PHARMACOGENOMICS and PHARMACEUTICAL RESEARCH, DEVELOPMENT and THERAPY

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Current Pharmaceutical R&D and Therapy

Drug Discovery Research

The Discovery Process

- High-throughput screening of libraries of compounds against targets to active molecules, called ‘hits’
- Chemical optimization of hits in broader array of tests to generate ‘leads’
- Further characterization of ‘leads’ to generate ‘development candidates’

Discovery Targets are the Main Issue

- All known effective drugs are directed against a few hundred receptors or enzymes

- Much effort and money has been wasted on drug discovery against non-validated targets
  - precedented targets are valued but limit breakthrough innovation
  - targets based on scientific hypothesis are risky

Genomics or Genetics Approach?

- Genomics
  - data mining of sequences
  - targets need much functional validation to relate them to a disease process
  - amenable to high throughput screening

- Genetics
  - identifying disease-related susceptibility genes
  - always relevant, but not automatically valid as a target
  - often not amenable to high throughput screening

Functional Validation Methods

- Differential gene expression
- Transgenic Animals
- Proteomics

- a drug generally requires a sub-Angstrom fit with its target receptor or enzyme

- in general, we can't predict the folding of a protein with sufficient accuracy

DNA Microarrays or ‘Chips”

- A microarray of oligonucleotides or DNA clones on a glass plate
- Used to
  - test for SNPs or other sequence variations
  - profile gene expression in a cell or organism
- DNA chips enable large scale, fast, inexpensive DNA tests

Potential Applications of Pharmacogenomics In Pharmaceutical R&D and Drug Therapy

- Identify new therapeutic targets
- Identify new disease mechanisms
- Identify new disease susceptibility genes

Clinical Research & Development

Drug Development
Why do compounds fail clinically?

- **Pharmacokinetics**
  Variability in absorption and metabolism

- **Safety**
  Rare occurrence of serious adverse events

- **Efficacy**
  - Unrecognized disease heterogeneity
  - Variable therapeutic responses

- **Effectiveness**

Establishing efficacy

- Heterogeneous groups of patients, with polymorphic genetic backgrounds

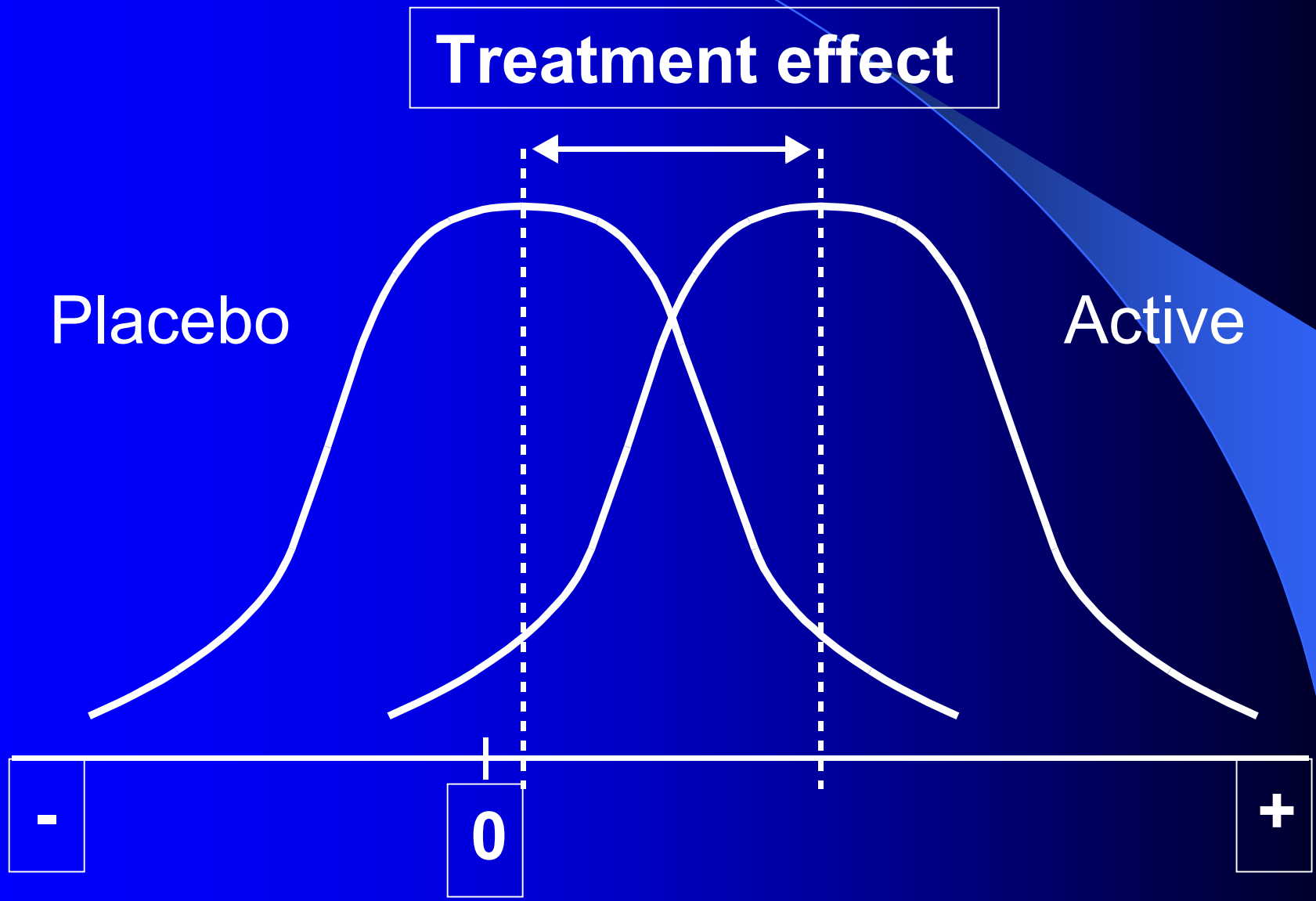
  - different underlying disease susceptibility genes

  - genetic polymorphism of the drug target

  - different non-disease genetic background

- Fixed, rather than individually optimal dosage

Clinical trials results



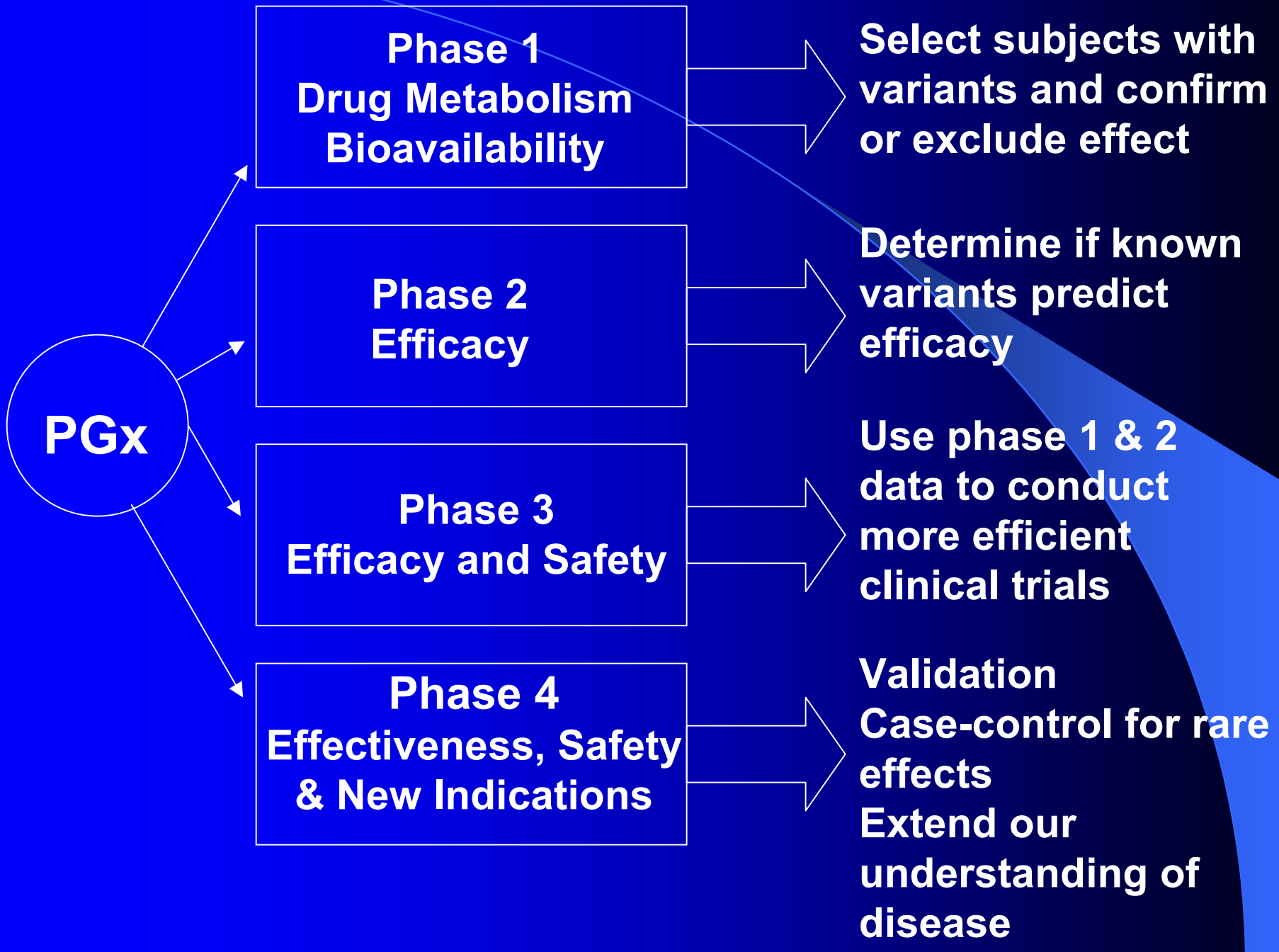
How can genomics help ?

- **Pharmacokinetics – metabolism genes**
  - **Predict profiles in individuals and populations**

- **Safety – drug target genes**
  - **Identify predisposition to side effects**

- **Efficacy – disease susceptibility and drug target genes**
  - **Confirm clinical diagnosis and distinguish disease subtypes**

- **Effectiveness – diseased susceptibility genes**
  - **Identify prognostic variables (disease severity progression rate, associated conditions)**


PGx
Phase 1
Drug Metabolism
Bioavailability
Phase 2
Efficacy
Phase 3
Efficacy and Safety
Phase 4
Effectiveness, Safety
& New Indications
Select subjects with variants and confirm or exclude effect
Determine if known variants predict efficacy
Use phase 1 & 2 data to conduct more efficient clinical trials
Validation
Case-control for rare effects
Extend our understanding of disease

APOE Genotyping in AD Clinical Trials

APOE genotype, and more specifically the E4 allelle, is associated with

- age of onset of AD
- family history of AD
- gender

But not with

- rate of decline
- efficacy of galantamine (Reminyl) or donepezil (Aricept®) treatment

Future of drug development

Today:

Drug development based on populations – Undifferentiated treatment

Tomorrow:

Drug development takes into account variation between individuals – Differentiated treatment

Current label information

- **Herceptin: "indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 Proteins. Her2 protein overexpression is observed in 25%-30% of primary breast cancers"**

- **Risperdal: "The enzyme catalyzing hydroxylation of risperidone to 9-OH risperidone is CYP 2D6, also called debrisoquin dehydroxylase. CYP 2D6 is subject to genetic polymorphism (about 6-8% of Caucasians and a very low percent of Asians have little or no activity)"**

Potential Applications of Pharmacogenomics In Pharmaceutical R&D and Drug Therapy

Research

- Identify new therapeutic targets
- Identify new disease mechanisms
- Identify new disease susceptibility genes

Development

- Correlate genotype with drug efficacy, safety and metabolism
- Stratification of disease subtypes (better diagnosis)
- Validate responders and non-responders to a drug
- Correlate genotype with disease progression

Therapy

Drug Therapy

Rational drug therapy: the issue

- **"If it were not for the great variability among individuals, medicine might as well be a science and not an art" Sir William Ossler, 1892** [Roses, A.D.: Nature 405: 857, 2000]
- **Little rational polytherapy**
- **How to apply statistical 'truths' to an individual patient's therapy?**

Single nucleotide polymorphisms [SNPs] markers

- A polymorphism occurs about once every 1000 nucleotides between individuals:

  ATATAGCCGAGTTGACTATGGTACTG
  ATATAGCCGAGTTGACTATGGTACTG

- Can occur in coding regions: cSNPs
- May or may not have functional consequences
- Amenable to large-scale automated scoring on chips

PHARMACOGENOMICS
What Are the Implications Of These Genetic Variations

- Some differences have functional consequences and account for variation

  - in disease phenotype or in disease susceptibility
  - in drug response or side effect propensity

- Not all people will react to the same extent, with the same response to the same dose of the same drug

- Some differences can be useful biomarkers

Prediction of drug response

- **…a combination of 6 polymorphisms in neurotransmitter-receptor related genes resulted in a 76.7% success in the prediction of the clozapine response (p=0.0001)….[**Arranz, MJ.: Lancet Vol 355, No. 9215: 1615-6, 2000**]**
- **…responsiveness of asthma patients to albuterol was connected to 2 common SNP haplotype markers for beta2-receptor…[**Drysdale, CM.: Proceedings of the National Academy of Sciences, US, Vol 97, No 19: 10483-8, 2000**]**

A Vision on the Future

- Individual patients will receive customized therapeutic advice, based on their likely response to different medicines
- This advice will pertain to

  - choice, based on efficacy, safety, effectiveness

  - dose and regimen

A Vision on the Future

- This advice will be derived from information of the individual patient's DNA
- SNPs will be the genetic markers of choice
- The technology platform will be microarrays ('chips') that contain panels of abbreviated SNP linkage disequilibrium profiles

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Therapy

- Select most likely effective drug
- Individualize dosing
- Minimize safety risk
- Cost effective health care management