Systems Biology in Drug Discovery & Development: Impact and Challenges

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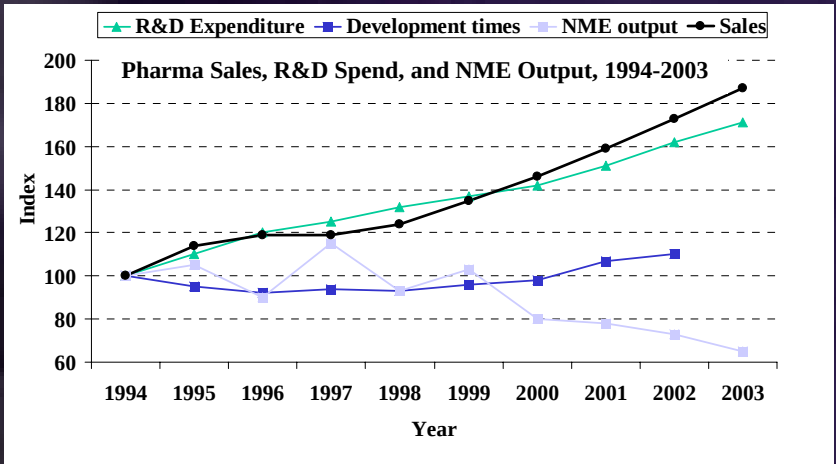
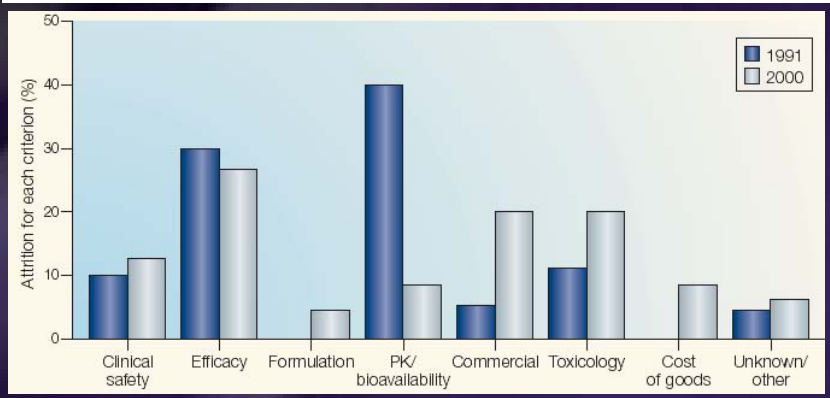
Pathways Capability

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

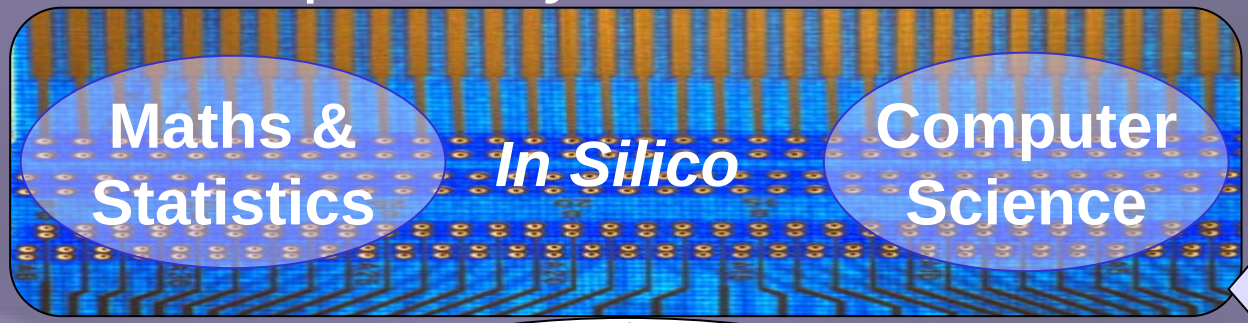
Post-Genome Issues

- 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



Model

Engineering

Experiment

Pathway Analysis

Wet Lab

Quantitative Biology

- 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

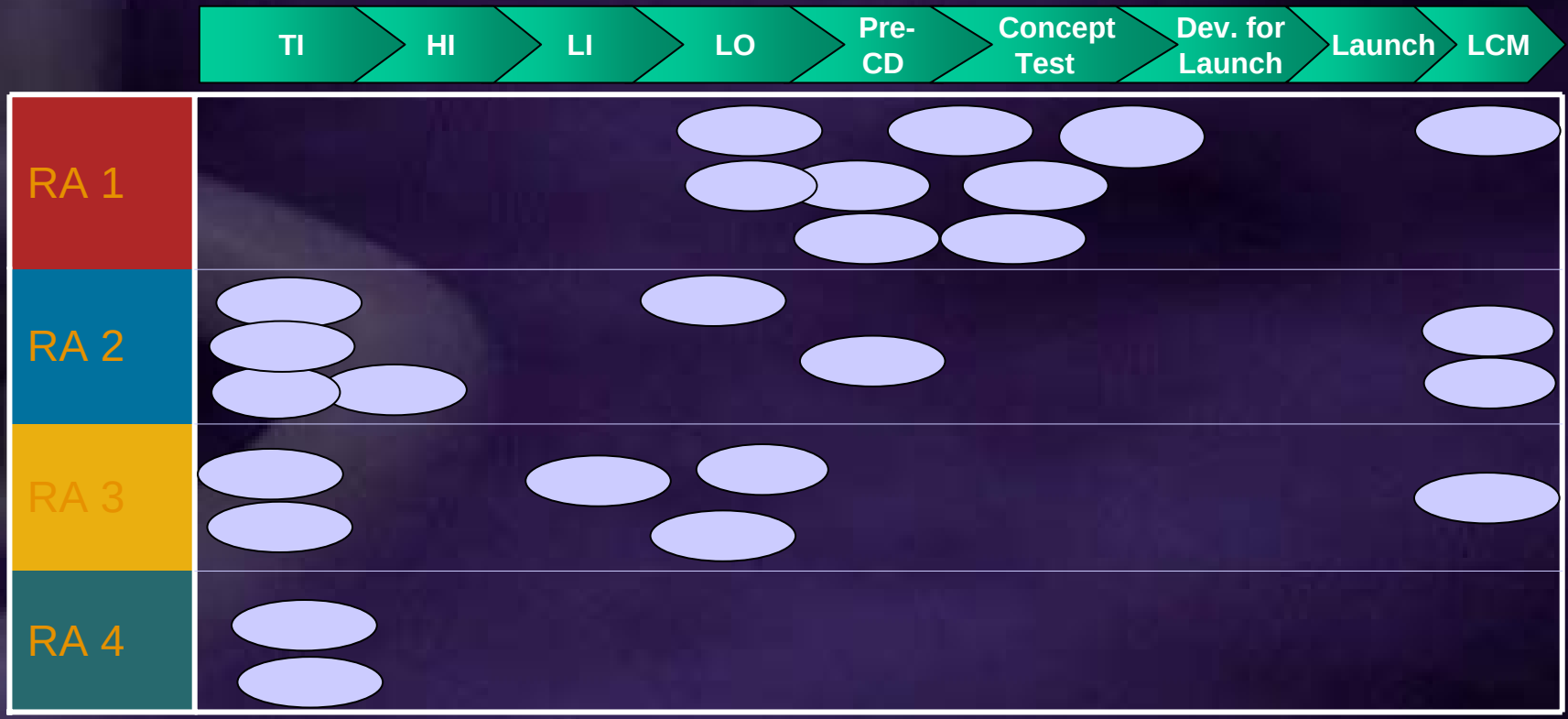
Compound Evaluation/Selection

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.

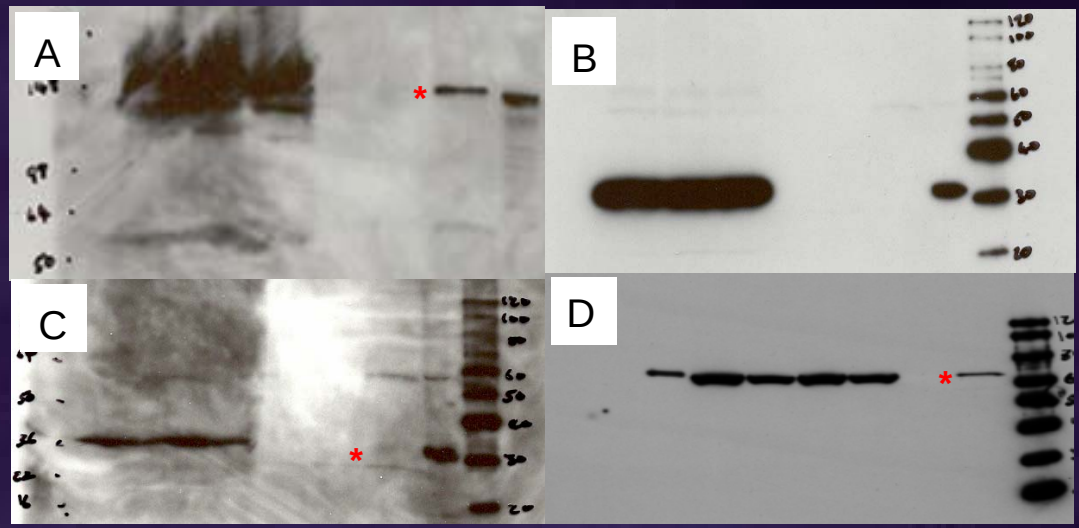
Primary data generation & analysis

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

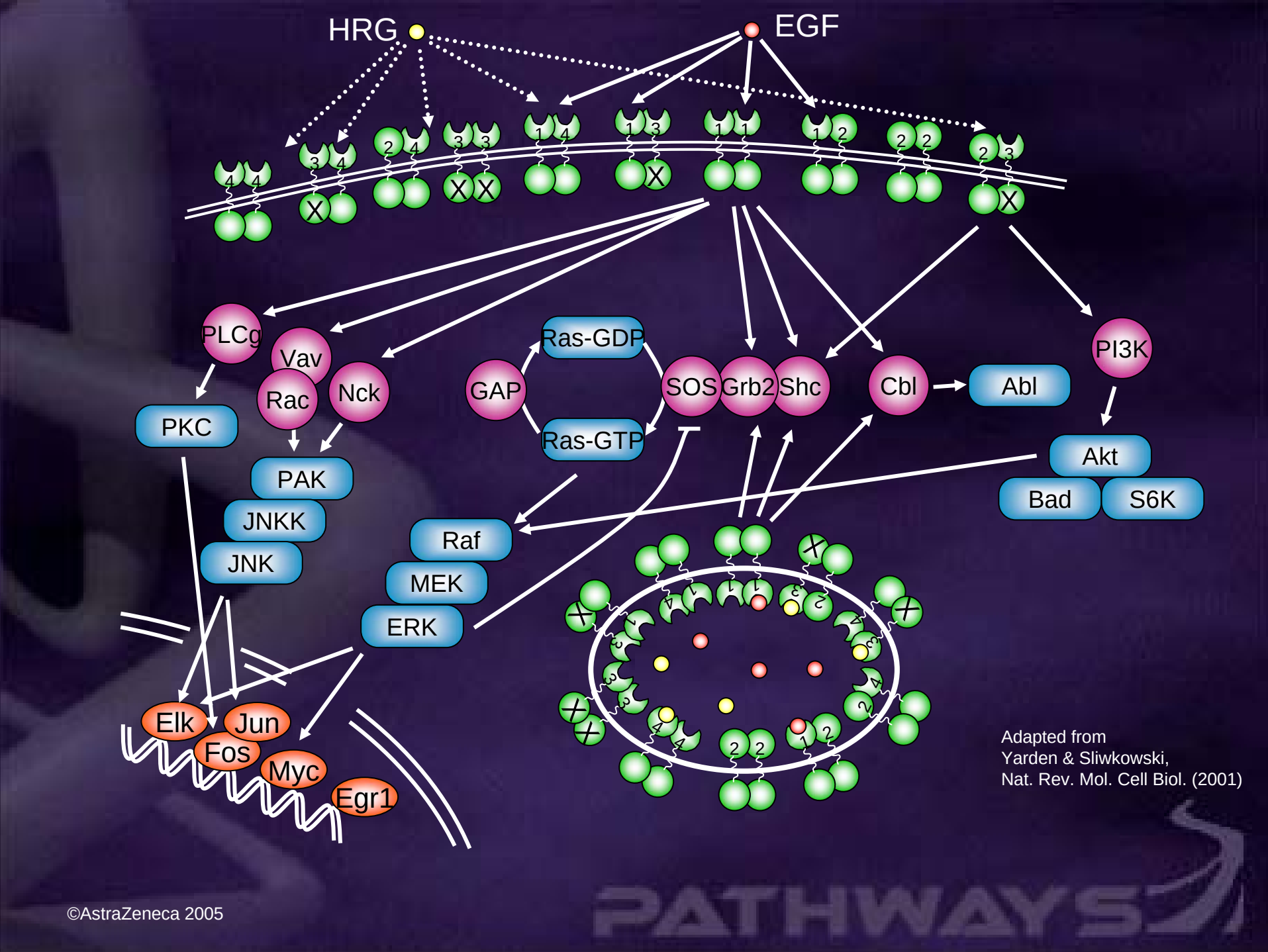


Delivery to Discovery Team

- 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


HRG
EGF
PLCg
Vav
Rac
Nck
PKC
PAK
JNKK
JNK
Ras-GDP
GAP
Ras-GTP
SOS
Grb2
Shc
Cbl
Abl
PI3K
Akt
Bad
S6K
Raf
MEK
ERK
Elk
Jun
Fos
Myc
Egr1
Adapted from
Yarden & Sliwkowski,
Nat. Rev. Mol. Cell Biol. (2001)
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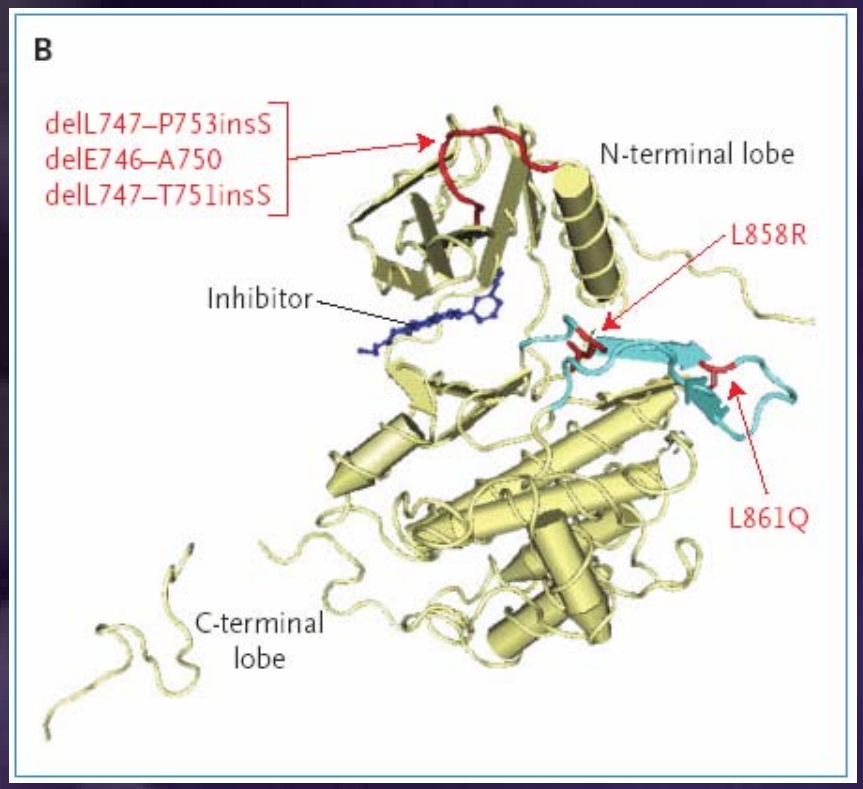
ErbB Mutants



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

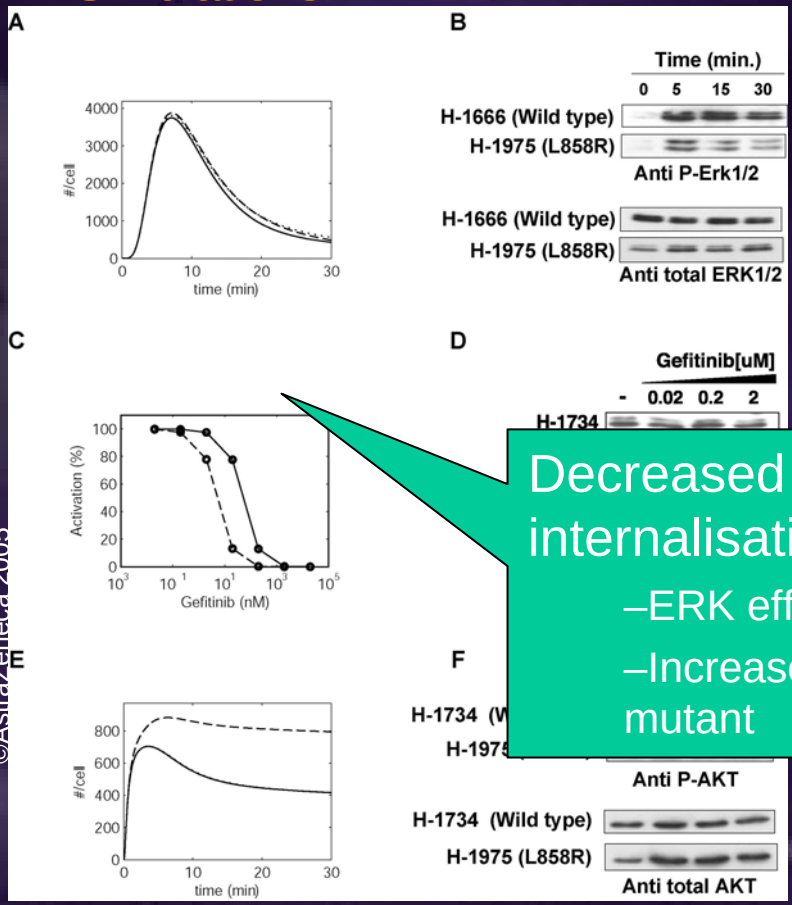
Questions

- 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

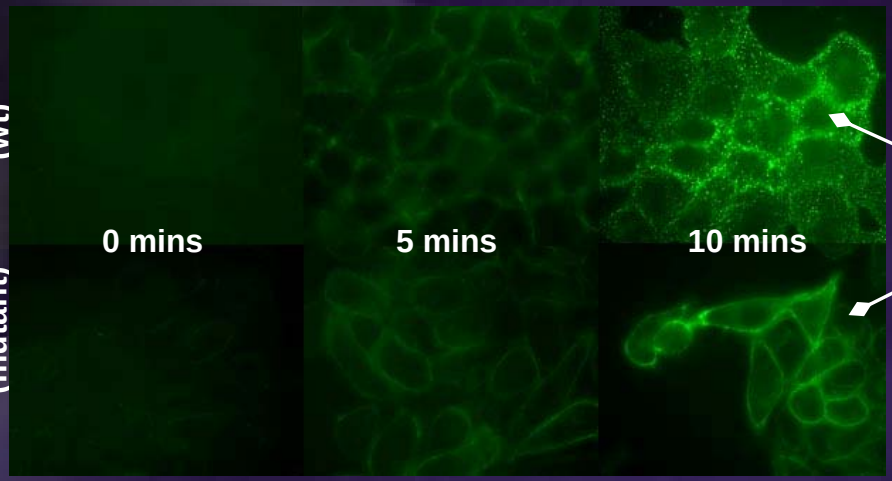


Decreased receptor internalisation explains

- –ERK effects
- –Increased AKT activity in mutant

Experimental Verification:

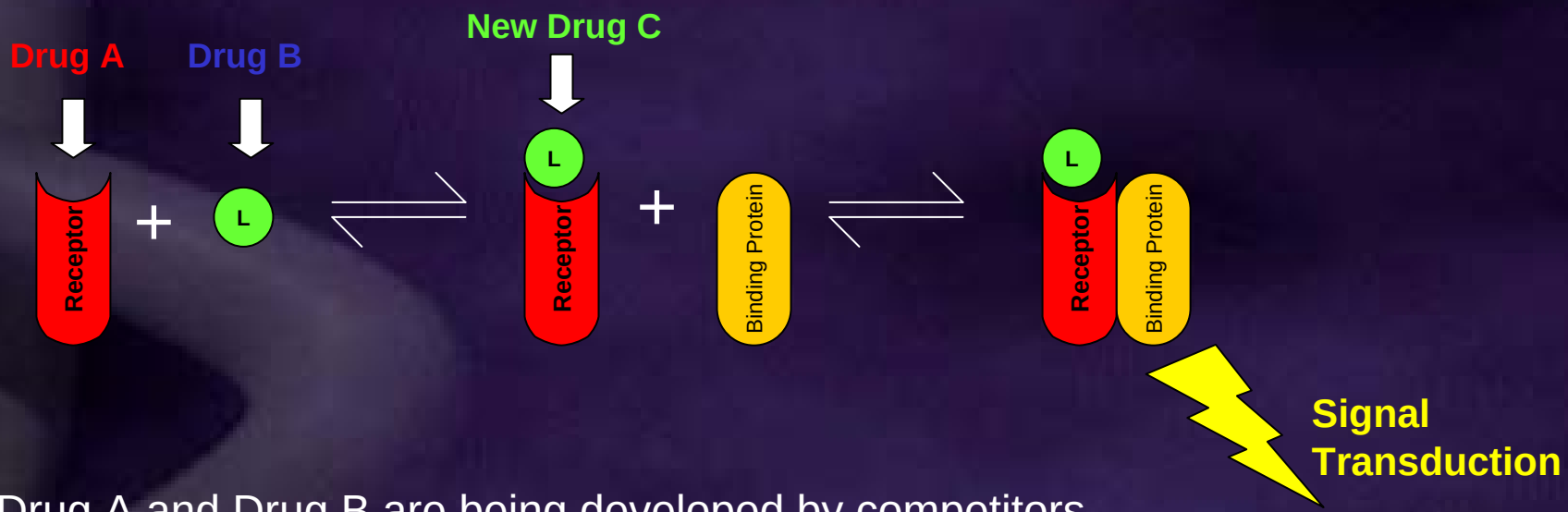
Fluorescent Microscopy tracking cellular internalisation of EGF &/ or EGFr



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

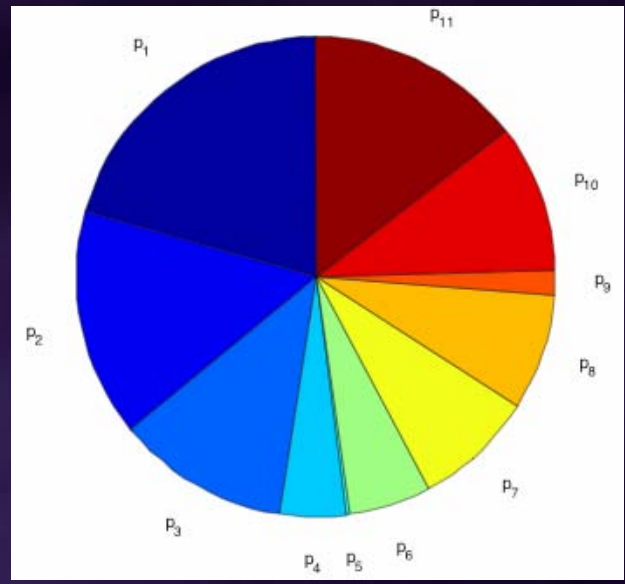
➢Can an antibody against the complex ligand -receptor be more efficacious?

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

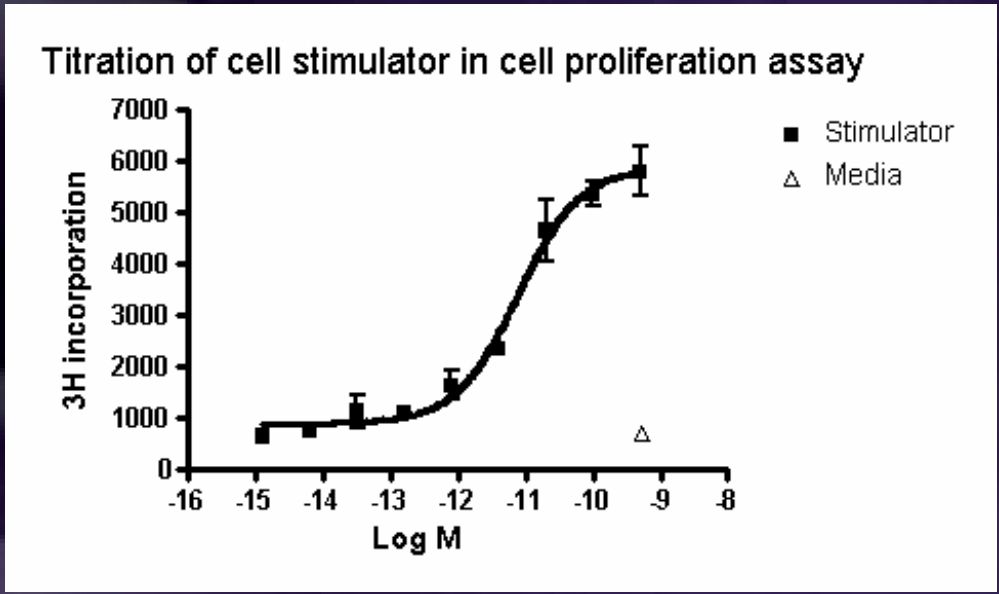
The impact of parameters uncertainties on model output was evaluated by sensitivity analysis

- 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

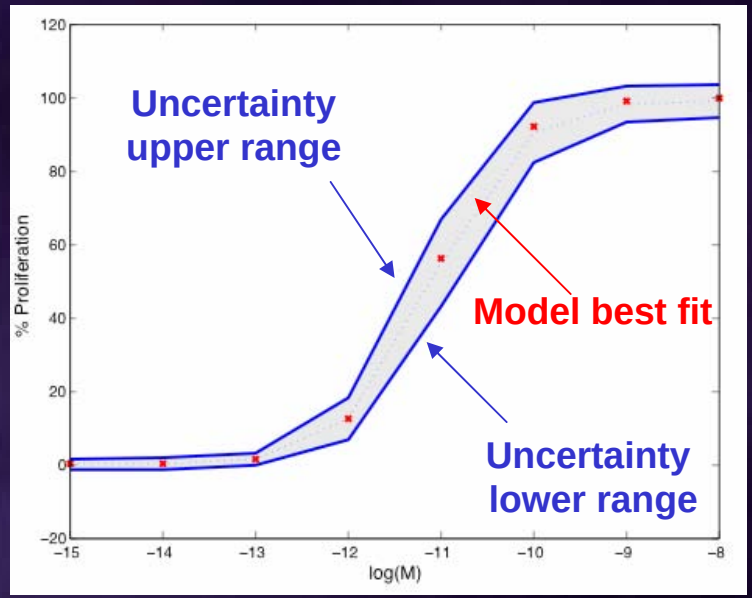


Model was calibrated to *in-vitro* cell proliferation data

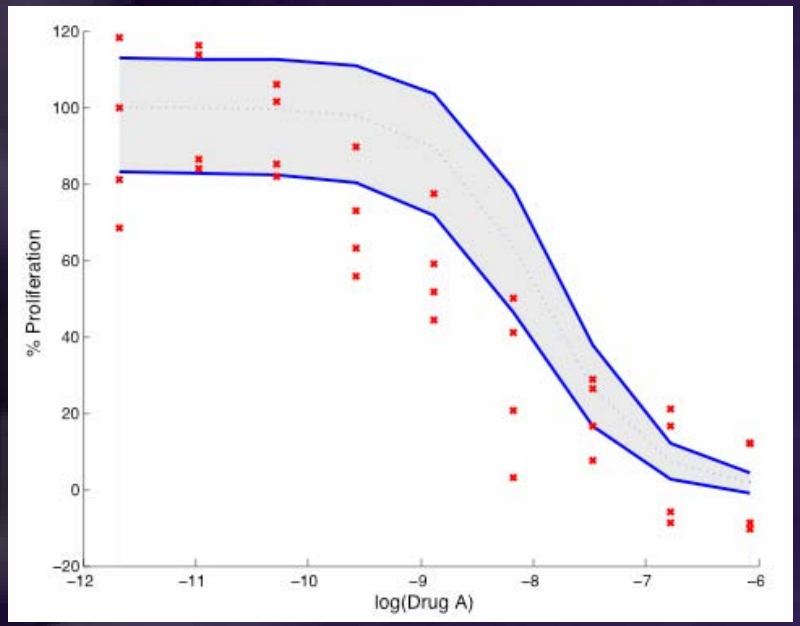
Experimental Data

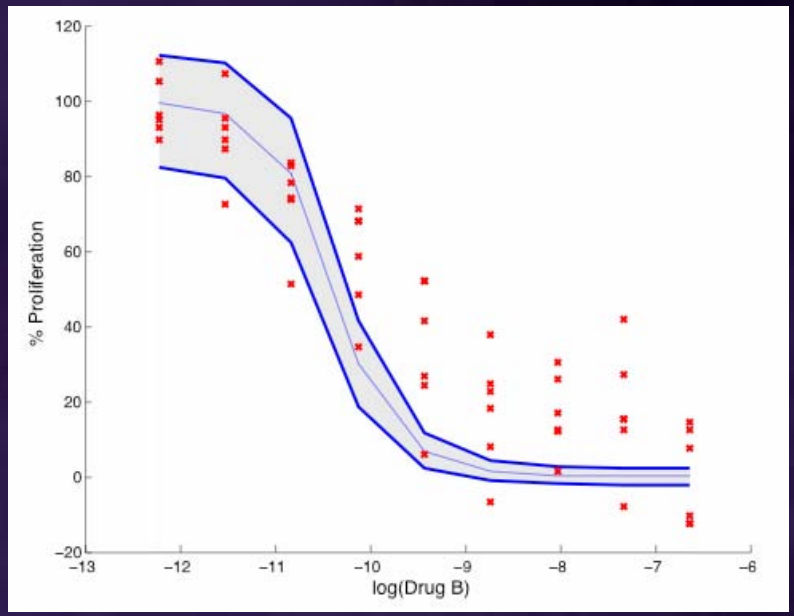


Simulation results



Model validation



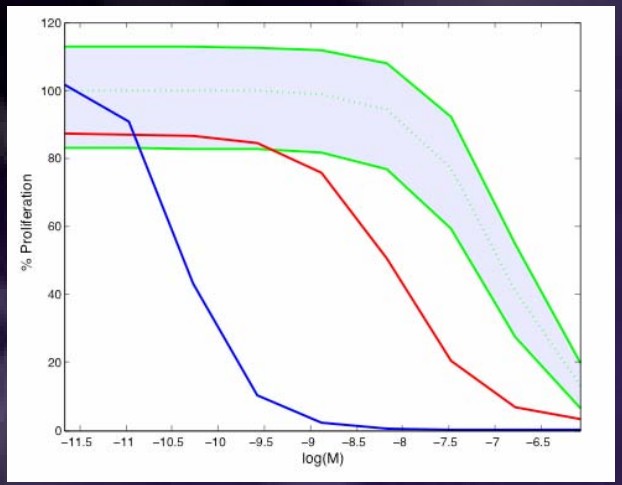


Drug A LogIC50		Drug B LogIC50	
Experimental	*Predicted*	*Experimental*	*Predicted*
-8.354 -9.022	-8.4 (lower) -7.5 (upper)	-9.974 -10.26 -10.15	-10.7 (lower) -10.1 (upper)

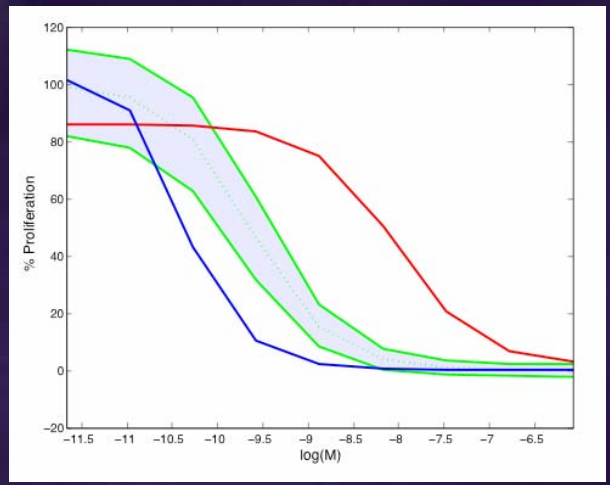
Model prediction

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

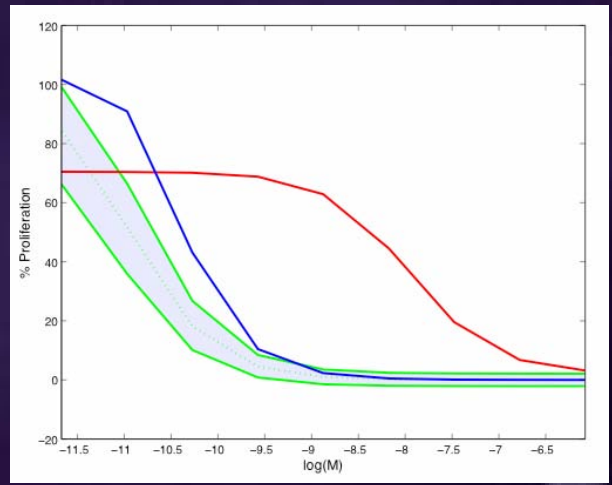
if Kd Drug C=Kd Drug A



If Kd Drug C=Kd Drug B



Required Kd for Drug C to outperform Drug A and B

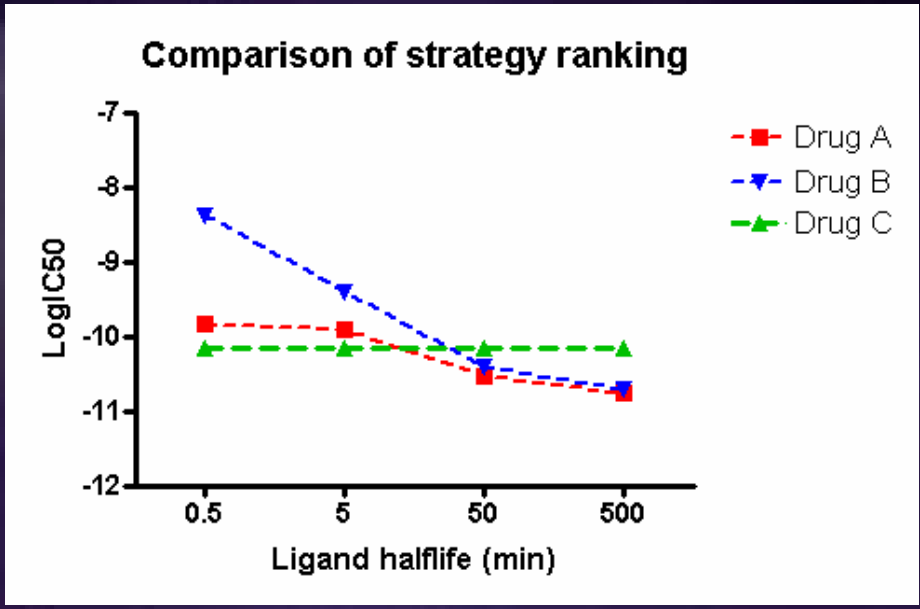


Drug A, Drug B, Drug C

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

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