The Technology is the Target

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April 2015

Synopsis

- Introduction
- Research overview
  - Cancer Research UK Formulation Unit
  - EU IMI – OrBiTo
- Current directions – cancer research & treatment
- Future issues

Gavin Halbert

- Pharmacist, Chemist & Qualified Person
  - Graduated 1979
- Director, Cancer Research Formulation Unit – 1992
  - Started in 1983
- Drugs into patients
- Range of formulation and product experience

Pharmacy is about making things! – Dr Alan Baillie ad nauseam

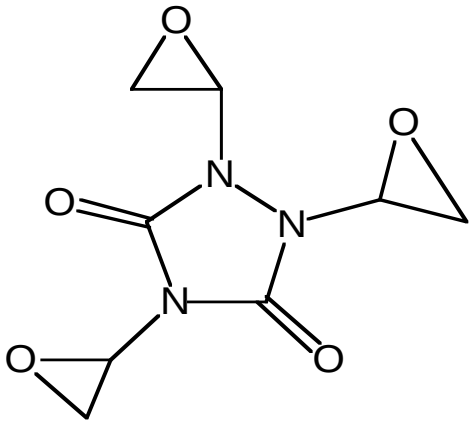
CANCER RESEARCH UK

My first encounter

- 1984 - 1, 2, 4-triglycidyl urazol - Limited solubility & stability
  - Would not dissolve at patient's bedside!

- Formulation and manufacture, Strathclyde
- Clinical trial in Beatson, Glasgow

- Phase 1 IV bolus in saline
- Starting @ 30mg/m^2 escalating to 900 mg/m^2
- MTD 800 mg/m^2
- 2 partial responses
- Half-life 2.1 min



Cancer Chemother Pharmacol (1984) 12: 198–200

Cancer Chemotherapy and Pharmacology

The analysis and animal pharmacokinetics of 1,2,4, triglycidyl urazol using a high-pressure liquid chromatographic technique

J. Welsh[1], J. F. B. Stuart[1,2], A. Setanoians[1], R. G. G. Blackie[1], P. Billiaert[1,2], G. Halbert[1], and K. C. Calman[1]

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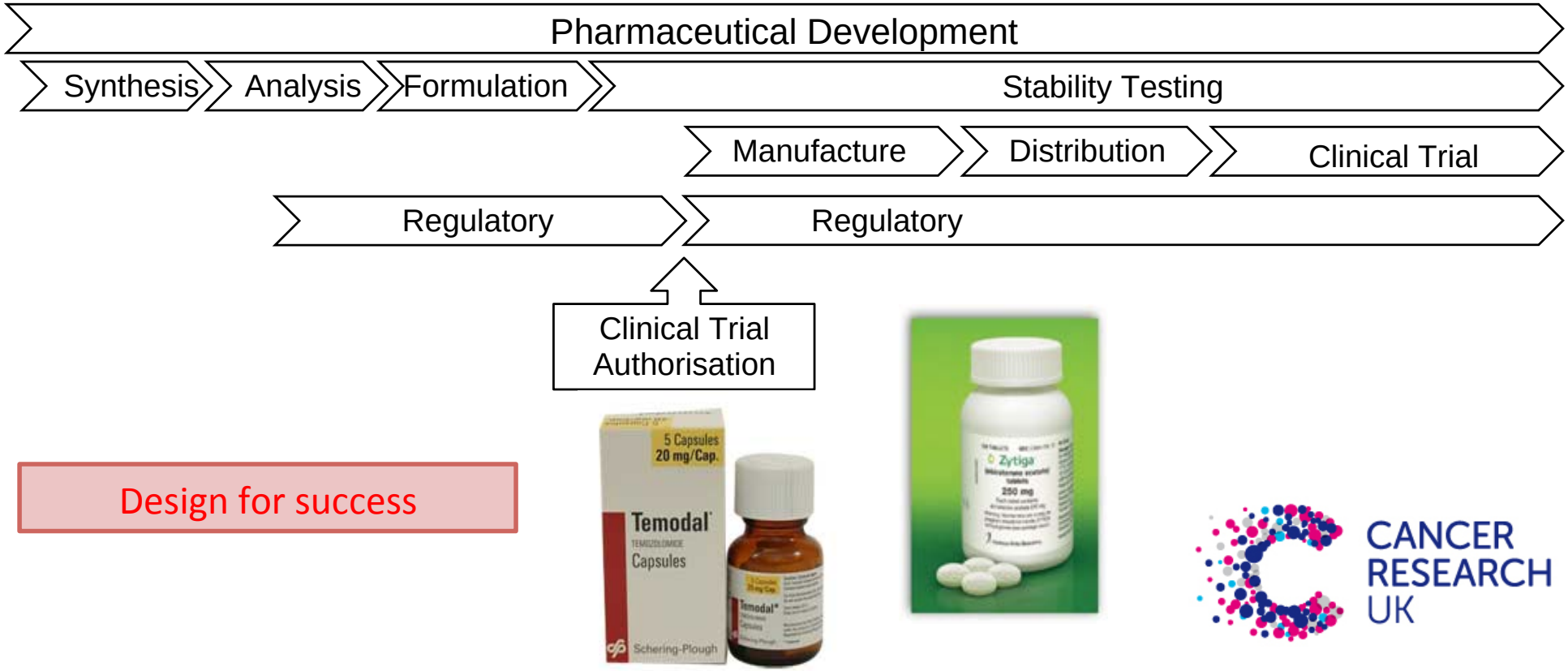
[2] Department of Pharmaceutics, University of Strathclyde, Glasgow, Scotland

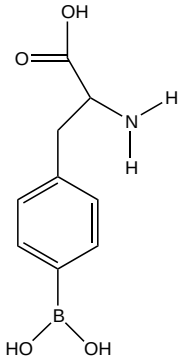
Cancer Research UK Formulation Unit

- Bench to Bedside / Powder to Product / Molecule to Medicine
  - Pharmaceutical translational research

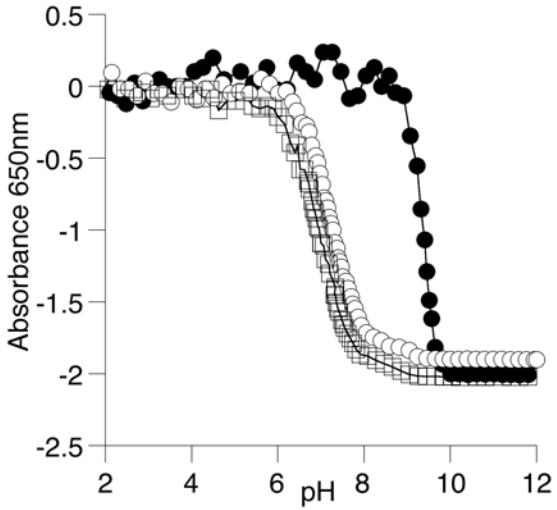


Formulation Unit Research

- Boronphenylalanine
  - 900mg/kg dose
- Solubility
  - Free drug 1g/L
  - Fructose complex 30g/L
  - Mannitol complex 100g/L



Precipitation of boron phenyl alanine

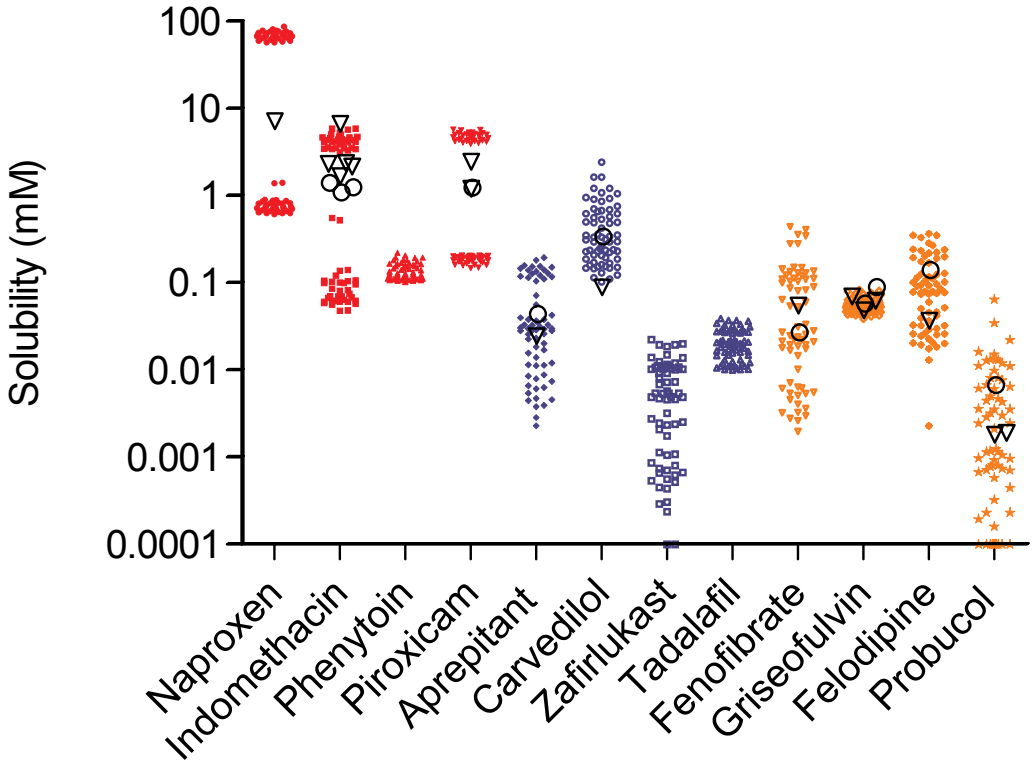


European Union Innovative Medicines Initiative
Oral Biopharmaceutical Tools

- Prediction of in vivo performance from in vitro data
  - Poor – or hit and miss
- Current new drug candidates
  - Physicochemical issues
    - Solubility – affects dissolution – biopharmaceutical performance
- Research into new predictive tools
  - Enhance Biopharmaceutics Classification System
- Consortium of University and Academic researchers
  - October 2012

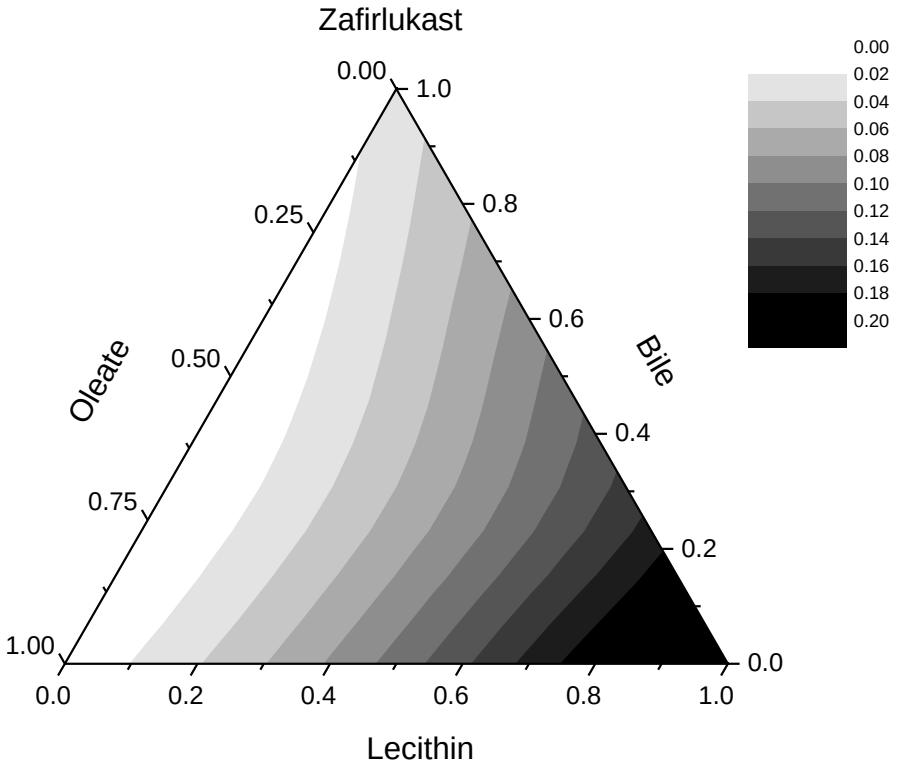
Biopharmaceutical Research

- Influence of media composition on equilibrium solubility
  - 8 factors & 2 levels or concentrations



Biopharmaceutical Research

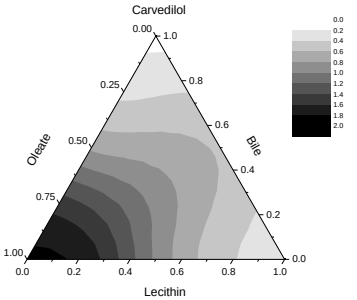
- Influence of media composition on equilibrium solubility
  - Phase diagram – biorelevant surfactants



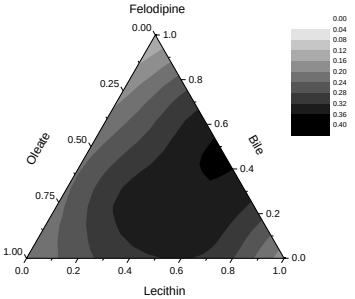
Biopharmaceutical Research

University of Strathclyde Science

Carvedilol

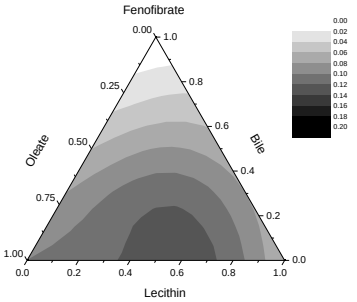


Felodipine

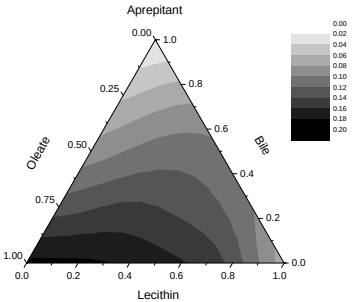


No two drugs are the same!

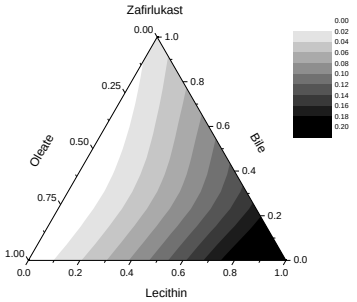
Fenofibrate



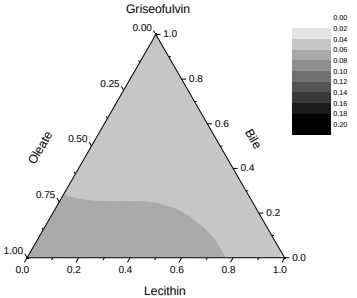
Aprepitant



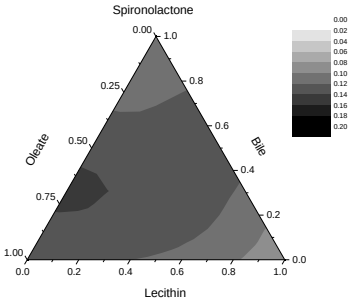
Zafirlukast



Griseofulvin



Spironolactone



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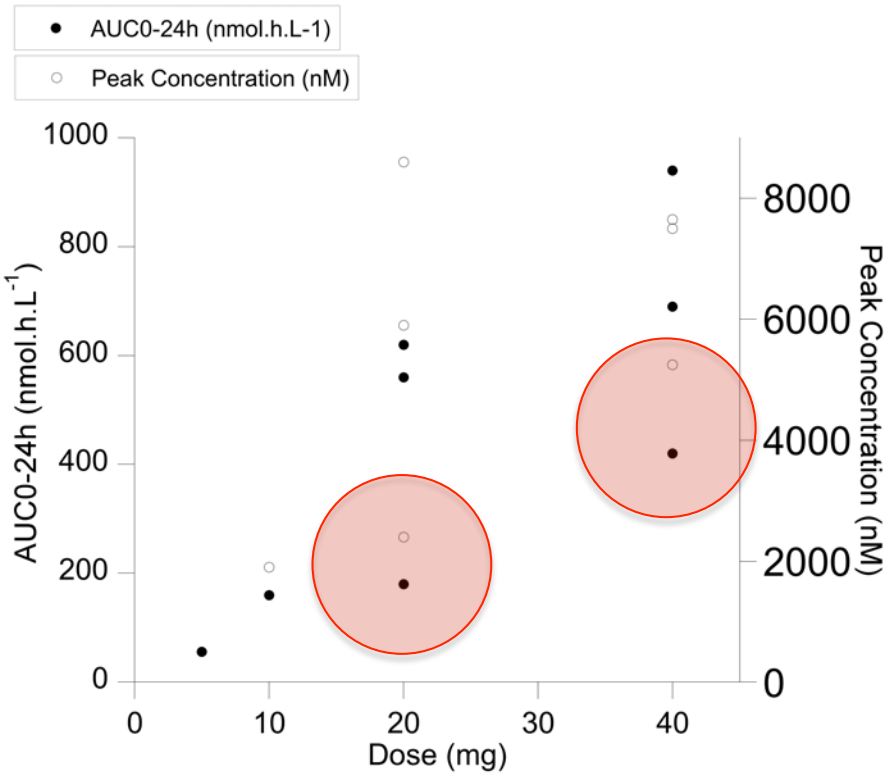
Formulation Unit Research

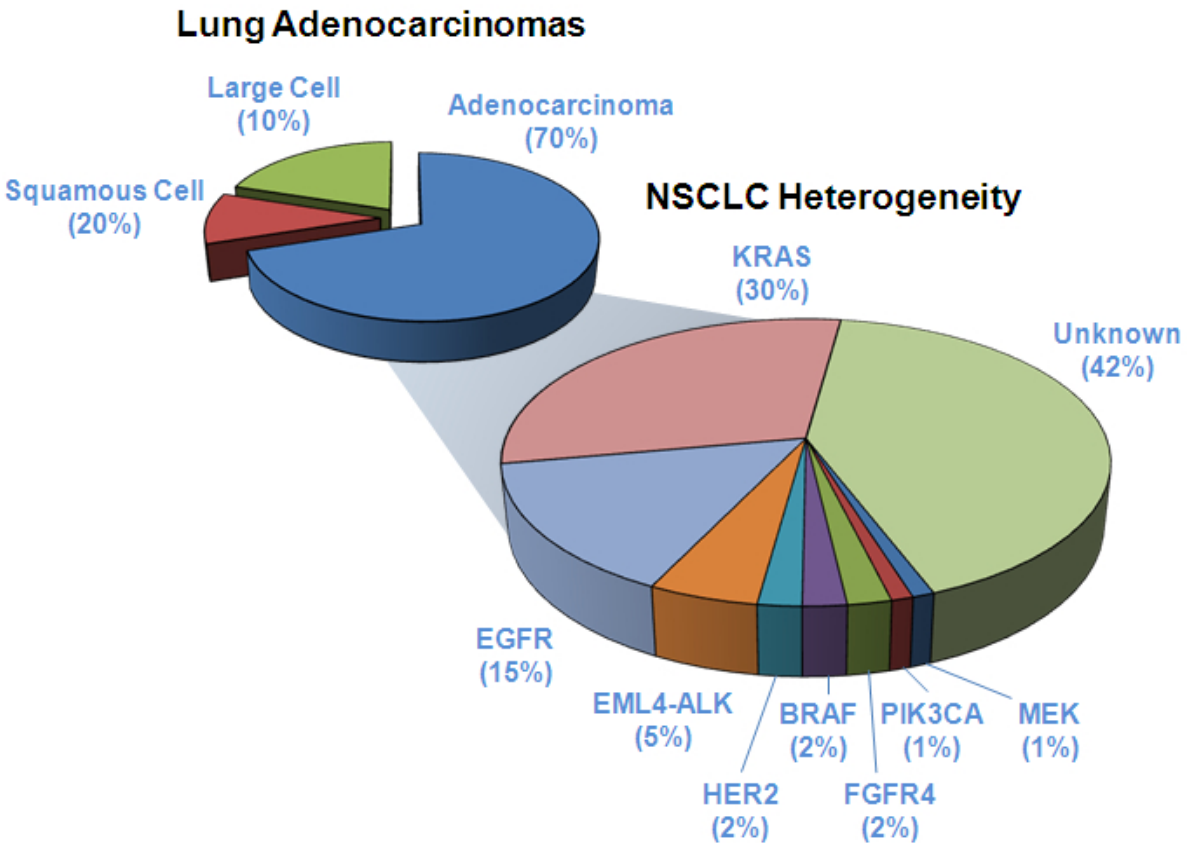
- Tyrosine Kinase Inhibitor
  - Weak base
  - Low solubility
- Bioavailability
  - Stomach acid dissolution dependent



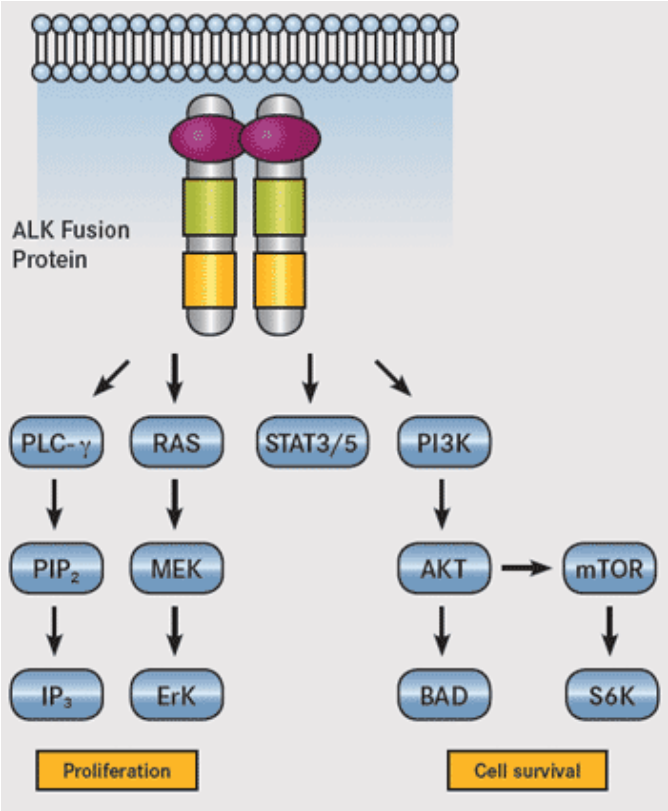
Transparent Formulation

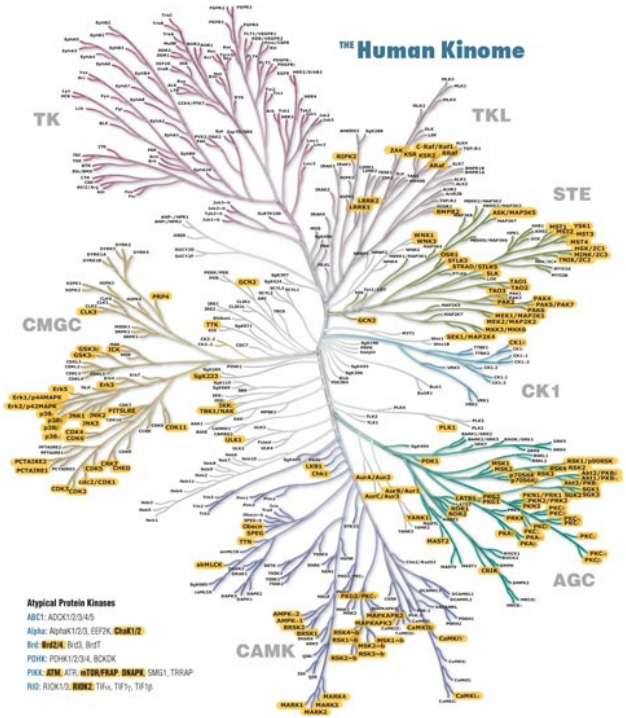
Science of cancer

- Non-Small Cell Lung Cancer – 30,000 cases per year (80% of cases)
- ALK mutation 5% - 1,500 patients per annum

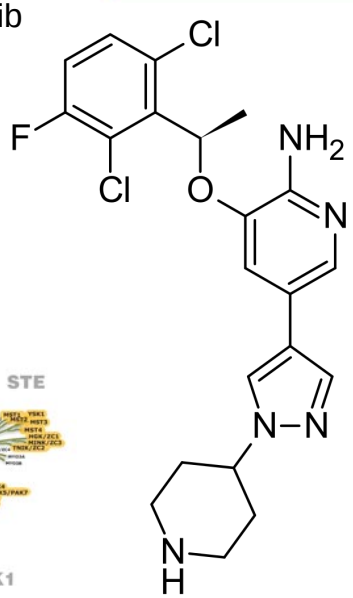


Anaplastic Lymphoma Kinase





crizotinib



Human kinome ≈ 500 enzymes
2% of human genes
Influences 30% human proteins

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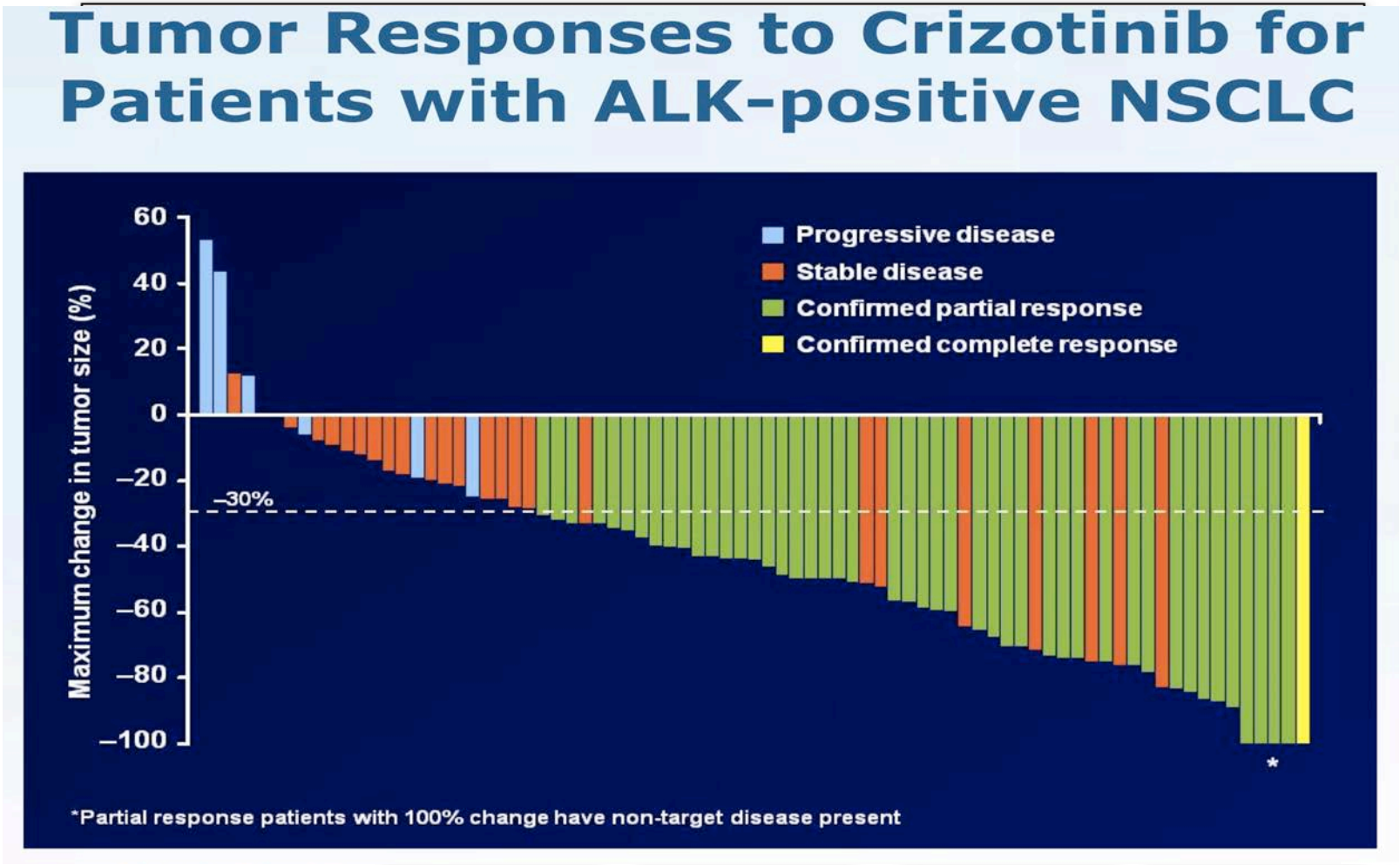
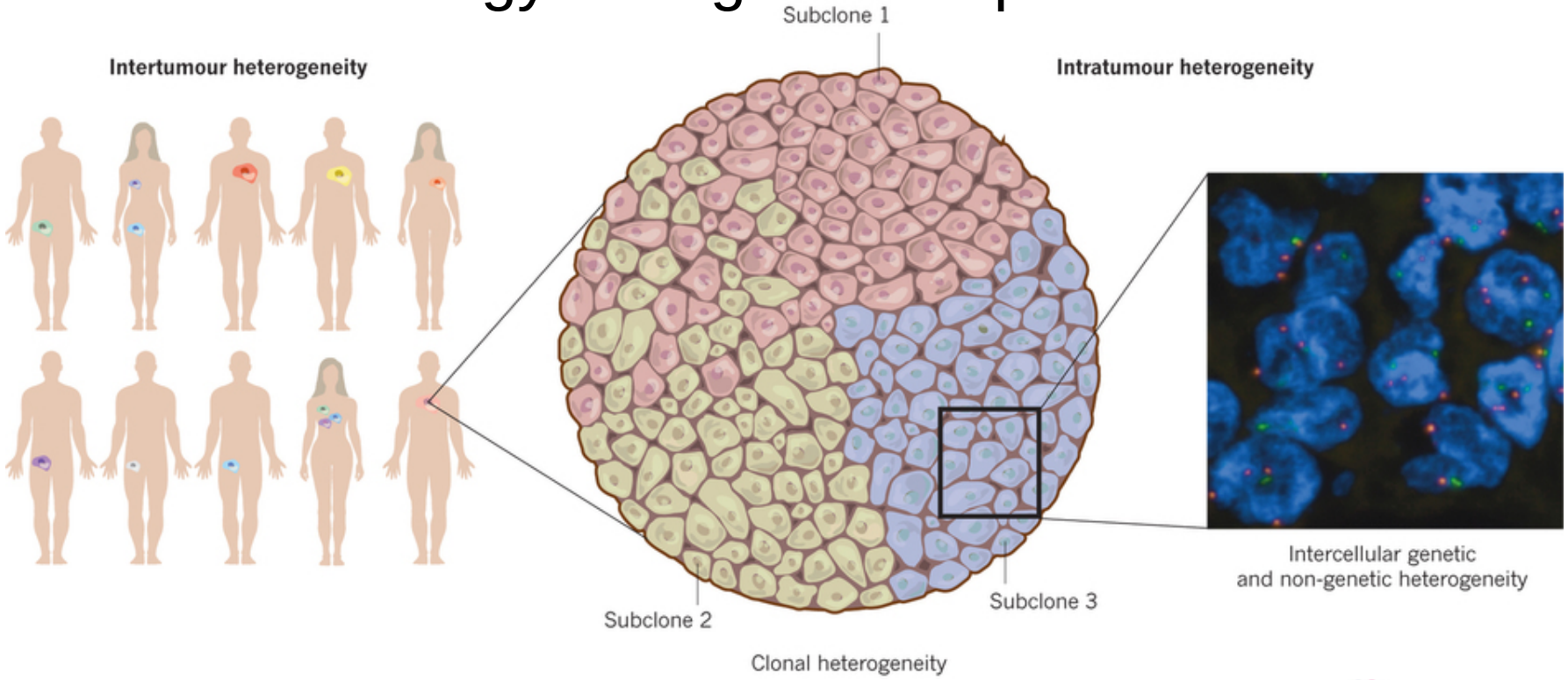
Stratified Medicine



Response Rate 50%

Treatment in Practice

- Tumour heterogeneity
- Tumour biology changes in response to treatment



Burrell, R., et.al., Nature 2013, 501, 38–345

Basic Arithmetic

30,000 NSCLC patients per annum
5% = 1,500 ALK positive patients
50% response = 750 patients/year
Average Drug Development Cost = £2 billion

Current Formulation Unit Project – 300 patients per annum

Need to do More to Achieve Less

Future Issues

Paradigm Shift Required

Acknowledgements

- Cancer Research UK Formulation Unit Staff
  - Many and varied since 1992
- Cancer Researchers and Clinicians
- Cancer Patients
- Pharmaceutical Scientists
- Cancer Research UK for Funding

Thank you

- Questions