The many ways of getting lost in Translational Medicine
Translational Medicine:
- Definition
- Considerations
- Scope
- Goals of TM in Drug discovery

Some examples of TM:
- 3 successful ones (Hope so!)
- 1 lost in translation
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.
A paradigm shift in the biomedical research enterprise

Patient-centered medicine
A paradigm shift in the biomedical research enterprise

- Basic research
- Drug discovery research
- Clinical development

- Patient-centered medicine
- Patients associations

- Combinatorial chemistry, HTS, NMR, robotics
- Molecular biology tools: siRNA, Transgenics
- Institutional Grant support
- Supported by EMEA (IMI) and FDA
- -omics
- Bioinformatics
- -omics
- Biobanks
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
Translational Medicine scope

Patient

Unmet need

Samples

Genetic studies

Biobank

Target identification

Drug discovery programme

Compounds

Target validation

Biomarkers of stratification

Biomarkers of toxicity

Online clinical endpoints

Surrogate endpoints

PK/PD biomarkers

In vitro (transgenic mice, antibodies)

In vivo (siRNA)

Candidate

in vitro + in vivo + ADME + tox

Phase I

Phase 2/3
Translational Medicine scope

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Phase 1

Phase 2 / 3

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Target validation

PK /PD biomarkers

biomarkers surrogate end points clinical endpoints

Regulatory tox package

in vitro + in vivo + ADME+ tox

Biobank

In vivo (transgenic mice, antibodies)

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Translational Medicine scope

Translational Medicine scope

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Biomarkers of toxicity

Biomarkers of stratification

Pharmacogenomics

PK/PD biomarkers

Regulatory tox package

Phase 1

Phase 2 / 3

Candidate

in vitro + in vivo + ADME+ tox

Personalised medicine

Drug candidate

Phase I

Phase 2 / 3

PK /PD biomarkers

biomarkers surrogate end points clinical endpoints

DRUG

Biomarkers

In vivo (transgenic mice, antibodies)

In vitro (siRNA)
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)
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.
Translational Medicine

Some examples
Example 1: the value of a model

Patient → Target identification → Samples → Biomarkers of toxicity → PK/PD biomarkers → Phase 2/3 → Compounds → Drug discovery programme

Patient → Unmet need → Genetic studies → Biomarkers of stratification → Phase I → in vitro + in vivo + ADME+ tox → Candidate

Biomarkers of toxicity → TNFα → Target validation → Surrogate endpoints → Clinical endpoints → Compounds → Drug discovery programme

In vivo (transgenic mice, antibodies) → In vitro (siRNA)
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
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**
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 success.

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

Marc Feldmann        Ravinder Maini

Crafoord prize 2000
Lasker award 2003
Example 2: bedside to bench to bedside

**Patient**

- Unmet need
- Genetic studies
- Target identification

**Samples**

- Biomarkers of stratification
- Biomarkers of toxicity

**Phase 2 / 3**

- PK / PD biomarkers
- surrogate end points
- clinical endpoints

**Drugs discovery programme**

- Compounds
- Target validation

**Phase I**

- Patient
- Samples

**candidate**

- in vitro + in vivo + ADME + tox

- In vivo (transgenic mice, antibodies)
- In vitro (siRNA)
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.
Diana terapéutica: PARADOR

PARADOR está validada clínicamente en artritis reumatoide 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.
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).
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
From bedside to bench and viceversa

A: no inhibe PARADOR
B: inhibe PARADOR

Induce hipertensión a dosis que dá niveles elevados de B
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 ??
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…
Example 3: from gene to treatment

Patient

Unmet need

Genetic studies

JAK2

Target identification

Biomarkers of toxicity

Biomarkers of stratification

Clinical biomarker

Compounds

Drug discovery programme

Target validation

Biomarkers of toxicity

Biomarkers of stratification

Clinical biomarker

Phase 2 / 3

Phase I

Diagnostic Response to treatment

in vitro + in vivo + ADME+ tox

Candidates

PK/PD biomarkers

surrogate endpoints clinical endpoints

Samples

In vivo (transgenic mice, antibodies)

In vitro (siRNA)
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...
JAK2 and myeloproliferative diseases

JAK2 - V617F

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

MPDs are the primary indication for an anti-JAK2 therapy

Pardani A et al. 2007. Leukemia. 21:1658
**JAK2 gain-of-function in MPD**

**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.

Bennett and Stroncek *Journal of Translational Medicine* 2006 4:41
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, Hagop Kantarjian, MD, Animesh Pardanani, MD, PhD, Deborah Thomas, MD, Jorge Cortes, MD, Ruben Mesa, MD, William Hogan, MD, John Redman, MD, Richard Levy MD, Jordan Fridman, PhD, Kris Vaddi, PhD, and Ayalew Tefferi, MD

**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

- 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
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.
Lost in Translation

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Phase 2 / 3

Phase I

PK/PD biomarkers

biomarkers surrogate end points clinical endpoints

Compounds

in vitro + in vivo + ADME+ tox

Candidate
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.
Single target or multitarget approach?

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

One cell may express several receptors.

The site of inflammation may express several cytokines.

Will the blockade of a single target be efficacious?

N. Godessart. ANYAS, 2005
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.
Chemokine receptors are GPCR!

GPCR

45%

Enzymes

28%

Ionic channels

5%

Nuclear receptors

2%

J.J. Onuffer & R. Horuk, 2002
Chemokine receptors are GPCR, but ligands are special ones!

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPCR</td>
<td>45%</td>
</tr>
<tr>
<td>Enzymes</td>
<td>28%</td>
</tr>
<tr>
<td>Ionic channels</td>
<td>5%</td>
</tr>
<tr>
<td>Nuclear receptors</td>
<td>2%</td>
</tr>
</tbody>
</table>
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.
Lost in translation in the clinic

<table>
<thead>
<tr>
<th>Target</th>
<th>Compound name and company</th>
<th>Development status</th>
<th>Disease</th>
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</thead>
<tbody>
<tr>
<td>CCR1</td>
<td>BX-471 (ZIK-811752)</td>
<td>Phase II</td>
<td>MS, Ps, eczema</td>
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<tr>
<td></td>
<td>(Berlex BioSciences/Schering AG)</td>
<td></td>
<td></td>
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<tr>
<td>CCR1</td>
<td>BX-471 (ZIK-811752)</td>
<td>Phase I</td>
<td>Alzheimer disease</td>
</tr>
<tr>
<td></td>
<td>(Berlex BioSciences/Schering AG)</td>
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<td></td>
</tr>
<tr>
<td>CCR1</td>
<td>MLN-3897 (Millennium Pharmaceuticals/Aventis)</td>
<td>Phase II</td>
<td>RA, MS, Ps</td>
</tr>
<tr>
<td>CCR2</td>
<td>MLN-1202 (antibody)</td>
<td>Phase II</td>
<td>RA</td>
</tr>
<tr>
<td></td>
<td>(Millennium Pharmaceuticals)</td>
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<td></td>
</tr>
<tr>
<td>CCR2</td>
<td>Unknown</td>
<td>Phase I</td>
<td>RA</td>
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<td></td>
<td>(Ibicyte Pharmaceuticals)</td>
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<td></td>
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<tr>
<td>CCR3</td>
<td>CAT-213 (antibody, Berlimimmun)</td>
<td>Phase II</td>
<td>Rhinitis, conjunctivitis</td>
</tr>
<tr>
<td></td>
<td>(Cambridge ATs)</td>
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<td></td>
</tr>
<tr>
<td>CCR3</td>
<td>GW-76.6944 (GlaxoSmithKline)</td>
<td>Phase II</td>
<td>Asthma, allergic rhinitis</td>
</tr>
<tr>
<td>CCR3</td>
<td>DPC-168 (Bristol-Myers Squibb)</td>
<td>Phase I</td>
<td>Asthma</td>
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<tr>
<td>CCR5</td>
<td>UK-427857 (Pfizer)</td>
<td>Phase II</td>
<td>HIV infection,</td>
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<tr>
<td></td>
<td>ONO-4126 (Otsuka Pharmaceutical/GlaxoSmithKline)</td>
<td>Phase II</td>
<td>HIV infection</td>
</tr>
<tr>
<td>CCR5</td>
<td>Rhox-353125/Sch-817690 (Schering-Plough)</td>
<td>Phase I</td>
<td>HIV infection</td>
</tr>
<tr>
<td>CXCR1/2</td>
<td>SB-332235 (GlaxoSmithKline)</td>
<td>Phase I</td>
<td>COPD, RA, Ps</td>
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<tr>
<td>CXCR4</td>
<td>AMD-3100 (AmorMED)</td>
<td>Phase II</td>
<td>Strom cell transplantation</td>
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<td>(AmorMED)</td>
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<tr>
<td>CXCR4</td>
<td>AMD-091 (AmorMED)</td>
<td>Phase I</td>
<td>Repair of cardiac tissue after heart attack</td>
</tr>
<tr>
<td></td>
<td>(AmorMED)</td>
<td></td>
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<tr>
<td></td>
<td>CTCE-6214 (Chemokine Therapeutics)</td>
<td>Phase II</td>
<td>Strom cell transplantation</td>
</tr>
</tbody>
</table>

Clinical developments terminated

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

Alive

- CCR5 antagonist: Maraviroc: AIDs - Market
- CCR9 antagonist: Phase 2 Crohn’s

N. Godessart. ANYAS, 2005
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 approach still valid ??
¡Gracias!

Departamento de Autoinmunidad