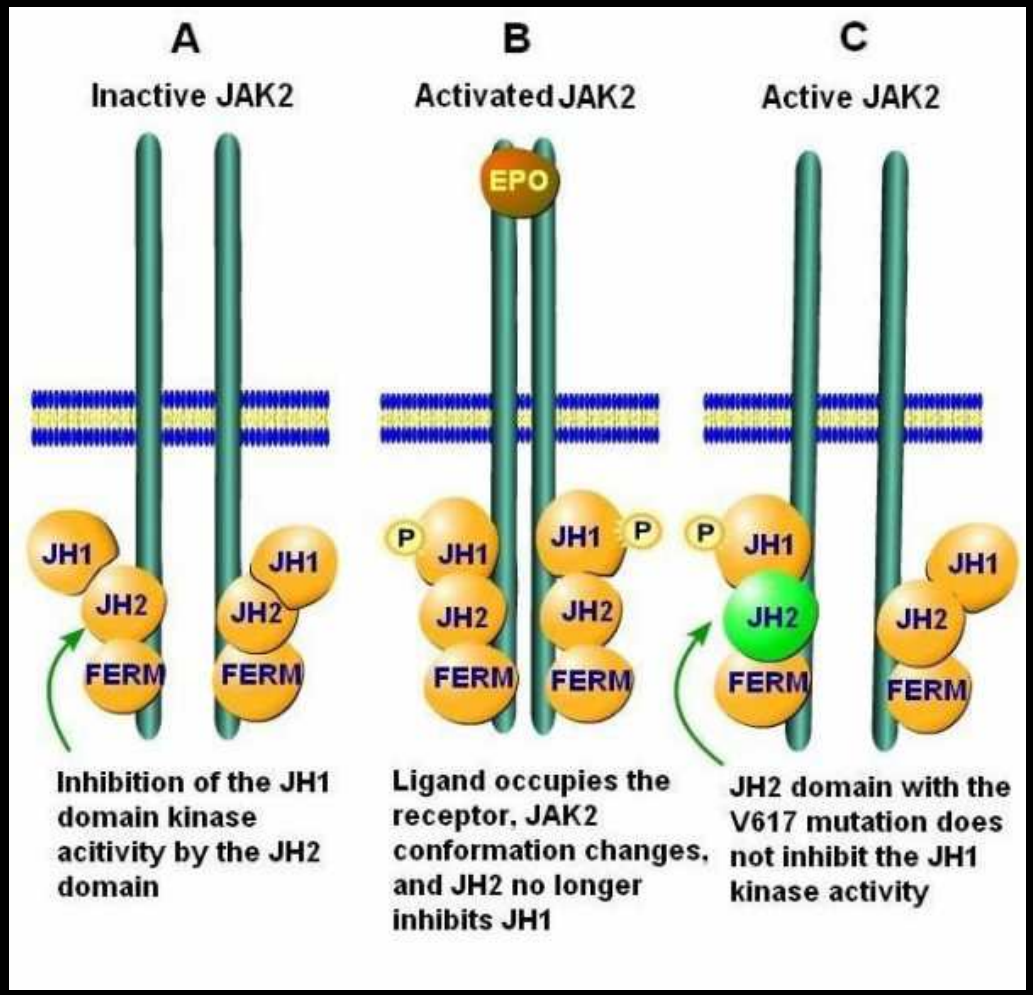
JAK2 gain-of-function in MPD



Bennett and Stroncek *Journal of Translational Medicine* 2006 **4**:41

A: In the absence of ligand, the kinase activity of the JH1 domain is inhibited by the JH2 domain and JAK2 is inactive.

B: When a cytokine like EPO binds to its receptor, the two strands of the receptor come closer together, JAK2 changes conformation, the JH1 kinase activity in no longer inhibited by JH2.

C: The *JAK2* V617F mutation prevents JH2 from inhibiting JH1 and JAK2 is active even when there is no ligand bound.

JAK2 and myeloproliferative diseases: POC

A phase I/II study of INCB018424, an oral, selective JAK inhibitor, in patients with primary myelofibrosis (PMF) and post polycythemia vera/essential thrombocythemia myelofibrosis (Post-PV/ET MF)

Srdan Verstovsek, MD, PhD,[1] Hagop Kantarjian, MD,[1] Animesh Pardanani, MD, PhD,[2] Deborah Thomas, MD,[1] Jorge Cortes, MD,[1] Ruben Mesa, MD,[2] William Hogan, MD,[2] John Redman, MD,[3] Richard Levy MD,[3] Jordan Fridman, PhD,[3] Kris Vaddi, PhD,[3] and Ayalew Tefferi, MD[2]

- **Phase I dose escalation study (ASH 2007)**
  - Identified the starting dose of 25 mg BID as a highly effective dose in reducing splenomegaly and constitutional symptoms
  - Identified 25 mg BID as MTD, with reversible thrombocytopenia as the dose-limiting toxicity

INCB018424:

- Is well tolerated at clinically active doses
  - Reversible thrombocytopenia is the dose limiting toxicity
    - Manageable with dose reduction (or if necessary, dose interruption) in most patients
- Is associated with marked and durable improvement in spleen size
- Is associated with marked and durable improvement in constitutional symptoms
- Results in striking reduction in systemic cytokine levels

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Personalized medicine

Identification of clinical biomarkers: pharmacogenomics

- Predictors of Efficacy:

Her2/neu protein overexpression: predicts response to trastuzumab.
Bcr/Abl-positive patients with chronic myeloid leukemia to predcite response to Glivec

- Predictors of Toxicity:

UGT1A1 (UDP glucurinosil transferase) genetic variants predicts toxicity with irinotecan.
Dihydropyrimidine dehydrogenase deficiency: higher toxicity following 5-fluorouracil treatment.

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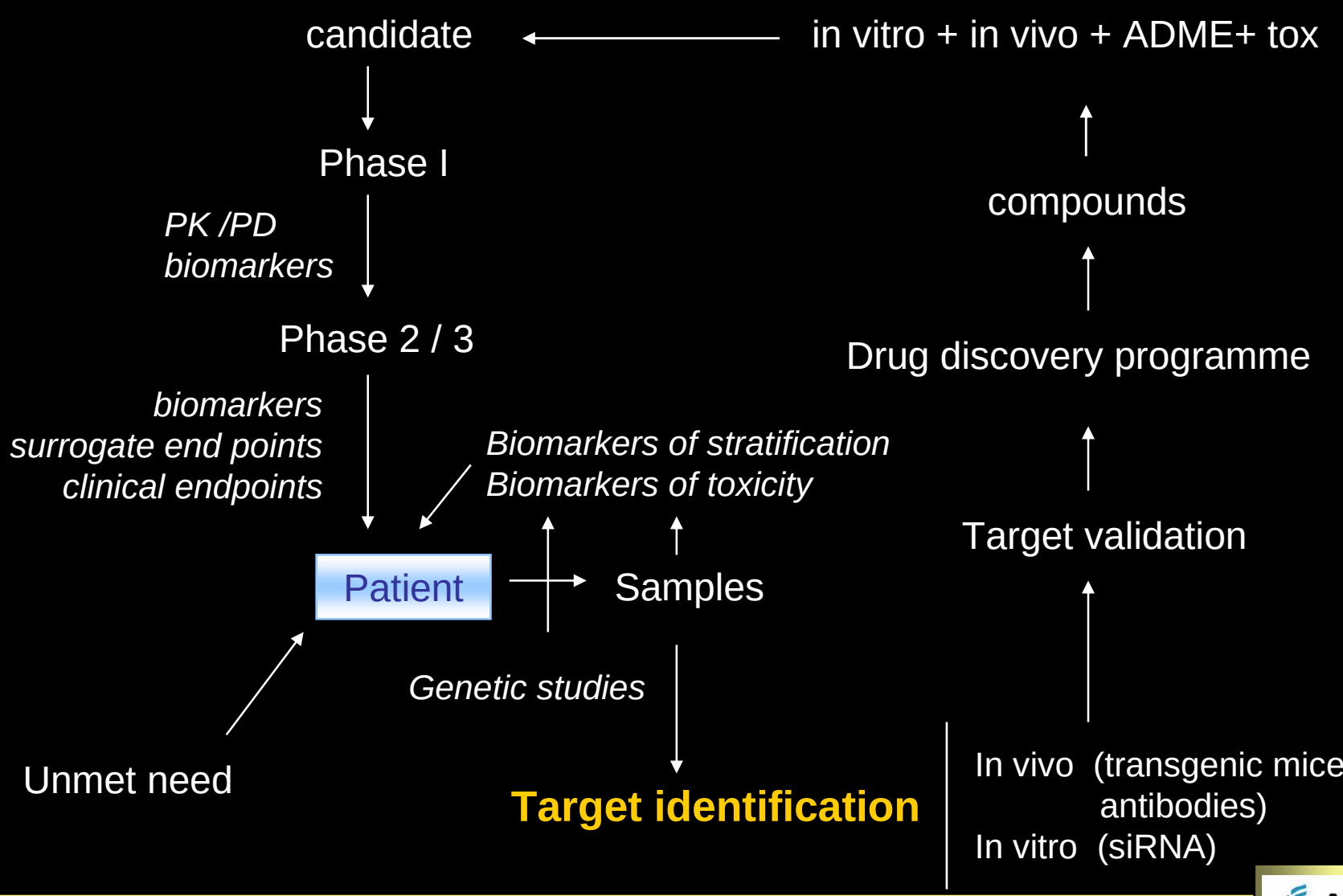
Lost in Translation



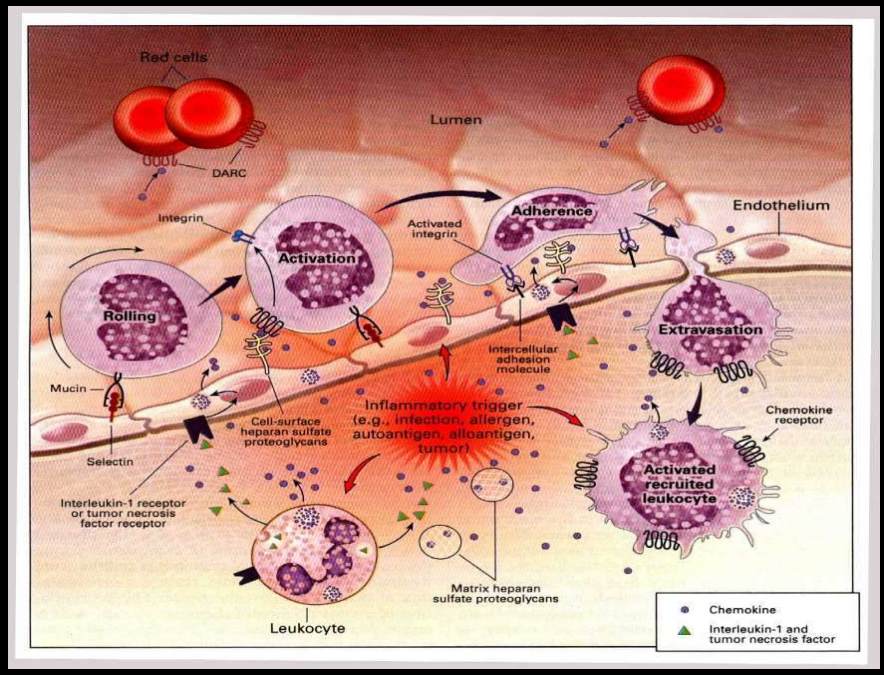
Chemokine receptors: target identification

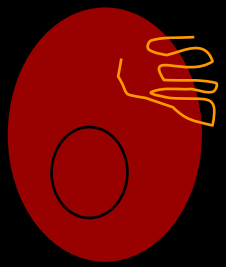
Chemokines are cytokines that play a role in cell migration.

Cell migration is important in infections processes, but…

Excessive cell migration to an inflammed tissue leads to chronic inflammation

Blockade of cell migration is a potential way to control chronic inflammatory processes





Ligand gradient

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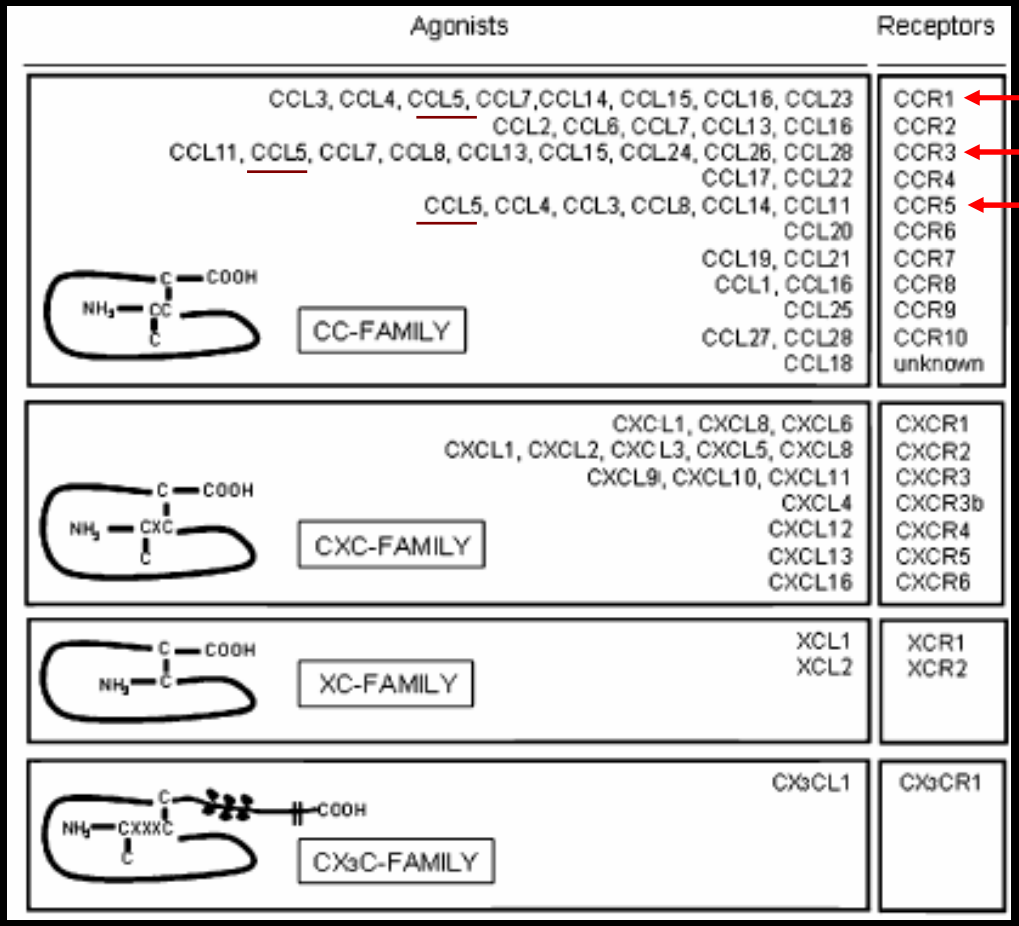
Single target or multitarget approach ?

A complex family, with redundancy and promiscutity in their relationships.



One cell may express several receptors

The site of infammation may express several cytokines

Will the blockade of a single target be efficaceous ?

N. Godessart . *ANYAS, 2005*

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Target validation

High levels of a chemokine found in blood and inflamed tissues

Cells infiltrating the lesion expressed the cognate chemokine receptor

In vivo studies in mice deficient in a particular chemokine receptor showed improvement in several models of inflammatory diseases.

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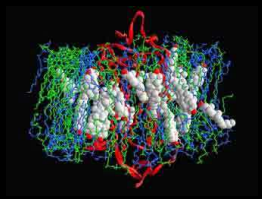
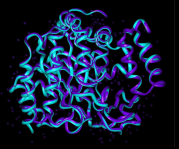
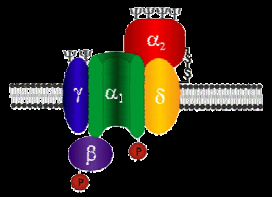
Chemokine receptors are GPCR !

GPCR  *45%*

Enzymes  *28%*

Ionic channels 

5%

Nuclear receptors  *2%*

(a)

Class A Rhodopsin-like	Class B Calcitonin and secretin-like	Class C Metabotropic glutamate and pheromone	Class D Fungal pheromone	Class E cAMP receptors (*Dictyostelium*)	Frizzled and smoothened-like

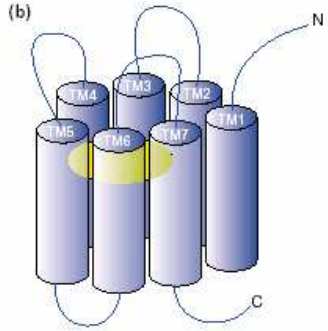
Rhodopsin

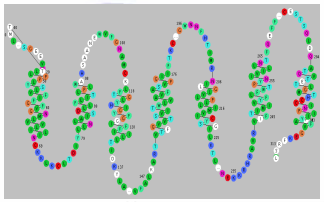
Amine
- 5-HT
- Muscarinic
- Purine
- Adenosine
- Dopamine
- Histamine
- Octopamine
- Adrenoceptor

Protein and peptide
- Chemokine
- Angiotensin
- Neuropeptide Y
- Tachykinin
- Cholecystokinin
- Endothelin
- Melanocortin
- Somatostatin
- Bradykinin
- Bombesin
- Neurotensin
- Galanin
- Neuromedin U
- Opioid
- fMLP
- Thrombin
- LH
- TSH
- FSH
- Gonadotropin
- Orexin and neuropeptide FF
- Vasopressin and oxytocin
- C5a anaphylatoxin
- Proteinase activated

Other
- Prostaglandin
- Prostacyclin
- Thromboxane
- Cannabinoid
- edg receptors

(b)





TRENDS in Pharmacological Sciences

JJ Onuffer & R Horuk, 2002

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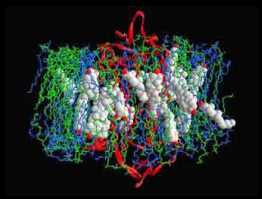
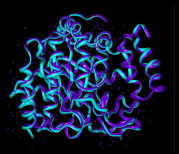
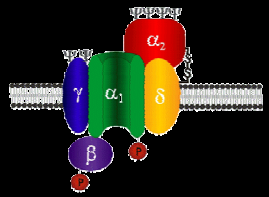
Chemokine receptors are GPCR, but ligands are special ones !

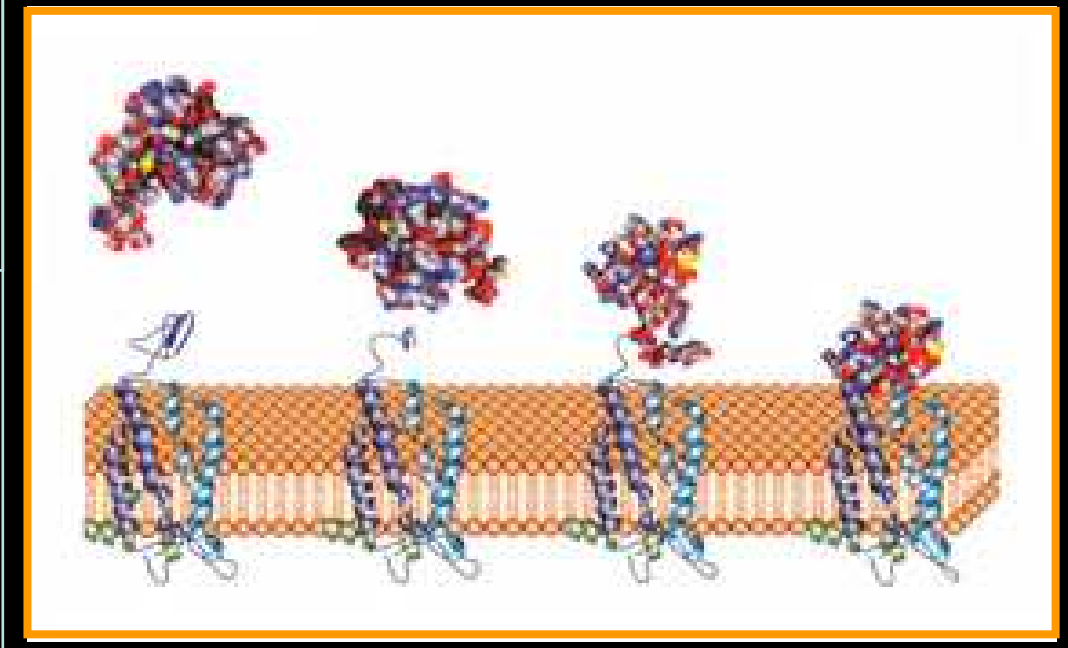
GPCR  45%

Enzymes  28%

Ionic channels 

5%

Nuclear receptors  2%



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Chemokine receptors are GPCR, but ligands are special ones !

The chemokine receptor system in humans and mice is not totally homologous.

Interaction of chemokine and their ligands are much more complex than other well known GPCR.

Some compounds were very potent against the human receptor but inactive against the mouse or rat one.

Our compounds were active in a mouse model of arthritis, but not in the rat model.

We stopped the program.

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Lost in translation in the clinic

TABLE 2. Chemokine receptor antagonists reported to be in clinical development

Target	Compound name and company	Development status	Disease
CCR1	BX-471 (ZK-811752) (Berlex Biosciences/Schering AG)	Phase II	MS, Pso, eczema
	BX-471 (ZK-811752) (Berlex Biosciences/Schering AG)	Phase I	Alzheimer disease
	MLN-3897 (Millennium Pharmaceuticals/ Aventis)	Phase II	RA, MS, Pso
	MLN-3701 (Millennium Pharmaceuticals)	Phase I	RA
CCR2	MLN-1202 (antibody) (Millenium Pharmaceuticals)	Phase II	RA
	Unknown (Incyte Pharmaceuticals)	Phase I	RA
CCR3	CAT-213 (antibody, bertilimumab) (Cambridge AT)	Phase II	Rhinitis, conjunctivitis
	GW-766994 (GlaxoSmithKline)	Phase II	Asthma, allergic rhinitis
	DPC-168 (Bristol-Myers Squibb)	Phase I	Asthma
CCR5	UK-427857 (Pfizer)	Phase II	HIV infection,
	ONO-4128 (Ono Pharmaceutical /GlaxoSmith-Kline)	Phase II	HIV infection
	Sch-351125/Sch-417690 (Schering-Plough)	Phase I	HIV infection
CXCR1/2	SB-332235 (GlaxoSmithKline)	Phase I	COPD, RA, Pso
CXCR4	AMD-3100 (AnorMED)	Phase II Phase I	Stem cell transplantation Repair of cardiac tissue after heart attack
	AMD-070 (AnorMED)	Phase I	HIV infection
	CTCE-0214 (Chemokine Therapeutics)	Phase II	Stem cell transplantation

N. Godessart. *ANYAS*, 2005

Clinical developments terminated

CCR1 antagonist	Pfizer - Arthritis
	Berlex – MS
Anti-CCR2 antibody	Millennium - Arthritis
Anti-MCP1 antibody	Novartis - Arthritis
CCR2 antagonist	Merck - MS
CXCR3 antagonist	Tularik - Psoriasis
CCR5 antagonist	Pfizer - Artritis
CXCR2 antagonists	AZ - COPD
Anti-IL-8 antibody	Abgenix – psoriasis

Alive

CCR5 antagonist Maraviroc: AIDs - Market

CCR9 antagonist Phase 2 Crohn´s

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Points for improvement

Target selection is essential for success.

If evidences in favour of the target are strong, animal models may distract.

Pay attention to the differences between species in the target of interest.

Use human samples in cellular assays. Ideally, pathological ones.

Approach animal models of efficacy to human trials. Search for common biomarkers.

Develop, early in the discovery programme, PK / PD assays to reduce risk

Incorporate new treatment paradigms in the screening cascades: combination therapies in animal models.

Is the single-target aproach still valid ???

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Departamento de Autoinmunidad

¡ Gracias !