Programa Cooperación Farma-Biotech
Neurociencias

New Genetic Biomarkers

Ensuring the efficacy and safety of new drugs in Phase III trials

Barcelona, 15 de febrero 2011

CataloniaBIO
Associació catalana d'empreses de biotecnologia

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

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2. The Service

a) Therapeutic focus
b) Innovative proposal
c) Differential features facing the market
d) Current status of development
e) IPR protection

3. Availability for cooperation

1. The Company

R&D SOLUTIONS

✓ Project Management of R&D projects for Functional Food & Pharma companies.

✓ Historic **5 years in operation and constant growth.**

ABFUNCTIONAL ingredients

✓ In company R&D for development of functional ingredients **(**mostly **probiotics)** for application in **functional foods** and **food supplements**.

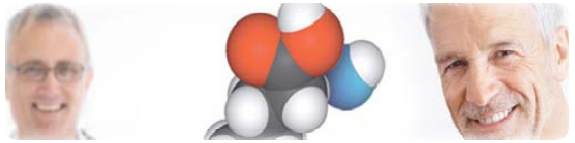
ABGENOTYPING experts in genetic medicine

✓ Development of **advanced genetic tools for Medical Diagnosis** (SNP, CNV)

✓ Services offered directly to medical professionals in order to improve their patient's treatments.

ABTherapeutics real medicine for real life

✓ Subsidiary dedicated to developing a braking approach in oncology: **membrane-lipid therapy** (innovative mechanism of action)



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2. The Service

a) Therapeutic focus

CURRENT THERAPEUTIC MODEL

Same diagnostic
Same treatment

PERSONALIZED MEDICINE

Same diagnostic + Genetic test

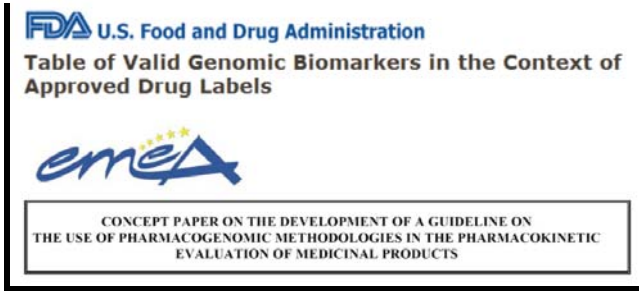
- **Increase dose drug**
- **Standard dose**
- **Dose reduction**
- **Drastic reduction in dose or drug change**

Test benefits

1. Decreased adverse reactions
2. Better treatment compliance
3. Increased probability of therapeutic success
4. Reduced clinical trial costs

• Since 2006 FDA publishes an official list of drugs for which the genetic analysis of patients is required prior to drug prescription.

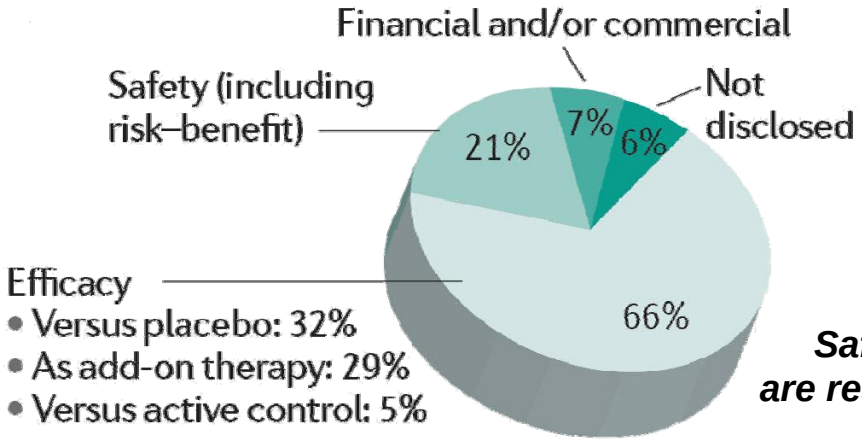
• Nowadays 10% of FDA labeled products contain pharmacogenetic information, and this percentage will increase in the future.



Food and Drug Administration - http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
EMEA - London, 23 April 2009. Doc. Ref. EMEA/CHMP/PGxWP/63270/2009
Ingelman-Sunderberg, M. (2008). *Pharmacogenomic* Biomarkers for Prediction of Severe Adverse Drug Reactions. N Engl. J. Med, 358, 637-639.

World's Pipeline in Neurological Degenerative Diseases (Alzheimer, Parkinson & ALS):

	PC	FI	FII	FIII
Parkinson D.	60	20	28	16
Alzheimer D.	103	73	63	17
ALS	43	9	12	5



Safety+ Efficacy are responsible of 87% of failures

~11 comp. likely to fail (~200 Million $)

(1) Arrowsmith J. *Phase III and submission failures 2007-2010*, Nature Reviews Drug Discovery 2011, vol. 10: pp.1
(2) Medtrack Business Intelligence 2011.

Effects of gene polymorphisms on drugs

Genes of the drugs' targets	May affect the drug-to-target interaction (*e.g* drug binding or target expression), thus lowering **efficacy**
Genes of drug-metabolizing enzymes	Effect on the pharmacokinetics of the drug or its metabolites, resulting in: ➢ Lower **efficacy** ➢ Increased **adverse events**
Genes of transporter proteins	Effect on the pharmacokinetics of the drug or its metabolites, resulting in: ➢ Lower **efficacy** ➢ Increased **adverse events**

Effects of gene polymorphisms on drugs

Genes of the drugs' targets

May affect the drug to target interaction (*e.g* drug binding or target expression), thus lowering **efficacy**

Safety and Efficacy may be compromised

Genes of detox enzymes

Effect on the pharmacokinetics of the drug or its metabolites, resulting in

- Lower **efficacy**
- Increased **adverse events**

Genes of transporter proteins

Effect on the pharmacokinetics of the drug or its metabolization:

Experimental data is scarce

- Increased **adverse events**

EMA opinion on pharmacogenetic analyses…

1. They are **required** when preclinical data shows that polymorphic enzymes are involved in the metabolism of the drug.

2. They are **recommended** whenever large interindividual pharmacokinetic variability is observed or safety concerns are observed.

3. Prospective sampling of DNA for genotype analysis *a posteriori* is always recommended

Effects on trial design

- Patients may be stratified by their genotype
- Dose may be scaled according to genotype
- Some patients may be excluded

(1) European Medicines Agency, *Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products* – Draft, EMA/CHMP/37646/2009

2. The Service

a) Therapeutic focus

- ✓ Genetic differences in genes encoding a drug's molecular target are a primary cause of personalized treatments.
- ✓ Moreover, around 40% of drugs are affected by polymorphic metabolizing enzymes (*detox*), such as CYP2A6, CYP2C9, CYP2C19 o CYP2D6, UGT1A, NAT1/2[1].
- ✓ Around 20-25 % of the efficacy of all drug treatment is significantly affected by genetic differences in drug metabolizing enzymes[1].
- ✓ Metabolizing enzymes are the leading cause of pharmacogenetic labeling (~70% of labels)[1], followed by drug targets.

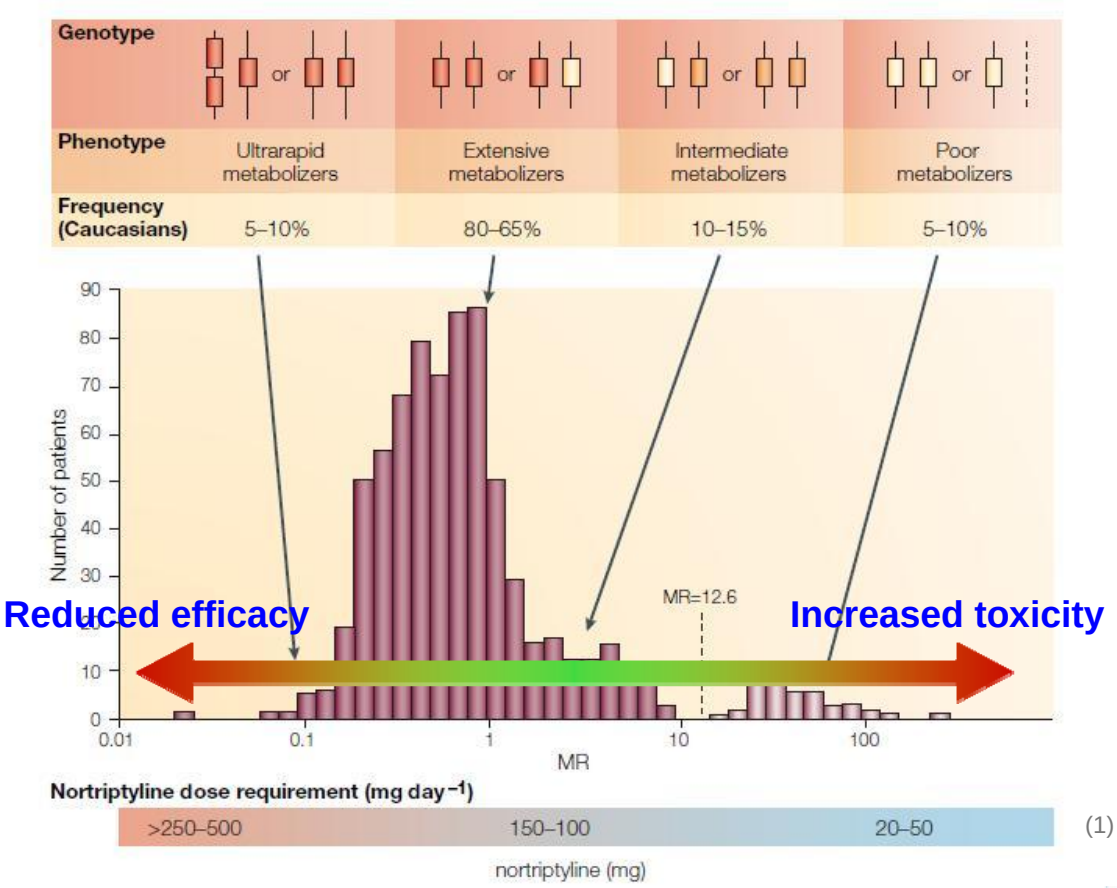
Both target and metabolizing enzymes should be included in pharmacogenetic analyses

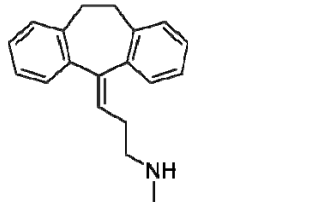
(1) European Medicines Agency, *Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products* – Draft, EMA/CHMP/37646/2009

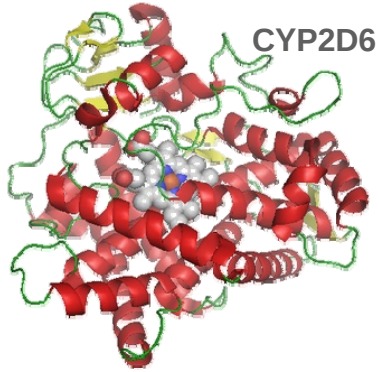
2. The Service

a) Therapeutic focus

Example: *Nortriptilin* and similar antidepressants display increased toxicity in subjects with low CYP2D6 activity, and reduced efficacy in subjects with increased CYP2D6 activity.







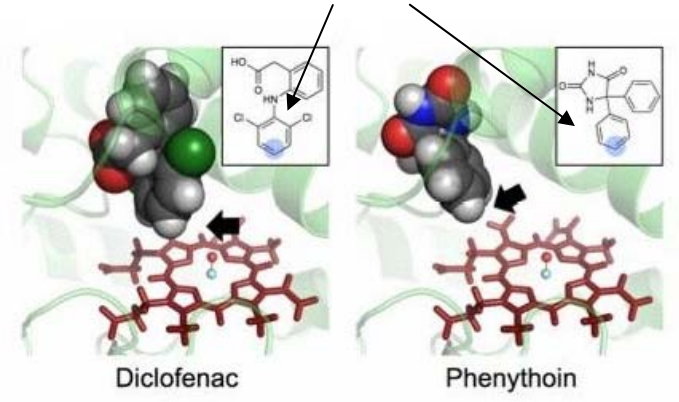
(1) Meyer, UA, *Pharmacogenetics*, Nature Reviews Genetics 2004, 5: p.669-76

How do we select SNP's?

- ✓ The role of typical polymorphic metabolizing enzymes[1] is assessed *in vitro* during preclinical development to decide whether to include their SNPs or not.
- ✓ However, there are more than 200 known genes that can participate in ADME processes.
- ✓ In vitro assays for many of them are not available, and evaluating all their SNPs in a phase-III trial can be very expensive.

✓ Candidate enzymes can be selected by means of *in silico* analyses

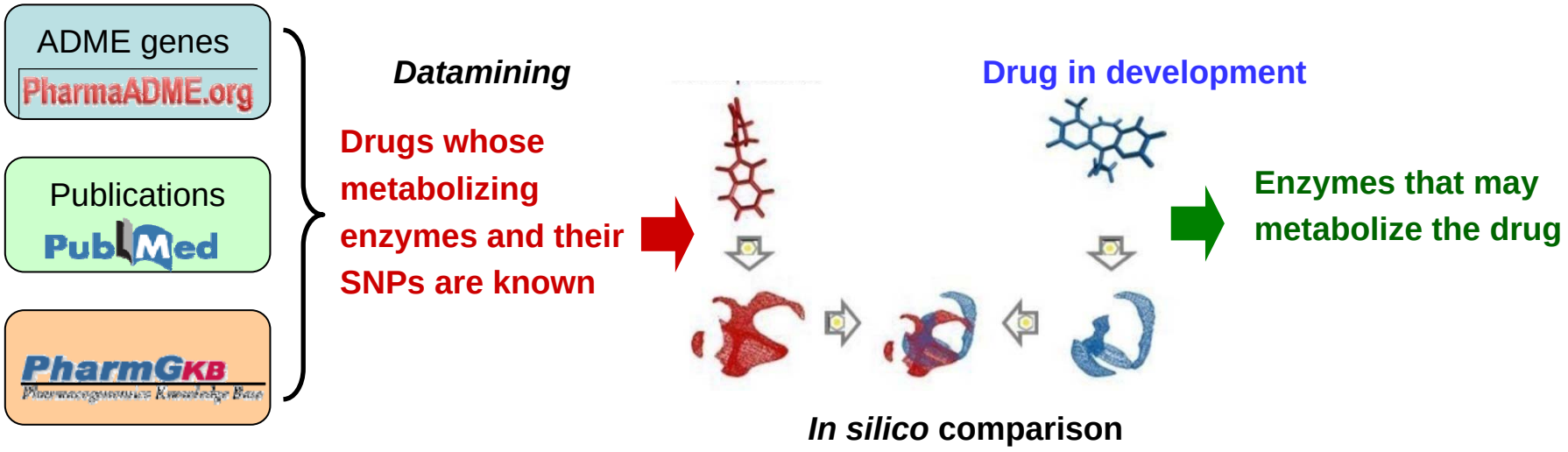
Similarity between CYP2C9 substrates



(1) CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 y CYP3A4; UGT1A1, UGT1A3

How do we select SNP's?

- ✓ Data on phase-I and II metabolism is available for many compounds.
- ✓ The new drug may display global or local similarities to these drugs
- ✓ Therefore, we can compile a list of enzymes which are likely to metabolize the new drug, based on small molecule comparison and enzyme docking.



2. The Service

c) Differential features facing the market

Genes	Our proposal	Marketed ADME pharmacogenetic analyses
Target	SNPs included	SNPs not included
Common polymorphic metabolizing enzymes	Those with *in silico* or experimental evidences are included	All are included, even if experimental data shows that many do not affect the drug
Other metabolizing enzymes	Those with *in silico* or experimental evidences are included	Either not included or all included

E.g. One out of 5 drugs is metabolized through CYP2D6. Evaluating its ~25 SNPs[1] in all drugs would be wasting money.

(1) www.pharmgkb.org, info retrieved on Feb 10th 2011

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- ✓ Provides more information per SNP analyzed
- ✓ Reduces global cost.

(1) www.pharmgkb.org, info retrieved on Feb 10th 2011

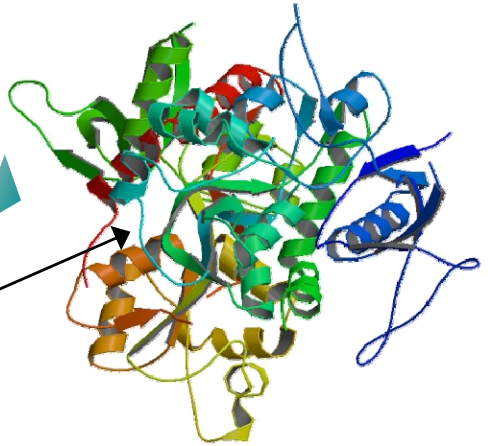
2. The Service

c) Differential features facing the market

Example: CI1041 o *Besonprodil*® (Pfizer Inc.)

NMDA receptor antagonist (N-methyl-D-aspartic), selective for NR1-NR2B dimers.

- The ~15 SNPs of the genes coding for NR1 and NR2B subunits (*grin1* and *grin2B*) would be analyzed.
- SNPs of any metabolizing enzyme with positive results during preclinical development would be analyzed.
- Additionally, only SNPs of other metabolizing enzymes and transporter proteins with *in silico* evidences would be analyzed.



SNPs in genes encoding the molecular target Besonprodil:

- ***grin1:*** C112T, C113T, G716A, A750G, G1001C, A290G, G301A, G308A, A1970G, G2108A, G6435A
- ***grin2B:*** G366C, C2664T, C3538T, T4197C, T5988C

2. The Service

c) Differential features facing the market

- ✓ Lower risk of adverse events due to drug overexposition (*poor metabolizers*) or metabolite overexposition (*ultrarapid metabolizers*).
- ✓ Higher chances of relating adverse events to genetic markers → better chances of product approval
- ✓ Description of new biomarkers → IP
- ✓ Exposure variability is reduced → sample size and costs are reduced (10% lower variability allows for a sample 20% smaller):

	Trial N = 1000	Trial N = 800
Cost of ~4000€/subject	4.0 Mill €	3.2 Mill €
Genotyping 500€/subject	-	0.4 Mill €
Total Cost	**4.0 Mill €**	**3.6 Mill €**

2. The Service

e) IPR protection

- ✓ New Biomarkers are protectable by IP.
- ✓ The protection can cover:
  - ➢ Methods for genetic testing based upon proprietary genetic biomarkers.
  - ➢ Diagnostic kits.
  - ➢ Improved therapeutic protocols for the treatment of the target disease.
- ✓ This protection allows to sell both the drug and the genetic test.

Genetic test to distinguish frontotemporal dementia from Alzheimer's disease

BIOLINK

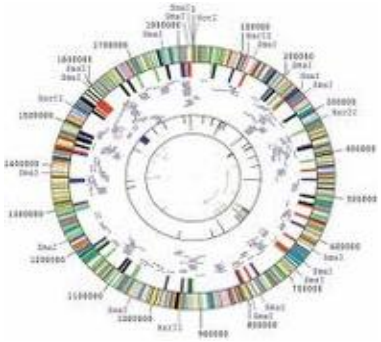
Discovery:

- Two multi-generational families were studied (137 individuals with 25 affecteds)
- Linkage analysis and positional cloning identified a single, disease gene on chromosome 9 that is causal for familial cases of FTD and/or motor neuron disease (MND)
- Several mutations were detected in the causal gene discovered on chromosome 9, though no mutations were found in *APP*, *PSEN1*, *PSEN2* or *MAPT*
- Significant two-point LOD score of 3.47; Multi-point LOD score of 3.70
- *In silico* analysis suggests the detected mutations affect binding of key splicing regulators and therefore may have functional relevance to disease

3. Availability for cooperation

In order to deliver the right planning and execution in each project, AB-BIOTICS offers the following assets to the Pharma industry:

- ✓ A team of widely-experienced PhD. geneticists in the area of Personalized Medicine and the discovery of new Biomarkers
- ✓ Full accredited laboratory to genetically test any kind of human samples
- ✓ Genetic analysis platforms to test both expression and mutation.
- ✓CRO services are also available, head count, hospitals and physicians.



Generalitat de Catalunya
www.gencat.cat

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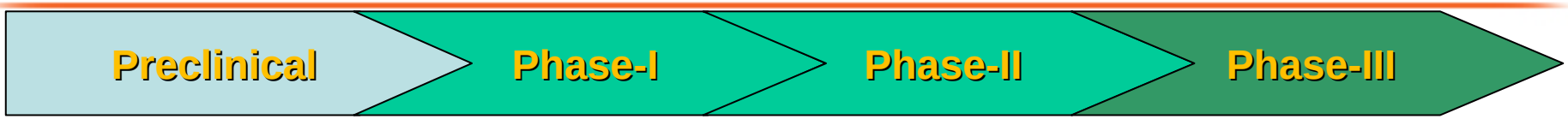
3. Availability for cooperation



- Search of SNPs in target gene(s)
- *In vitro* study of polymorphic enzymes
- In *silico* selection of additional metabolizing enzymes
- Phase-I and II designs may be influenced by available data

- Evaluation of common SNPs
- Design of phase-III depending on results obtained

- Validation of the effect of common SNPs
- Study of the effect of uncommon SNPs
- Reduced variability in efficacy data allowing for smaller trials

Consultancy:

➢Technical proposal

➢*In silico* analysis

➢ Advisory on phase-I and II clinical trial design

➢Biomarkers' patent search

Cost: ~40.000€

SNP's Analysis:

➢Up to 100 SNP's per patient (logistics included)

➢Data analysis

Consultancy:

➢Advisory on phase III clinical trial design

➢Biomarkers: Freedom to Operate

Cost: ~500€ per patient

SNP's Analysis:

➢Up to 100 SNP's per patient (logistics included)

➢Data analysis

Consultancy:

Patent protection

Cost: ~500€ per patient

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Thank You!

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