



Application of 'Omics Technologies and Pathway Biology in Pharmaceutical Development

University of Edinburgh

Pete Gaskin, Principal Consultant
20 March 2008

Who am I ?

- Degree in biochemistry
 - PhD in toxicology / drug metabolism
 - Mechanistic toxicology research
 - Regulatory toxicology
 - Project Management
 - Late candidate selection to Phase IIa POC
- Principal Consultant at Aptuit Consulting

What do I do ?

Advise clients on strategies for drug development

- Understanding mechanism of efficacy
- Understanding mechanisms of toxicity
- Understanding pathways of metabolism

- ...to select the best candidate
- ...to understand what is happening in animals/man
-to 'rescue' products

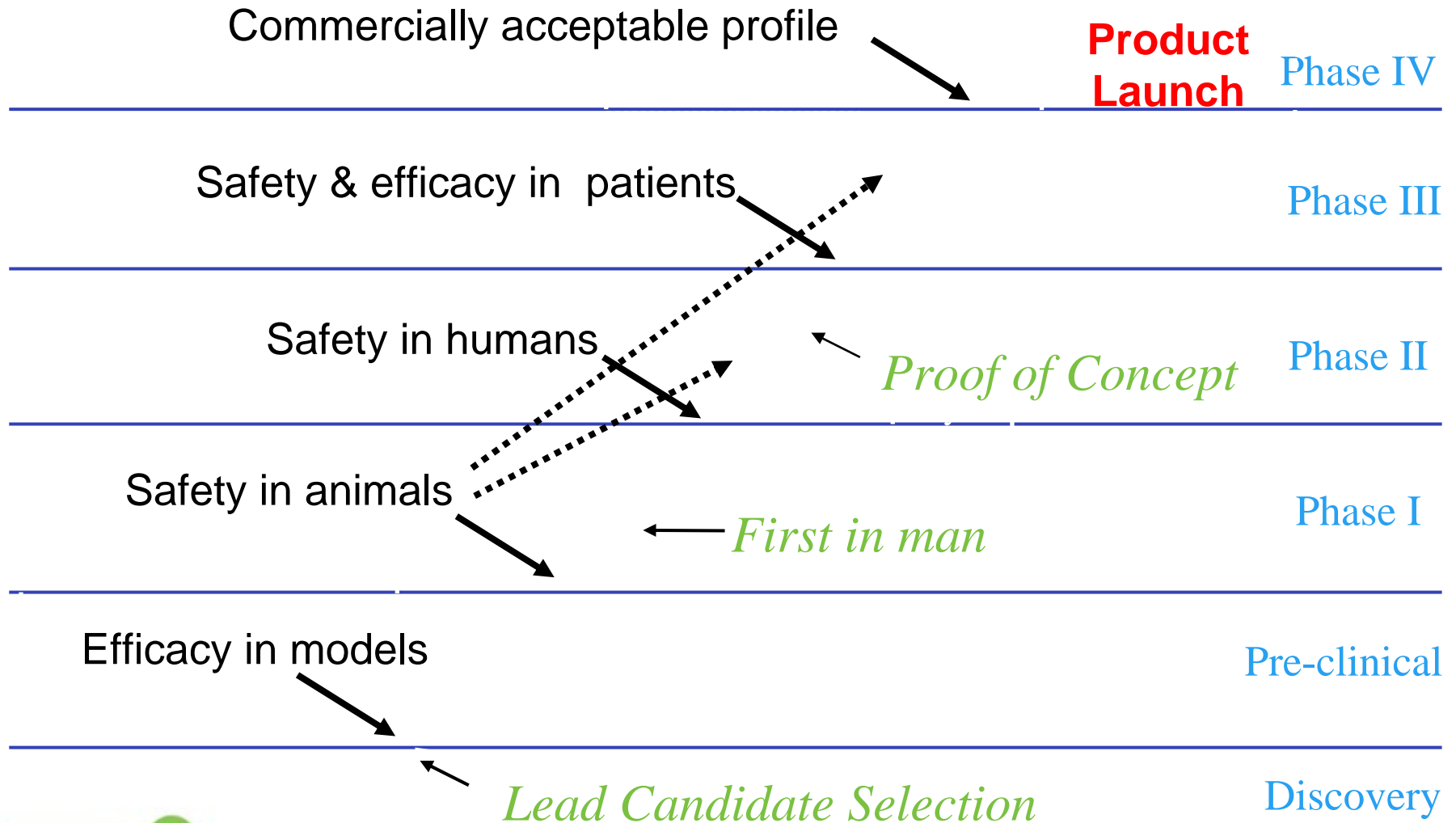
Why am I here ?

- To provide you with a background in drug development
- To discuss current issues in drug development
- To explore where new technologies are having an impact on drug development



Drug Development - the classic model

Stages of Drug Development



Discovery



Discovery

Target Identification



- Observation (e.g. penicillin)

- Basic biochemistry

- Haematology

- Clinical chemistry



to identify target organ(s)
and metabolic pathway(s)
affected

- Histopathology

- Luck

Chemistry



Chemistry (“CMC”)

- Structural motifs related to efficacy and toxicity
- Solubility and formulation
- Stability
- Impurities
- Scale up (mg → kg → tonne)

Lead Candidate Selection



Lead Candidate Selection

Typical Process

- Clinical Target / Indication
- Marketing Strategy
- Screening for unwanted receptor binding
- and Ion Channel interactions
- Efficacy studies in animal model(s)
 - Define therapeutic dose
 - Other efficacy at therapeutic dose
 - **Models often poor predictors**
- Screening safety studies (in vitro and in vivo)



Lead Candidate Selection

Efficacy Studies *In vivo*

- Choice of models critical (sometimes no suitable model)
- Supports rationale for clinical development (up to Phase II)
- Fundamental to drug being suitable for development
- Used to select between candidates (SAR)
- Efficacy dose vs exposure
- Used to predict efficacious dose in humans

Preclinical

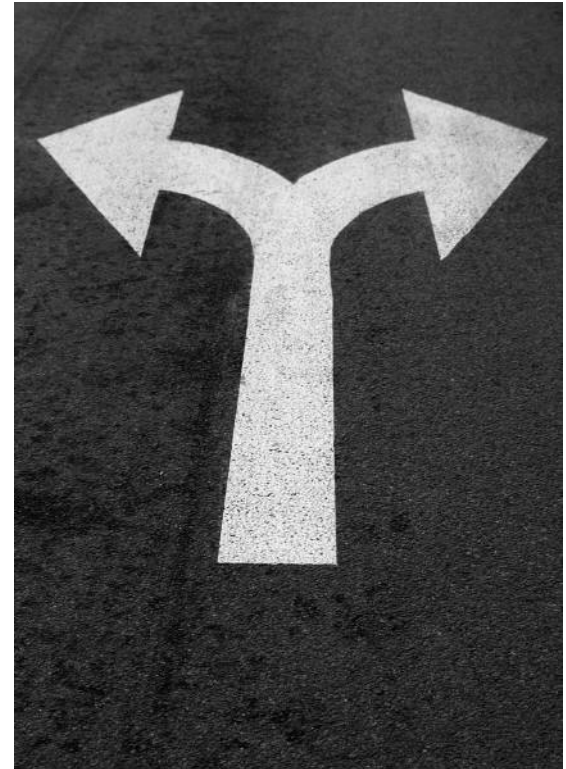


- Preclinical or 'Non-Clinical' studies are required prior to and during clinical trials
- In vitro and in vivo assays
- Designed to examine compound safety prior to first administration to man
- Design of studies covered by various guidelines
 - (ICH, FDA, EMEA, OECD)

Preclinical

ADME – where does the drug go?

- **A**bsorption
 - Bioavailability
- **D**istribution
 - Potential for tissue accumulation
- **M**etabolism
 - Choice of appropriate pre-clinical species
 - Potential metabolism in man
- **E**xcretion
 - Possible elimination rate/route



Drug Metabolism and Pharmacokinetic (PK) Studies:

In vitro

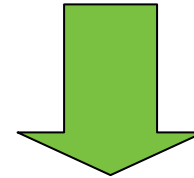
- To gain initial insight into possible metabolic pathways
- To assess possibility for drug-drug interactions
- To assess most appropriate species for pre-clinical

In vivo

- To gain information on bioavailability
- To obtain information on PK

Preclinical Toxicology Studies

- Endpoints include observation, clin chem, haematology, histopath, TK, etc
- Safe starting dose for Phase I
- MTD for calc of therapeutic window
- Findings at MTD
- Target organ(s)
- If human tests are not possible
 - Reprotox
 - Carcinogenicity



Preclinical Safety Pharmacology

Despite Efficacy there may be issues with the drug....

Safety Pharmacology = effects associated with extended primary pharmacology and secondary pharmacological actions

ICH guidelines require safety testing in major organ systems

- CNS
- Respiratory
- Cardiovascular
- Other organs (?)



Follow up studies may be required depending on outcome

Clinical



Clinical Phase I

- Conducted in a small group of healthy **volunteers** (20 -100)
- Subjects given the drug for short periods of time
- To evaluate **safety** and tolerability of the candidate drug
- Usually no greater than 28 day dosing (6-9 months to complete)

Combination of designs used, depending upon route of administration and target population

- Single Rising Dose
- Multiple Repeat Dose
- Food Interaction Studies
- *Effects in the Elderly (if appropriate)*

Clinical Phase II

Proof of Concept in Man

- Testing in **patient** population
- To determine the **efficacy** of the candidate drug
- To further assess safety in patients
- To establish a minimum and maximum effective dose
- Can take from 6 months to 3 years to complete

Phase IIa clinical trials for patient safety and efficacy

Phase IIb for selection of dose and regimen

PK and PD in the patients may differ from healthy volunteers

Clinical Phase III

- Pivotal Trials
- 1000-3000 patients
- Conducted in clinics / hospitals
- Provide additional information on:
 - treatment efficacy
 - potential side effects
 - safety of the investigational drug
- As for Phase II studies are randomized and double-blinded
- Can take up to 4 years to complete
- Long term toxicology studies, carcinogenicity and reprotox studies only conducted at this stage !!

Post-marketing studies

- To assess specific (rarely occurring) safety issues
- Change of indication
- Comparison with competitors
- Combination therapy
- Change of formulation



Drug Development - where new technologies fit in...

New Technologies Offer More Candidates

1. Combinatorial chemistry
2. HTS
 - Ligand binding assays
 - Cell based assays
3. ...etc

New Technologies Offer More Candidates

So now the pipeline
is full of candidates.....

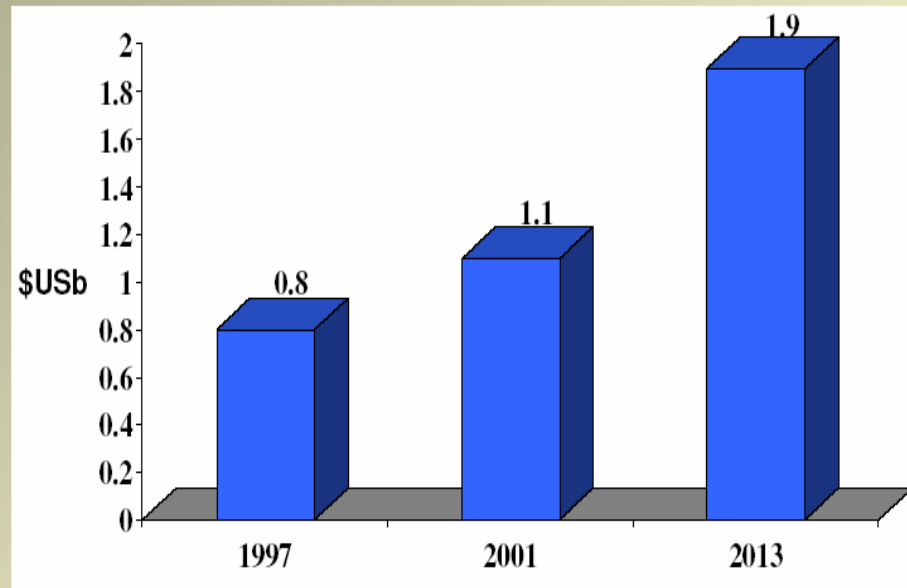


Developing drugs is getting more expensive

Why?

- High Attrition
- Regulatory Requirements
- Patient Recruitment
- Inefficient Processes

Cost of New Drug Development



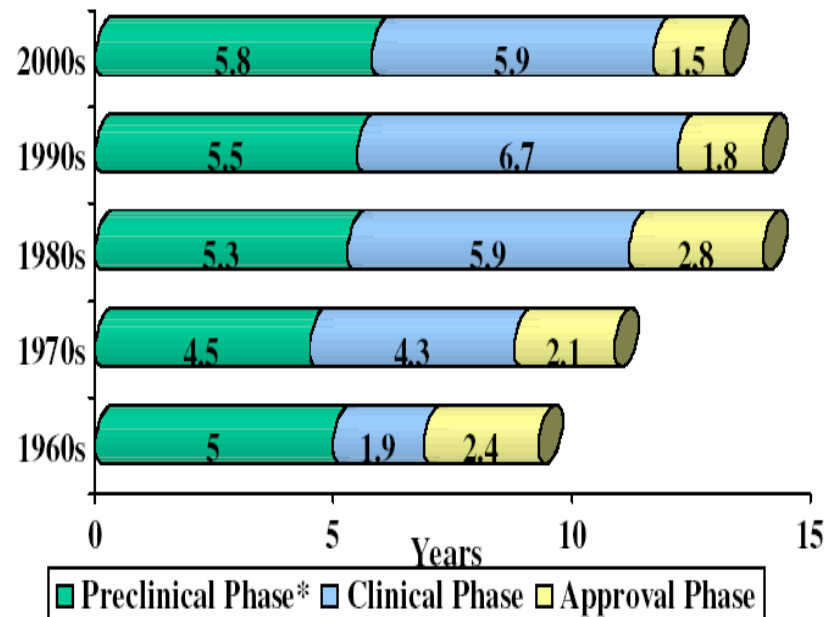
Source: DiMasi et al, Journal of Health Economics, 2003 March

Time to market has increased since the '60s

Why?

- Patient Recruitment
- Demands on Data
- Incomplete Application of Technologies
- Pipeline Volumes

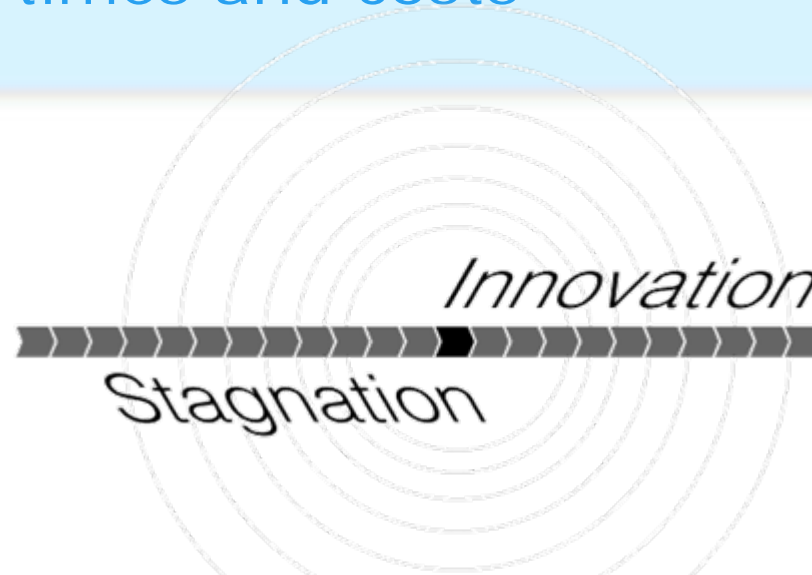
New Drug Development Times in US Spanning Five Decades, 1963-2005



*Preclinical phase=synthesis to IND filing

Source: Tufts CSDD, 2005

The regulators are responding to increasing development times and costs



**Challenge and Opportunity
on the Critical Path
to New Medical
Products**



U.S. Department of Health and Human Services
Food and Drug Administration

March 2004

Drug Development

- all you need to know in 5 bullet points !!

1. The Pharma Industry is in a mess
2. Developing drugs is too expensive and takes too long
3. The industry has developed great techniques to identify new targets and huge numbers of candidates
4. ...but until recently not the means to select the best ones to develop
5. You can help sort this out

How do 'omics and pathways biology fit into drug development?

- Better understanding of disease processes
- Weed out poor candidates
- Ensure time and £ spent wisely
- Smarter, safer drugs
- Drugs for currently untreatable conditions

Discovery

- **Genomics** to understand aetiology of disease
- **Lipidomics** to understand role of phospholipids in disease processes
- **Pathways biology** to better understand disease processes and how drugs interact with them

Toxicogenomics

- Lead Candidate Selection and Preclinical

Genomic Profiling - comparing toxins

From Ulrich & Friend (2002) Nature Reviews, 1:84-88

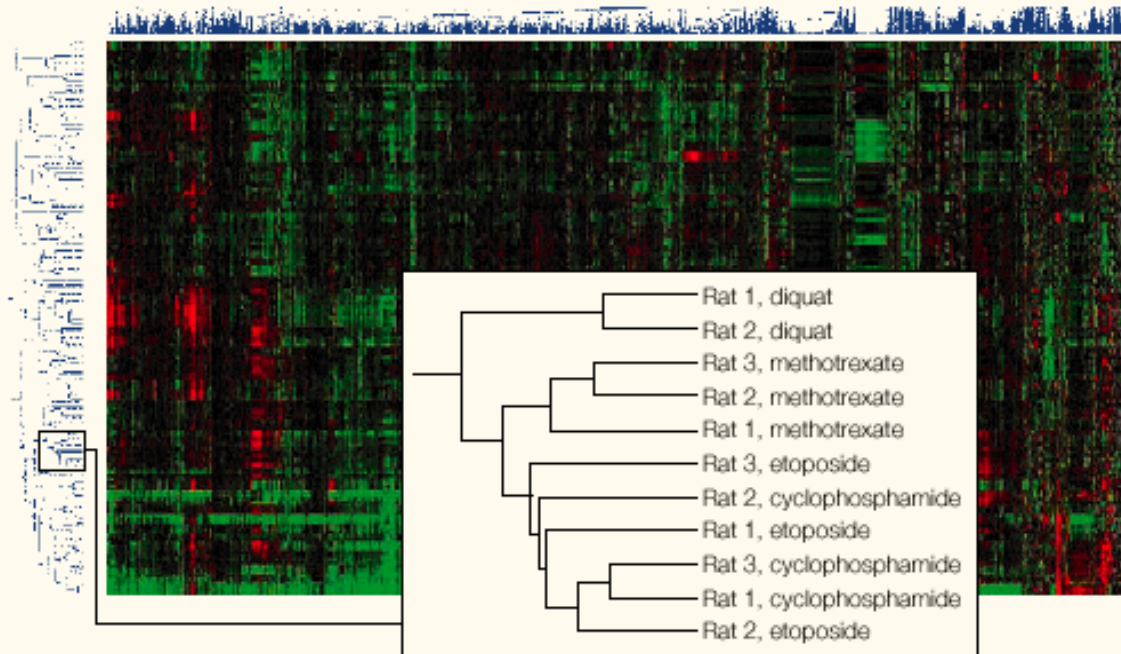
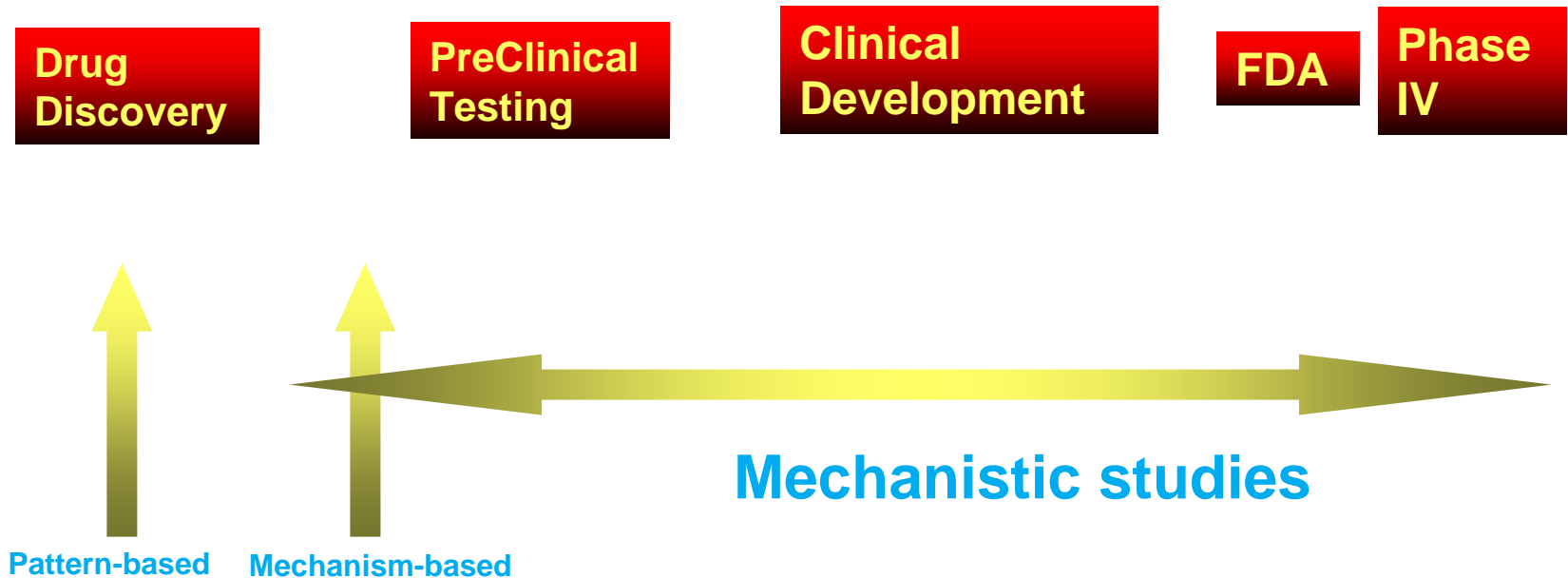


Figure 3 | **A compendium showing gene-expression changes induced by 48 different hepatotoxic compounds in the rat.** Rats were treated for 3 days at dose levels sufficient to produce hepatic toxicity within 7 days, then liver RNA was labelled and hybridized to a 25,000-element oligonucleotide array. The vertical axis shows the grouping of 146 separate treatments and the horizontal axis shows the grouping of 1,754 reporters with significant ($p < 0.01$) changes in expression. Reporters indicating that a gene is upregulated are shown in red, whereas reporters indicating that a gene is downregulated are shown in green. Reporters that do not indicate significant regulation in any specific experiment are shown in black. The highlighted data show a cluster formed by known DNA-damaging agents; also within this cluster is the herbicide diquat.

Toxicogenomics

- Discovery, preclinical and beyond

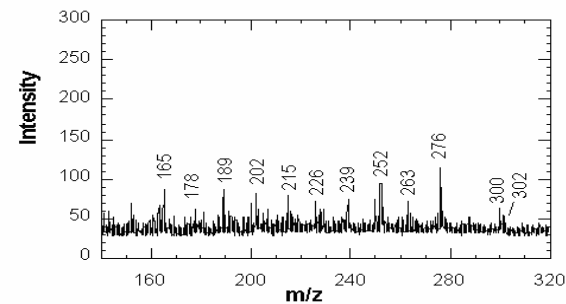
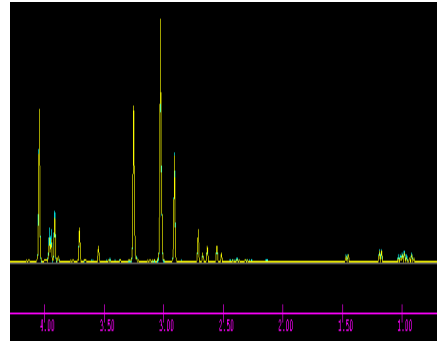
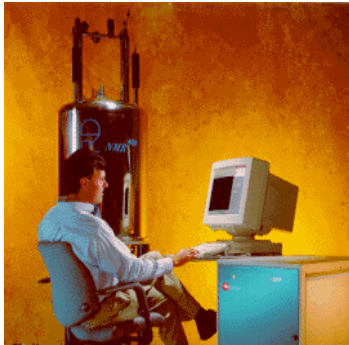
- Understand mechanism of toxicity
- Find toxicity biomarkers for translation into clinic



Metabolomics

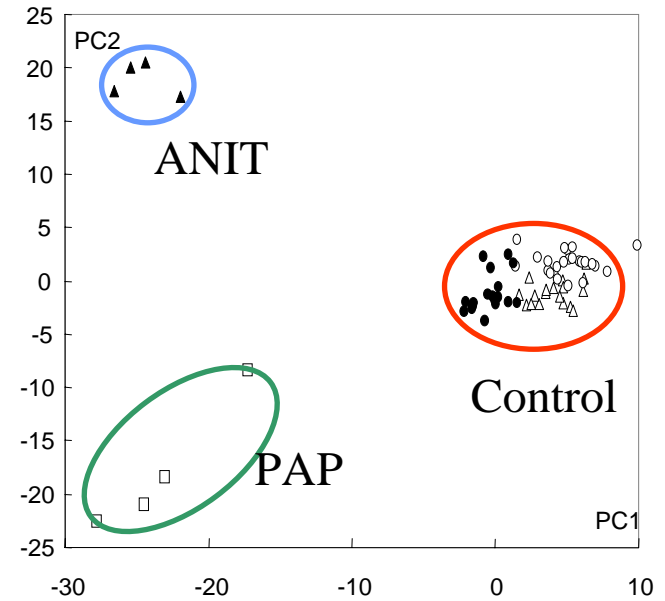
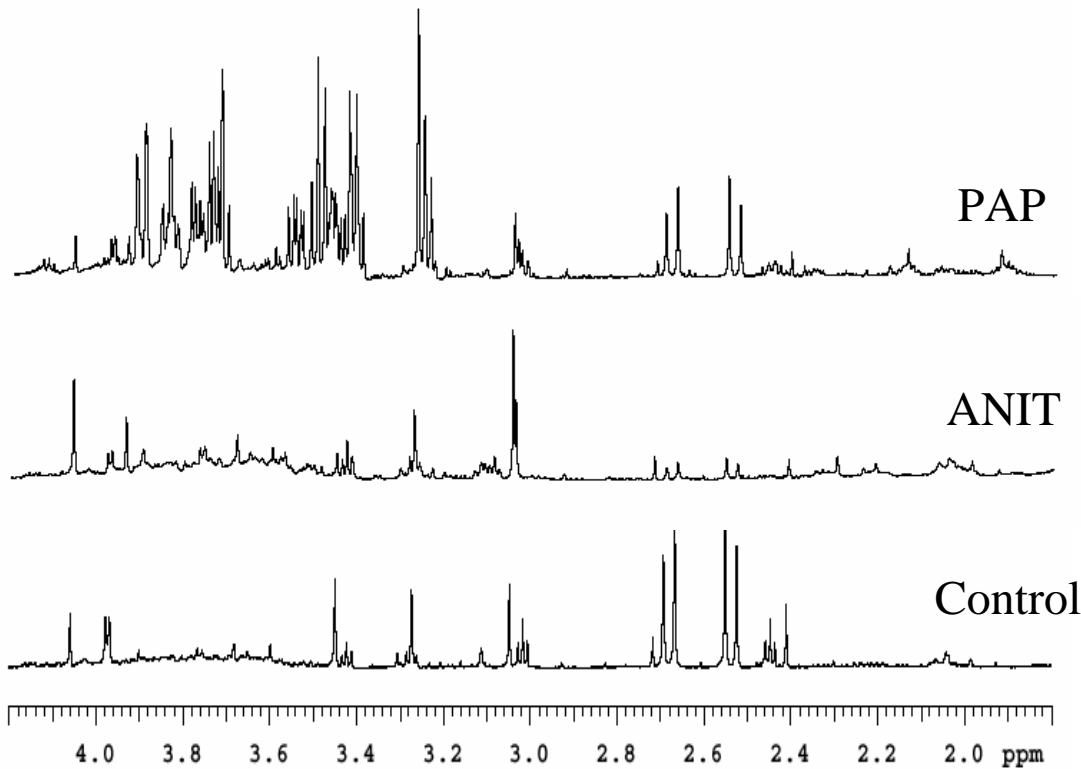
- Preclinical

- Quickly understand routes of metabolism
- Help to understand species differences



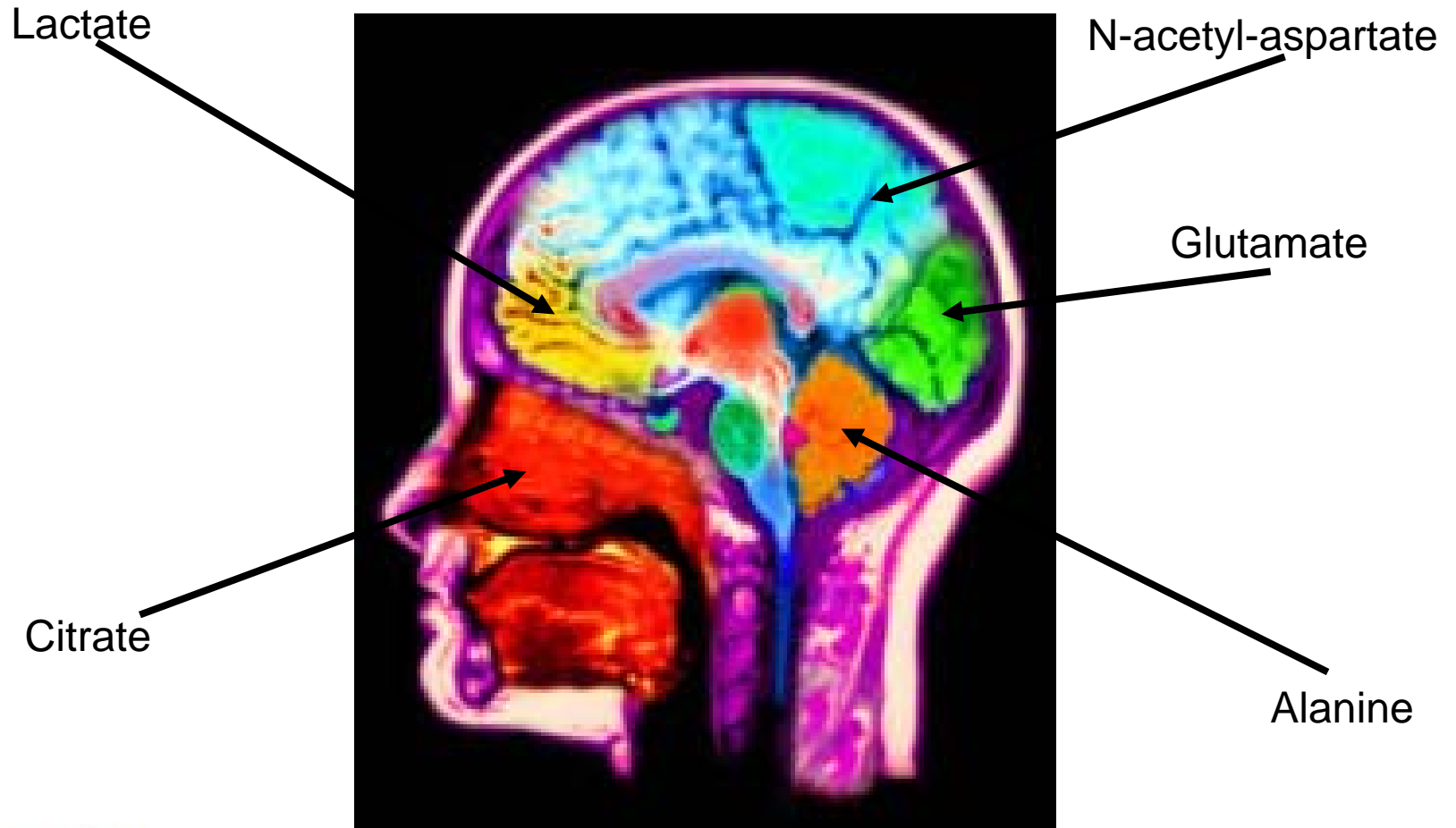
Metabolomics

- Preclinical toxicology



Principal Component Analysis

Metabolomics & Metabolite Imaging in the Clinic



Pharmacogenomics

- Concept of personalised medicine recognised by regulators

Guidance for Industry Pharmacogenomic Data Submissions

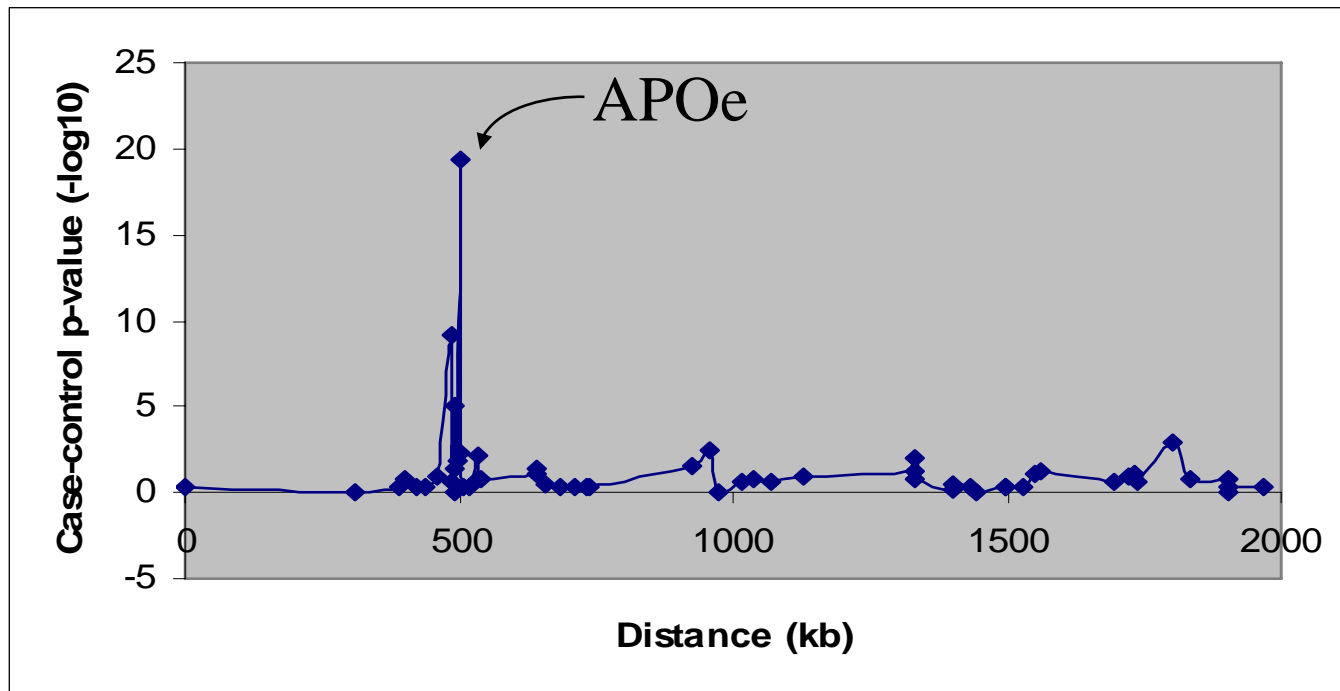
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

March 2005
Procedural

Pharmacogenomics

- Use of SNP markers

- Association of anonymous SNP markers with Alzheimer's Disease

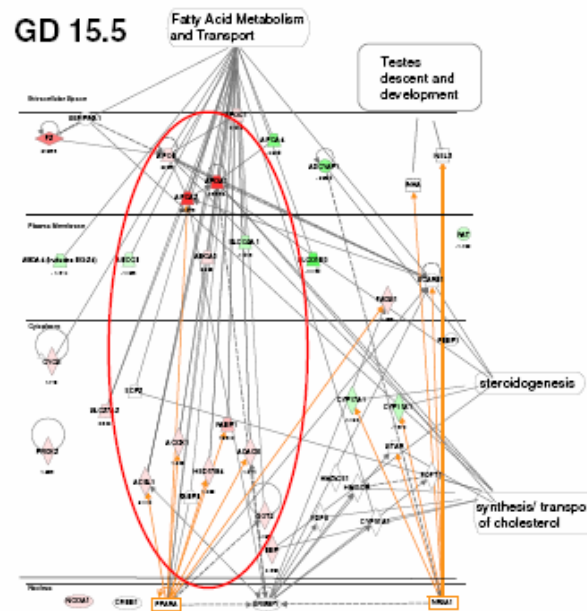


Pathways Biology

- Preclinical and beyond

- To understand mechanisms of toxicity

Network of genes in functional pathways postulated to be involved in phthalate-induced testicular mal-development (TMD) in Wistar rats at GD15.5



The diagrams show upregulated (red)- and downregulated (green)- genes that were affected in whole fetal testes following in utero exposure of rats dibutylphthalate (DBP) 500mg/Kg from GD 12 to GD 19. Orange lines show genes that are regulated by the transcription factors peroxisome proliferator receptor alpha (PPARA) and steroidogenic factor 1 (SF-1). Grey lines represent associations (of genes) to a particular functional category e.g steroidogenesis. Red oval shows fatty acid metabolism/transport genes regulated by PPARA (mostly up-regulated),

Plummer et al, Toxicological Sciences 97(2), 520-532, 2007

Pathways Biology

- Preclinical and beyond

- What are the **differences between cancer cells and normal cells?**
 - What are the key differences in **gene expression** between cancer cells and normal cells?
 - Which **cellular sub-systems** may be affected by cancer?
 - What are the **cellular processes (pathways)** that differ between cancer cells and normal cells?
 - Which **components (proteins)** of the pathways might be involved in cancer

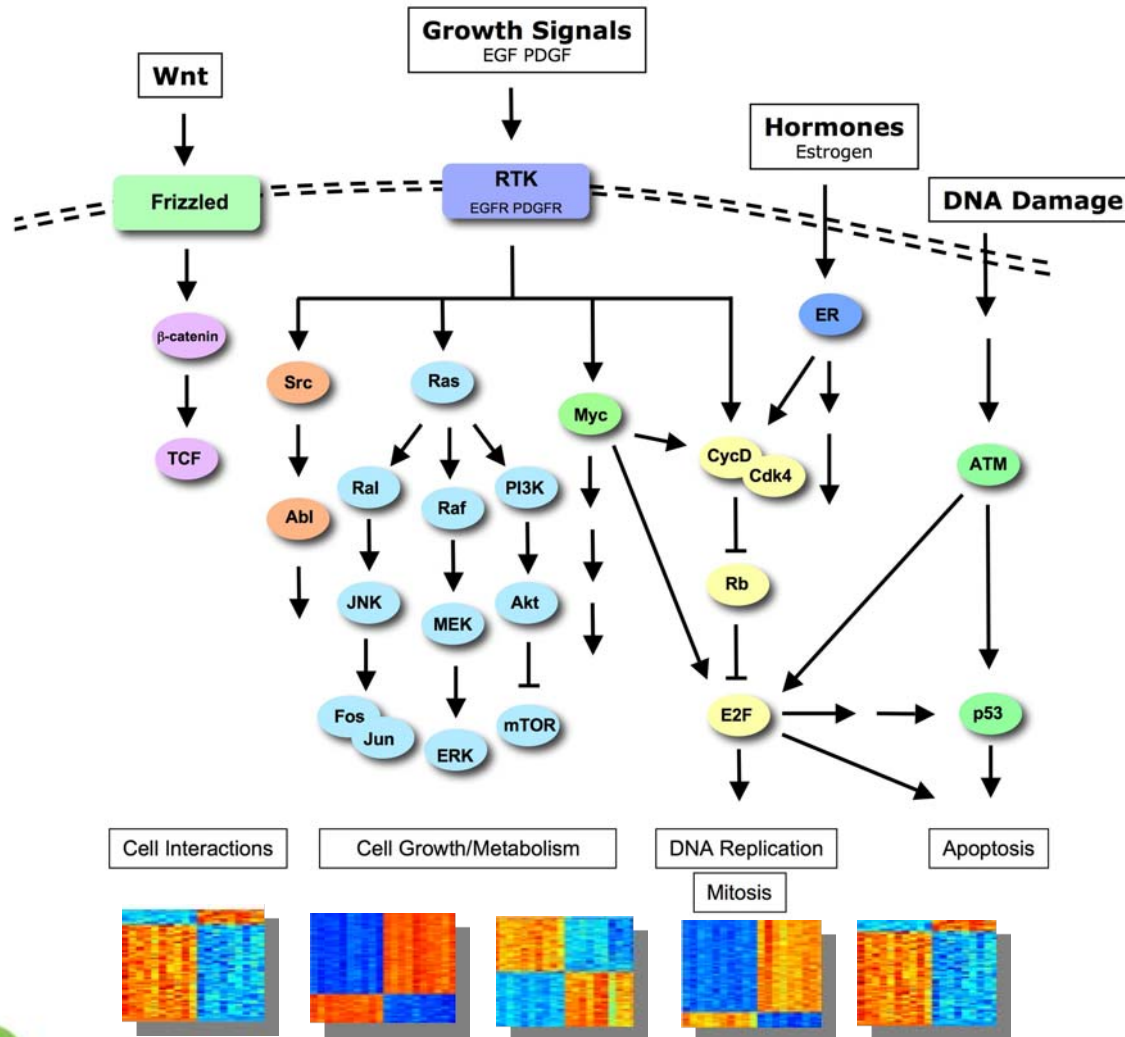
Pathways Biology

- Preclinical and beyond

- Looking at clusters – How do these proteins fit in with the context of cellular pathways?
- Are there polymorphisms in these proteins in individuals susceptible to cancer?
 - who to treat?
 - how to treat?
- Which pathways are active in different tumor cell lines?
 - develop more predictive models
 - translation from pre-clinical to clinic

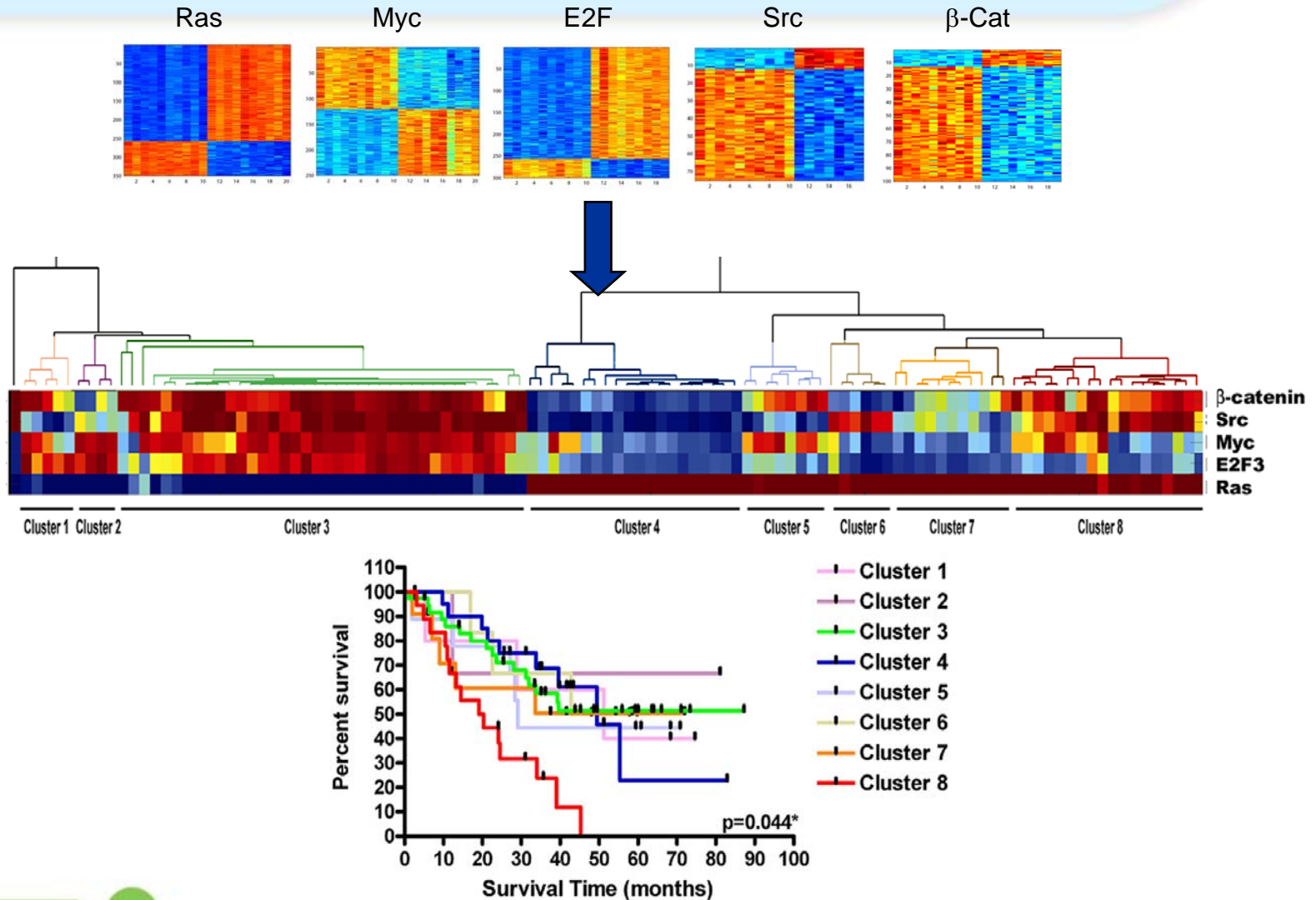
Pathways Biology

- Pathways leading to cancer



Pathways Biology

- Identifying active pathways in tumors



Pathways Biology

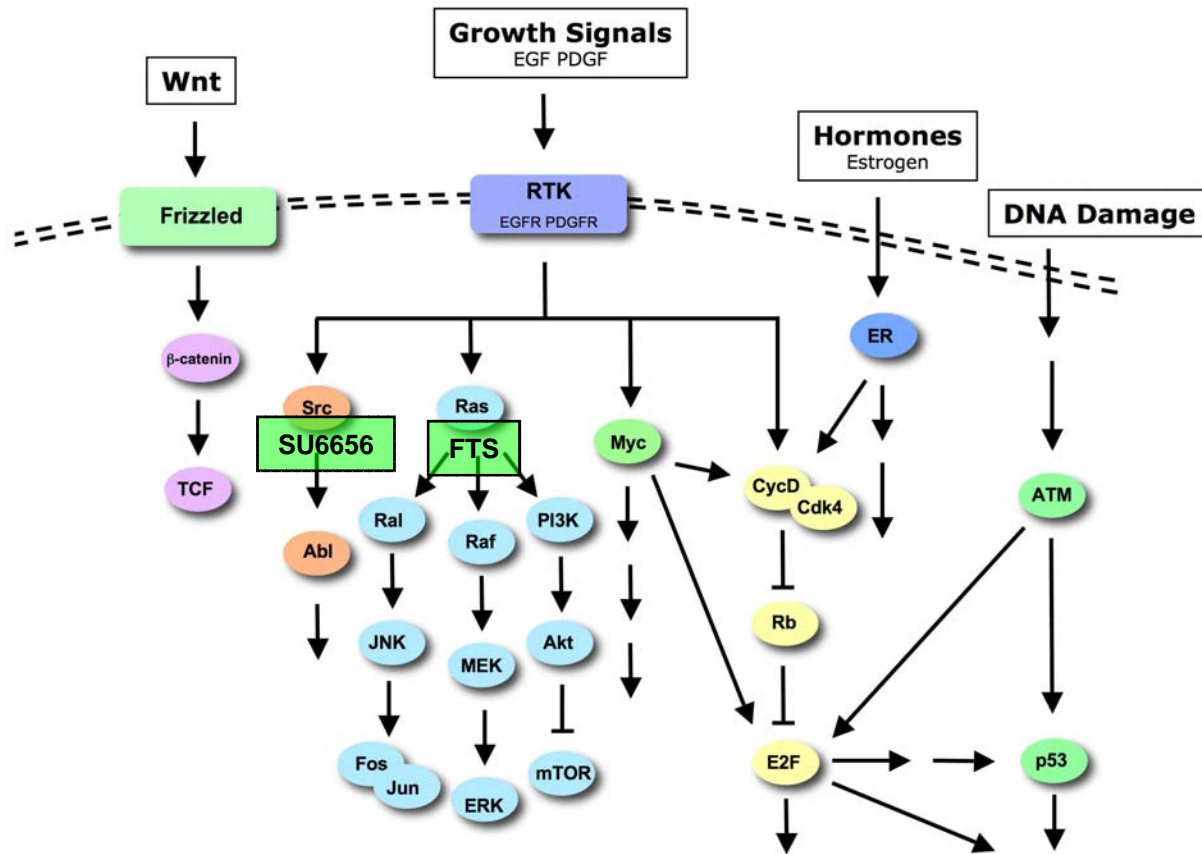
- Patient specific pathway profile



Can we use the profile
for an individual patient
to select best therapy ?

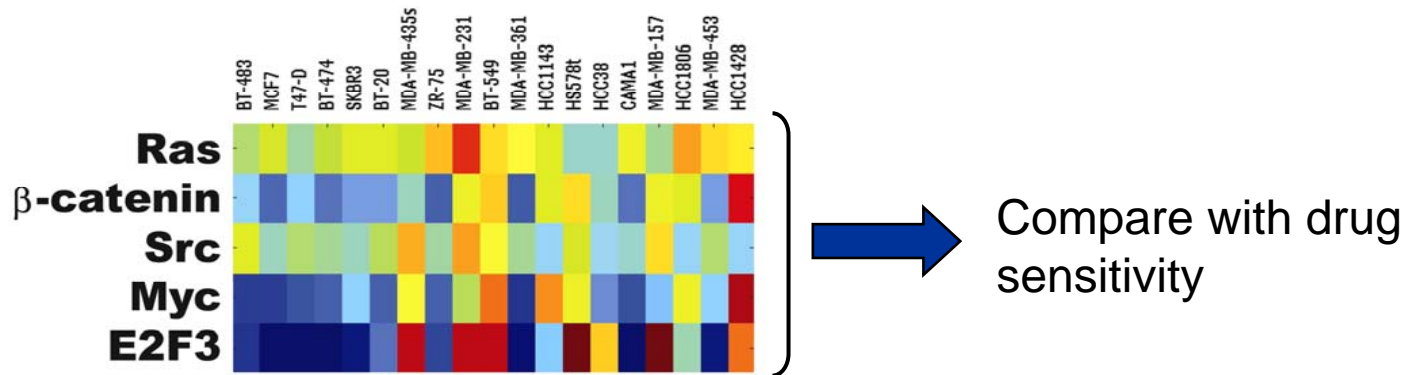
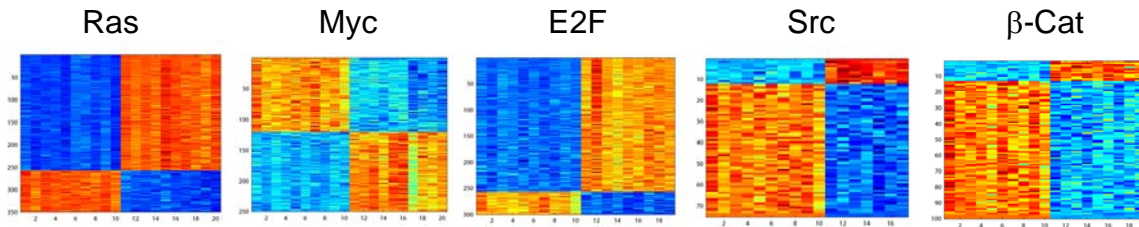
Pathways Biology

- Patient tailored therapy



Pathways Biology

- Improve predictability of in vitro and animal models



In Summary

- Developing drugs is expensive and takes too long
- Drug efficacy rates are poor
- 'Omics and Pathways Biology are being used to
 - understand disease processes better
 - select safer candidates for development
 - select more efficacious candidates for development
 - ensure money and time are better spent
 - develop tailored therapies

Thank You

Thanks for your time

.....any questions ?