

# Systems Biology in Drug Discovery & Development: Impact and Challenges

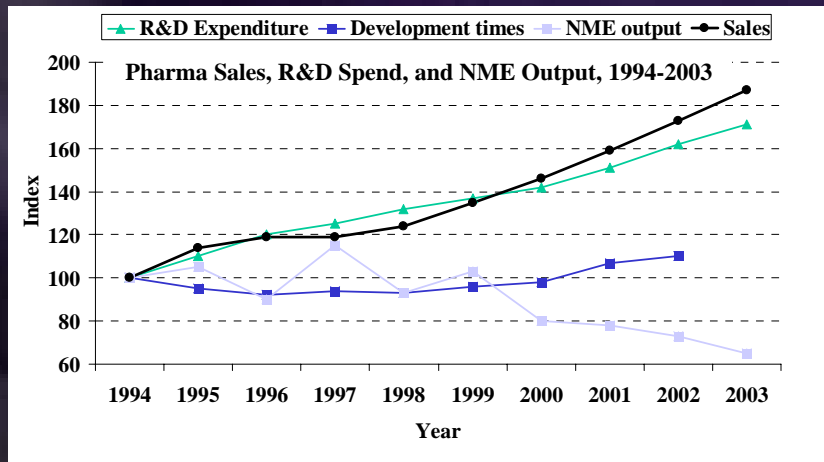
**Didier Scherrer**

Pathways Capability

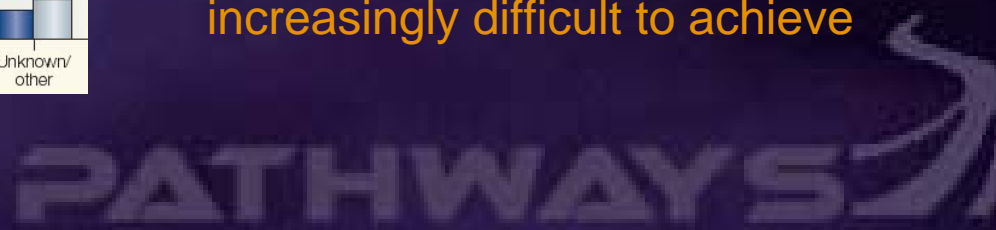
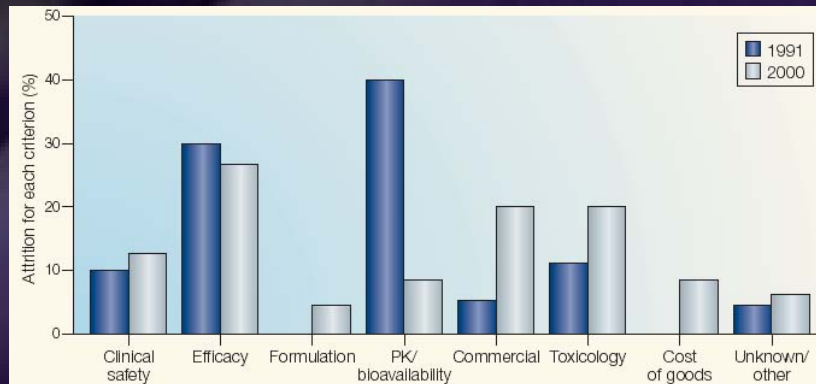
Global Discovery Enabling Capabilities & Sciences

**AstraZeneca**

# Challenges Faced by Pharmaceutical Industry



- Rising cost of R&D but not paralleled by increased number of NME approvals
- Increased risk due to increased difficulty of developing innovative molecular targets
- Continued attrition due to tox and lack of efficacy
- Regulatory environment more challenging: risk/benefit ratio increasingly difficult to achieve



# Post-Genome Issues

---

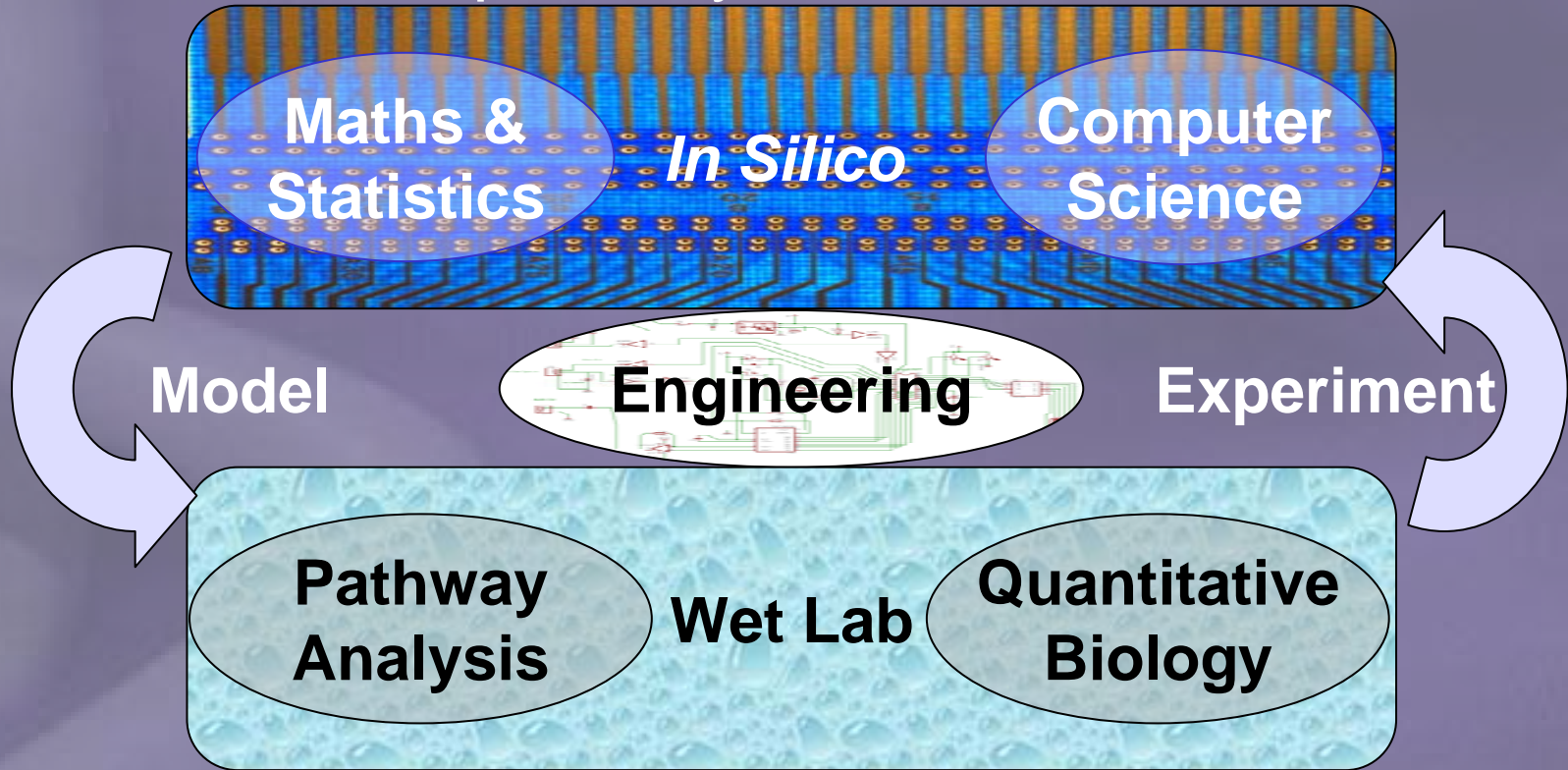
- Genetics & Molecular Biology have provided very detailed information on single entities associated with or linked to complex diseases
- Reductionist approach identifies single components (the “Parts List”) and, possibly, their function, but
  - Only parts of a complex system
  - No information on cellular/ system interactions

# Systems Biology

---

- Provide a context/framework
  - to understand biological responses within physiological networks, not in isolation
  - Test hypotheses
- Combination of mathematics, engineering and biology to create platforms to look at physiological networks systematically
  - Laboratory experimentation
  - Computational modelling
  - Informatics

# pathways



- Multidisciplinary, cross-functional project teams
- Integrated computational biology & experimental components

# Pathways Capability Core Activities

---

## Experimental

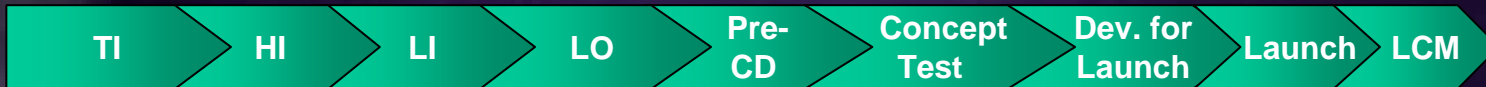
- Molecular & Cell Biology
- Protein interaction mapping
  - Mammalian Cells
  - Yeast
- Proteomics
- Mass Spectrometry

## Computational

- Mathematical modelling
- Informatics infrastructure
  - Databases
  - Text/ Literature Mining
- Statistics

# How can AZ Pathways Capability help?

---



**Therapeutic approach**

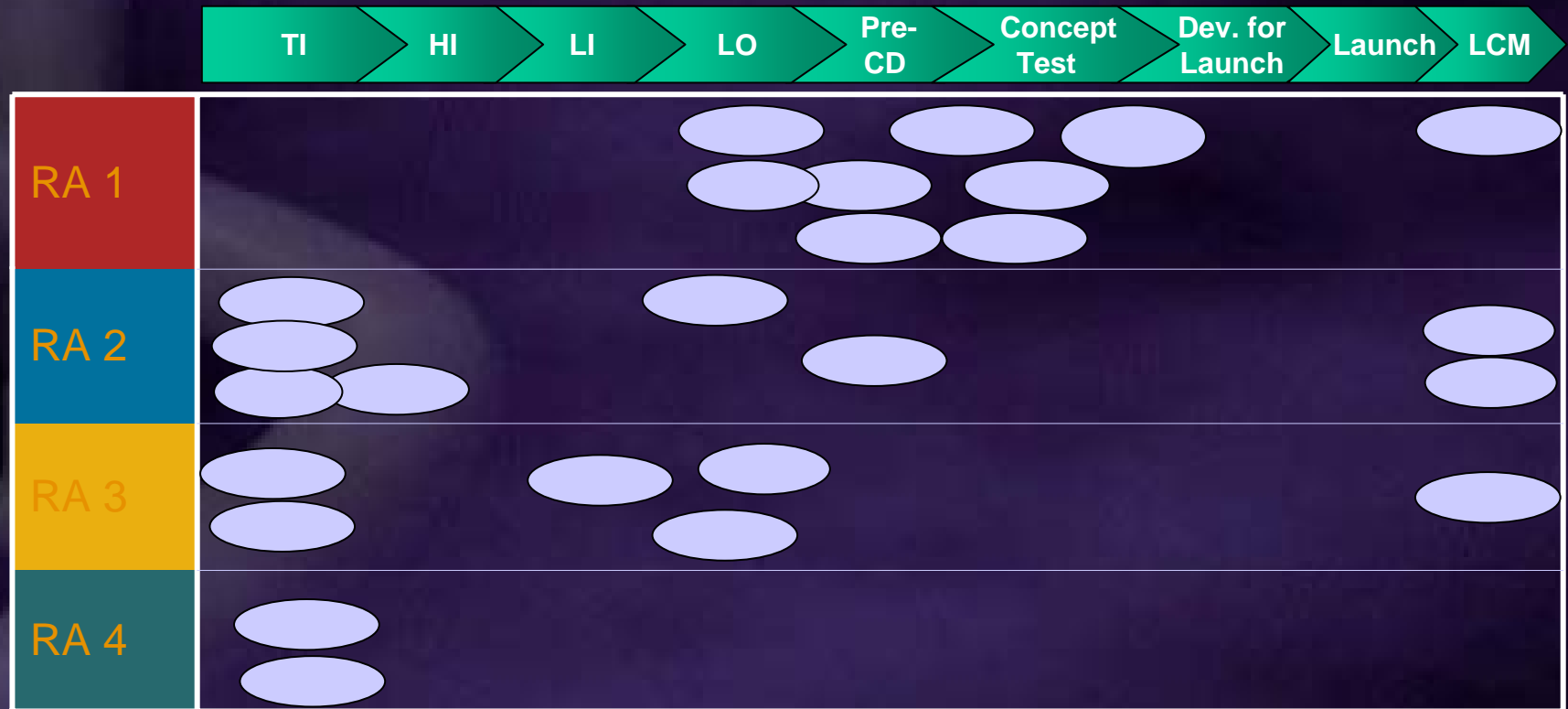
**Compound Evaluation/Selection**

**Biomarker Identification**

**Identification of areas of safety concern**

**Clinical trial design**

# Project Portfolio





Example 1  
Target from Genome Wide Screen

# Evidence to support functional role in disease?

---

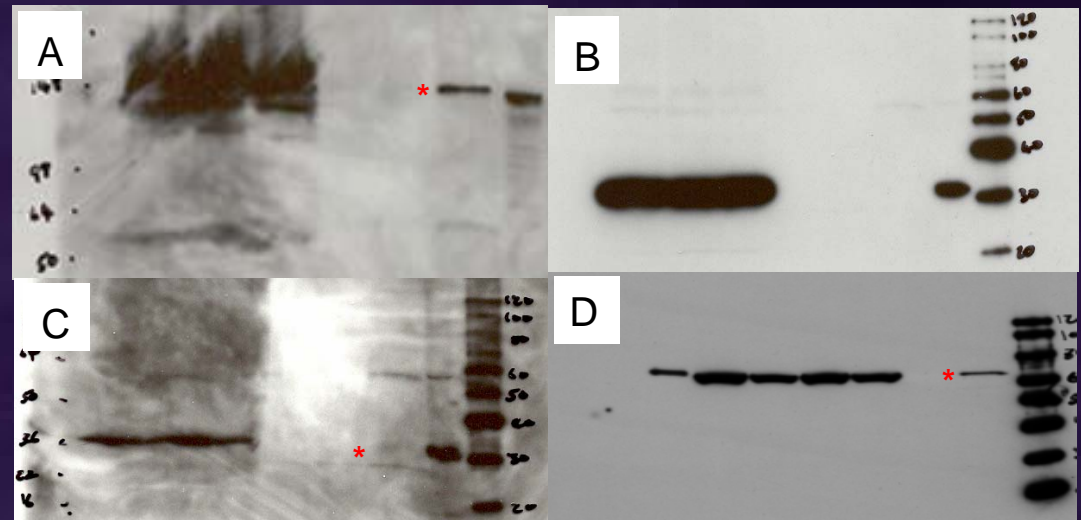
- Genome wide screen identified gene of potential interest with no known functional link to the disease.

## Primary data generation & analysis

1. IP/MS & Y2H screens -> “hit list”
2. Literature & text mining to add annotations to hit list
3. Interaction map built identifying new area of biology & generating hypotheses to test

# Interaction confirmation

- IP/Western
- Mammalian 2 hybrid matrix analysis
- Further literature annotations
- Hypothesis for functional association to disease



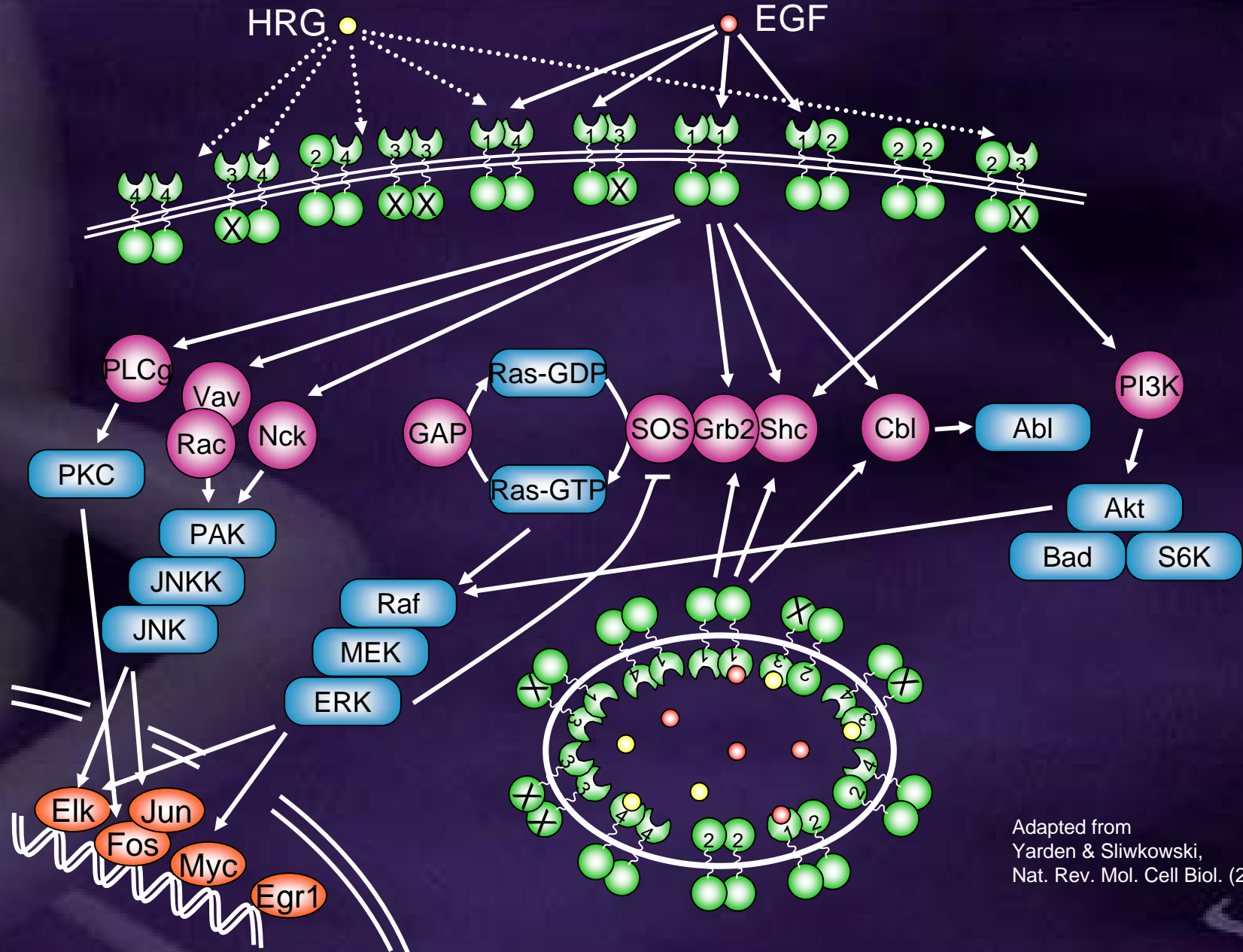
# Delivery to Discovery Team

---

- Functional confirmation of disease linkage
- Identification of specific interactions that may represent new points for therapeutic intervention
- Identification of potential areas of tox/safety concern
- Generation of screening tools and target IP

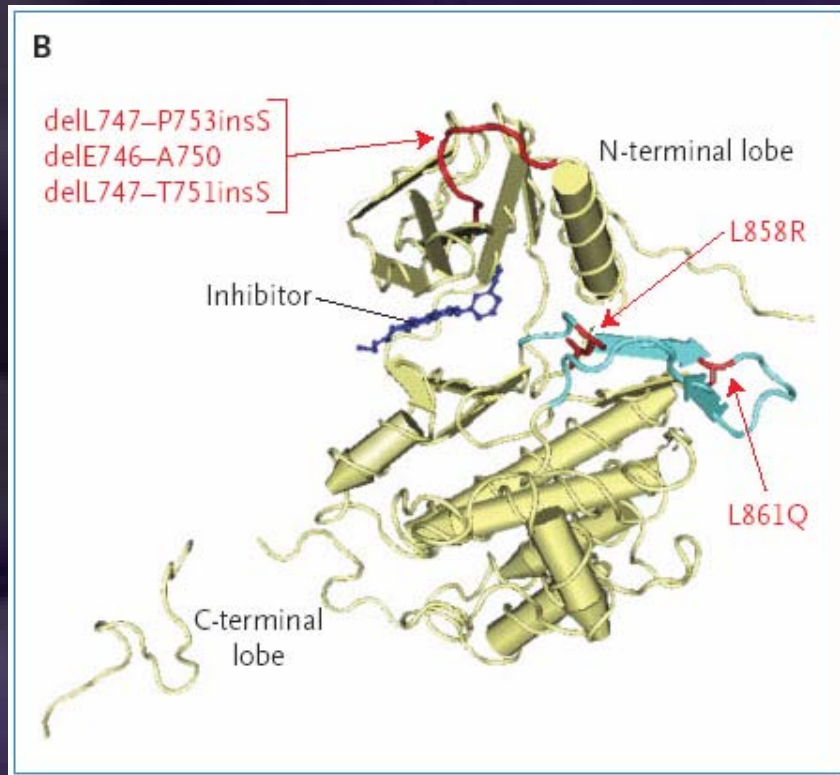
## Example 2: ErbB receptor signalling

Patients who are responsive to Gefitinib often have mutations in ErbB1



Adapted from  
 Yarden & Sliwkowski,  
 Nat. Rev. Mol. Cell Biol. (2001)

# ErbB Mutants



- ErbB1 Mutants
  - Deletion mutants
  - L858R
- Elevated phosphorylation
- Little difference in ERK signal between WT & Mutant
- Mutant has elevated AKT signalling

# Questions

---

- Why do these mutations predispose to a good response to gefitinib treatment?
- What is the mechanism of action?
  - Hypothesis: defect in ErbB1 internalisation may underlie mutant sensitivity to gefitinib

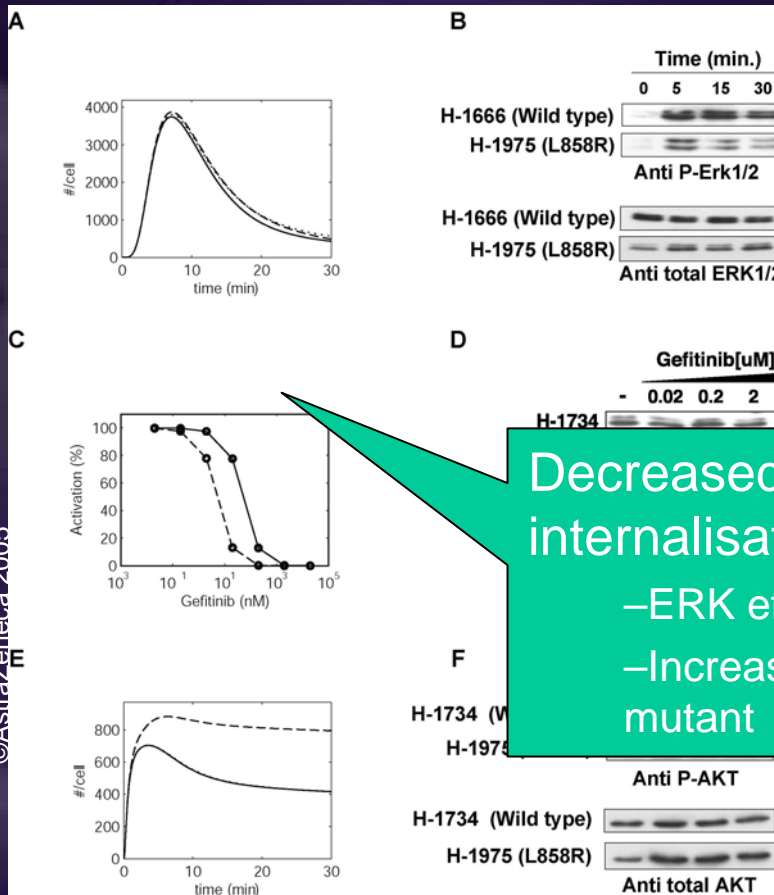


# ErbB Model provides insight to potential MoA of mutations

## ERK & AKT Signalling

### Simulations

### Published data



Decreased receptor internalisation explains

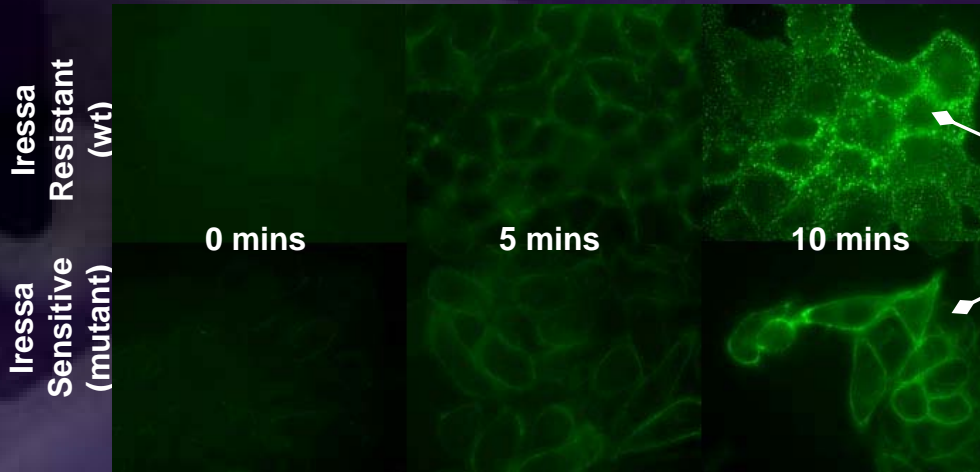
-ERK effects

-Increased AKT activity in mutant



# Experimental Verification:

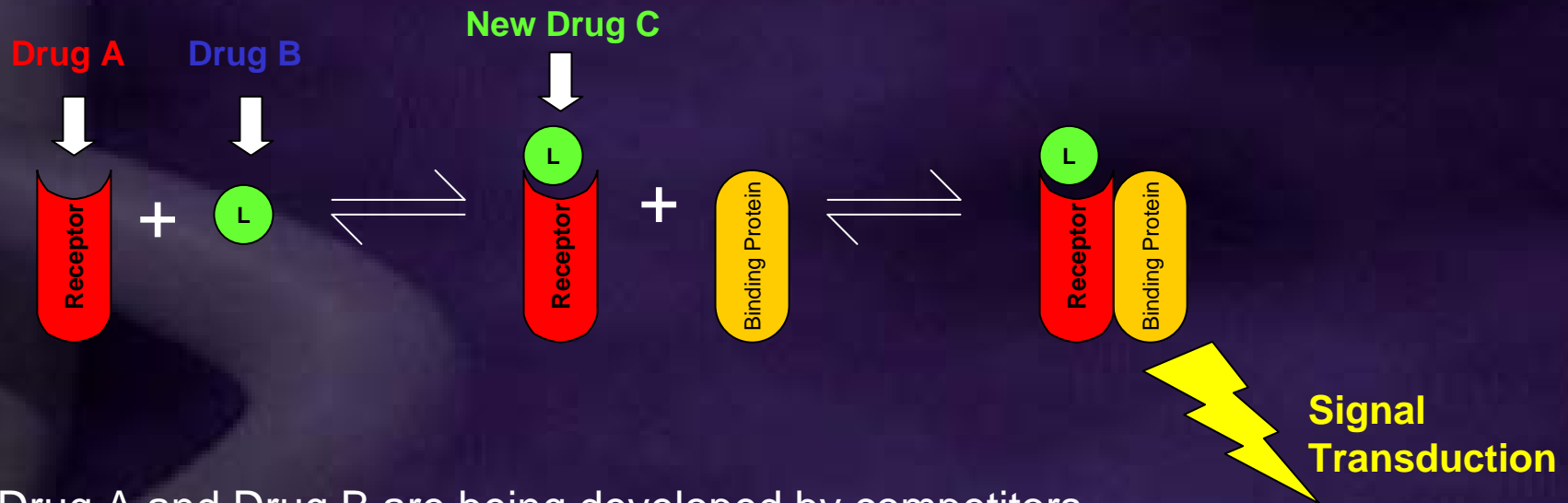
Fluorescent Microscopy tracking cellular internalisation of EGF &/ or EGFr



Cells with mutant ErbB1 receptors have an impaired ability to internalize, as suggested by simulations

Example 3:  
Evaluation of Biopharmaceutical  
Therapeutic Strategy

# Question from Research Team: Can a new therapeutic approach be more efficacious than drug A and B?



- Drug A and Drug B are being developed by competitors
- Drug A targets the receptor
- Drug B targets the ligand

➤ Can an antibody against the complex ligand -receptor be more efficacious?

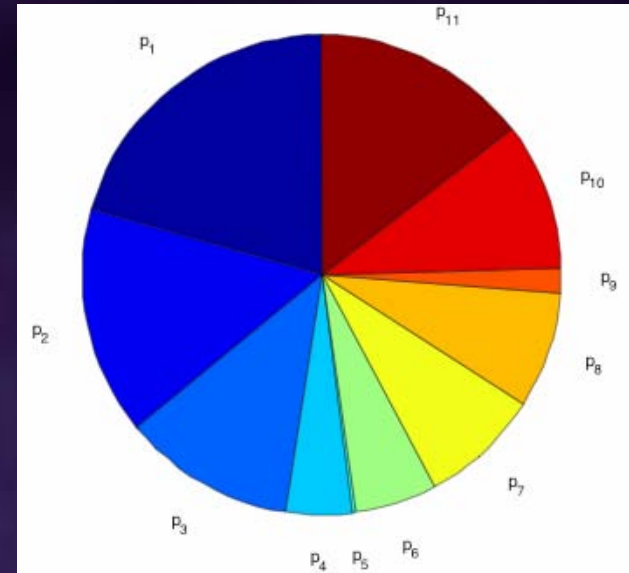
# In silico model of cell proliferation assay

---

- The biological components involved in the pathway were dynamically represented in a mathematical model
- The concentrations of each species and the reaction kinetics were obtained from:
  - Literature mining techniques (NLP)
  - Experimental measurement
- Model is then **CALIBRATED** and **VALIDATED** with experimental data
- The validated model is then used to **PREDICT** drug efficacy and rank drug strategies

# The impact of parameters uncertainties on model output was evaluated by sensitivity analysis

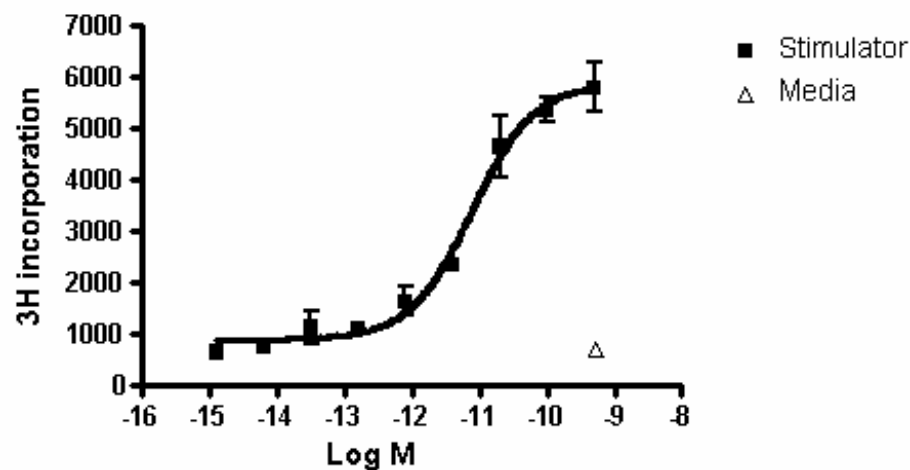
- Sensitivity analysis measures how the steady state output varies with each parameter value
- The parameters that had the biggest effect were deemed most sensitive, and were confirmed experimentally



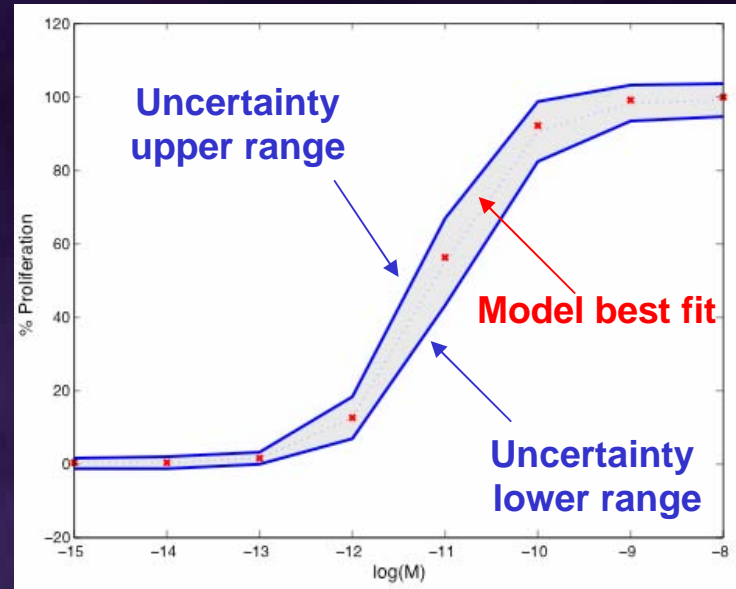
# Model was calibrated to *in-vitro* cell proliferation data

## Experimental Data

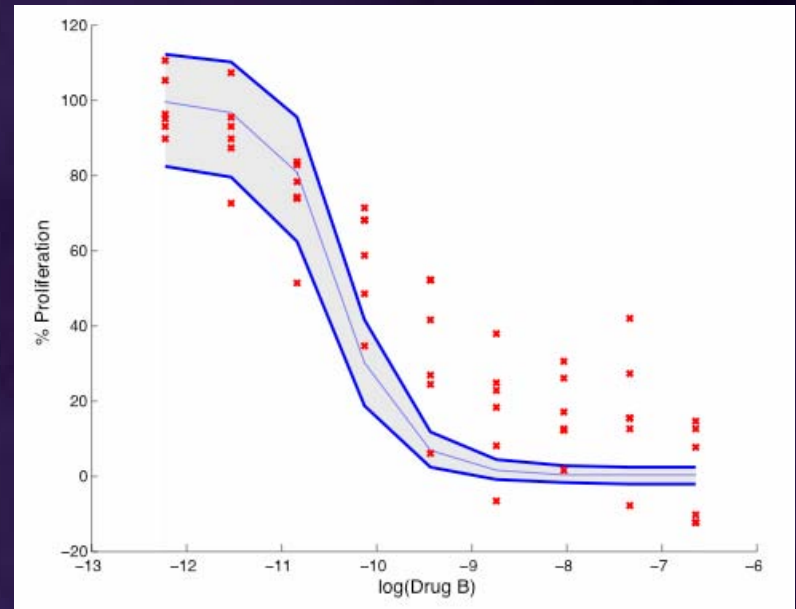
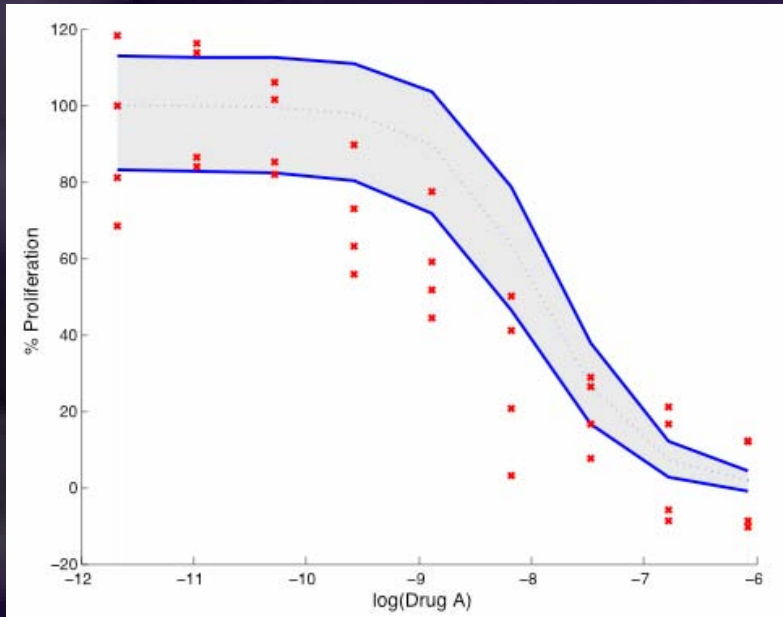
Titration of cell stimulator in cell proliferation assay



## Simulation results



# Model validation



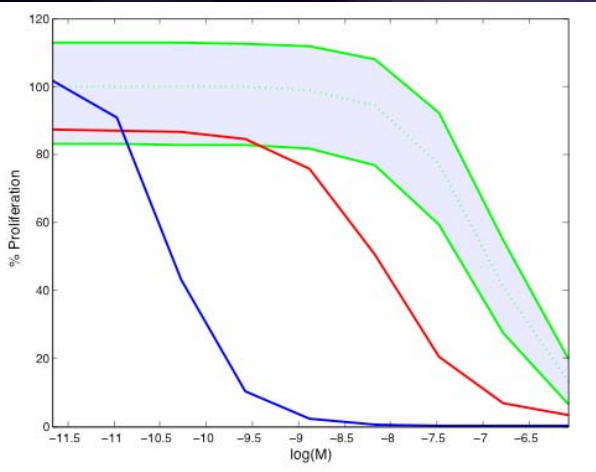
Drug A LogIC50		Drug B LogIC50	
<i>Experimental</i>	<i>Predicted</i>	<i>Experimental</i>	<i>Predicted</i>
-8.354	-8.4 (lower)	-9.974	-10.7 (lower)
-9.022	-7.5 (upper)	-10.26	-10.1 (upper)
		-10.15	



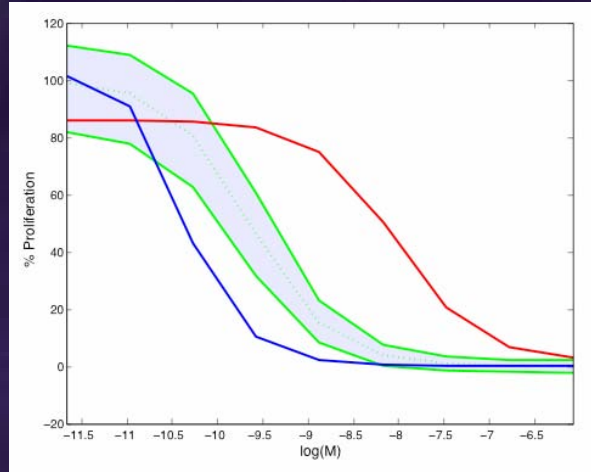
# Model prediction

- In the absence of compound, the model can predict how a novel therapeutic approach will compare to existing compounds

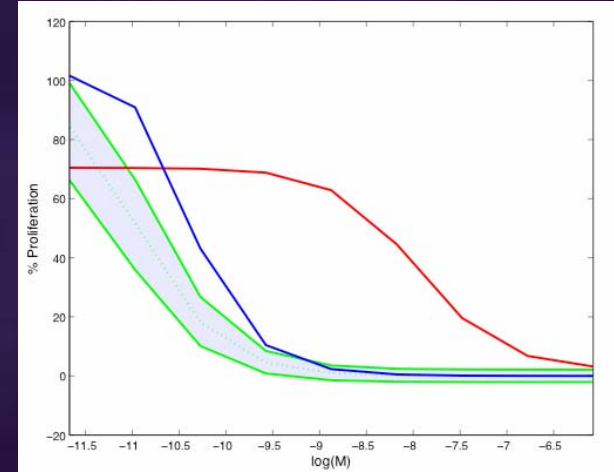
if  $K_d \text{ Drug C} = K_d \text{ Drug A}$



If  $K_d \text{ Drug C} = K_d \text{ Drug B}$



Required  $K_d$  for Drug C to outperform Drug A and B

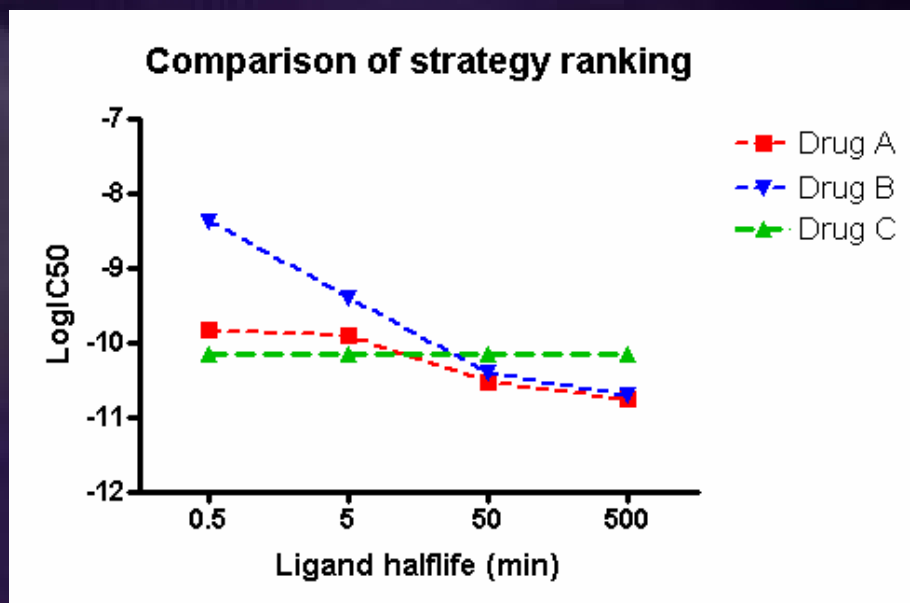


Drug A, Drug B, Drug C

# Model predictions

## *Impact of ligand turnover*

- Additional parameters were added to the model to recreate an *in vivo*-like context
- Impact of ligand turnover was evaluated on the compound ranking



- Ligand turnover can have a significant impact on compound ranking

# Conclusion

---

- Using an *in silico* model of cell proliferation, and in the absence of real compound, we were able to :
  - Compare a novel therapeutic approach to existing compounds
  - Defined the compound properties required to outperform competitor compounds
- This *in silico* approach allowed the evaluation of the therapeutic approaches in an *in vivo*-like context and showed that ligand turnover can have a significant impact on the compound ranking.

# Systems Biology Impact

---

- Leverage from different types of data generated
- Focus experimental/ development and clinical work
- Quicker than traditional approaches
- Applicable to all stages of Drug Discovery and Development
- Support decision making

# Systems Biology Challenges

---

- Setting the right expectations
- Robustness of models
- Approach not fully adopted yet
- Requires a new type of skillset

# Acknowledgements

---

- All members of the Pathways Capability & AZ project teams
- Doug Lauffenburger Lab, MIT
- Bart Hendriks
- Lead Pathways Scientists:
  - Dave Cook, Jack Beusmans, John Williams, Rob Tonge, Janice Nickson, Jonathan Swinton, Dougie Paterson