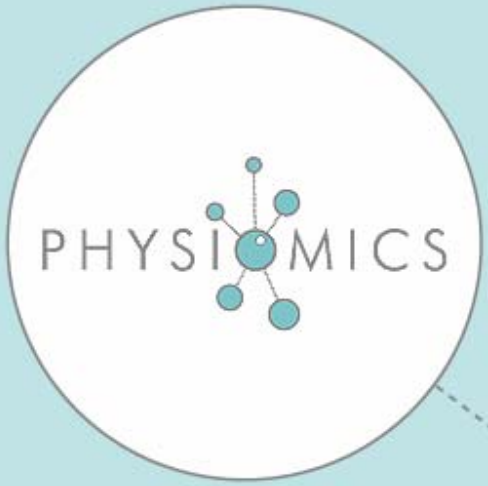


An Introduction to Physiomics

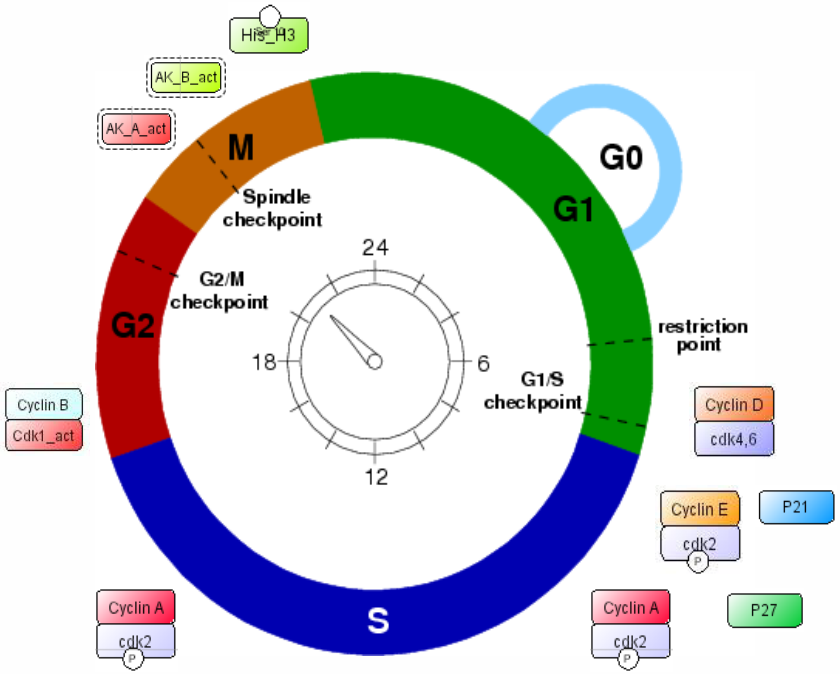
BioTuesday - Physiomics 20/02/07

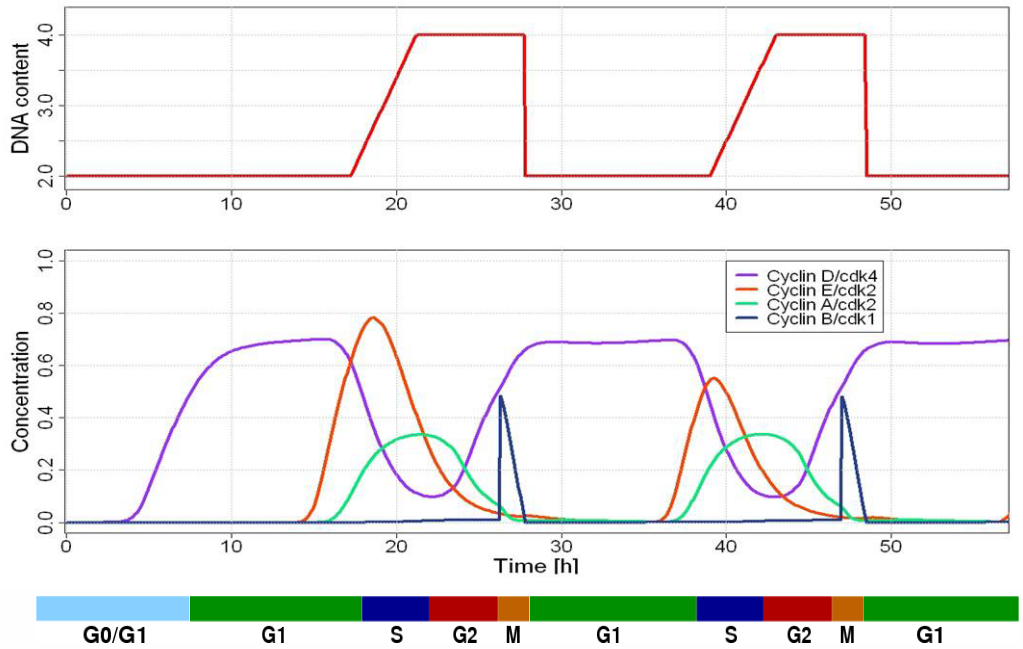
Prof David Fell, CSO

Physiomics plc

- **Aim: to balance risk and optimise investment in drug development by introducing integrative computational Systems Biology**
- **Founded 2001; UK-based; London Stock market listed 2004**
- **Focus on cancer**
- **Core technologies**
  - Cell cycle model; physiological whole body PK models (via BTS collaboration)
  - Patented software for creating "cell" populations (SystemCell® software)
  - Experience in applying simulation to pharmaceutical problems
- **Business: sell consultancy; joint development; license technology**
- **Collaborations:**
  - Bayer Technology Services
  - Cyclacel
  - Cronos Therapeutics (ValiRx)
  - Institute of Life Science, Swansea University (HPC)
  - EU contract (project Tempo)

Cell Cycle Model





Schematic representation of the cell cycle and its main players.

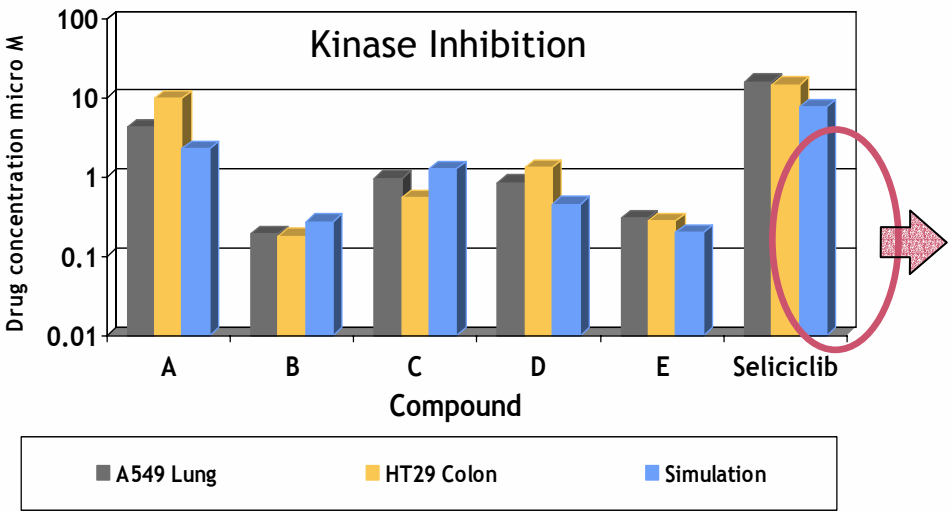
Two wild-type mammalian cell cycles starting from G0 arrest: DNA replication (top) and time courses of cyclins E, D, A & B in complex with cdks (bottom) are shown.

Case Study: Cyclacel CDK inhibitors Data Set - Different Activity Profiles

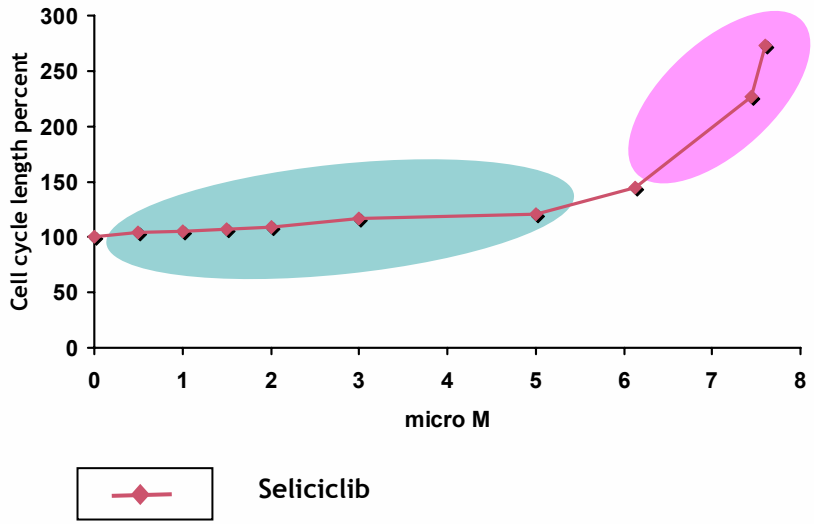
Molecule	Ki (μM)						Cytotoxicity (IC50, μM)	
	CycB-CDK1	CycA-CDK2	CycE-CDK2	CycD-CDK4	CycH CDK7	CycT CDK9	A549 Lung	HT29 Colon
A	0.200	0.002	0.001	0.540	0.300	0.480	4.23	9.90
B	0.330	0.420	0.109	0.003	0.019	0.029	0.19	0.18
C	33.898	0.481	0.104	1.430	0.126	0.002	0.96	0.54
D	0.022	0.060	0.028	0.018	0.028	0.001	0.85	1.32
E	0.451	1.059	0.149	0.068	0.002	0.000	0.30	0.28
Selicilib	0.909	0.065	0.003	7.692	0.023	0.244	15.90	14.60

Model Predicts the Right Cytotoxicity and the Dose Response (Cyclacel CDK inhibitors)

Different cytotoxic profiles predicted…



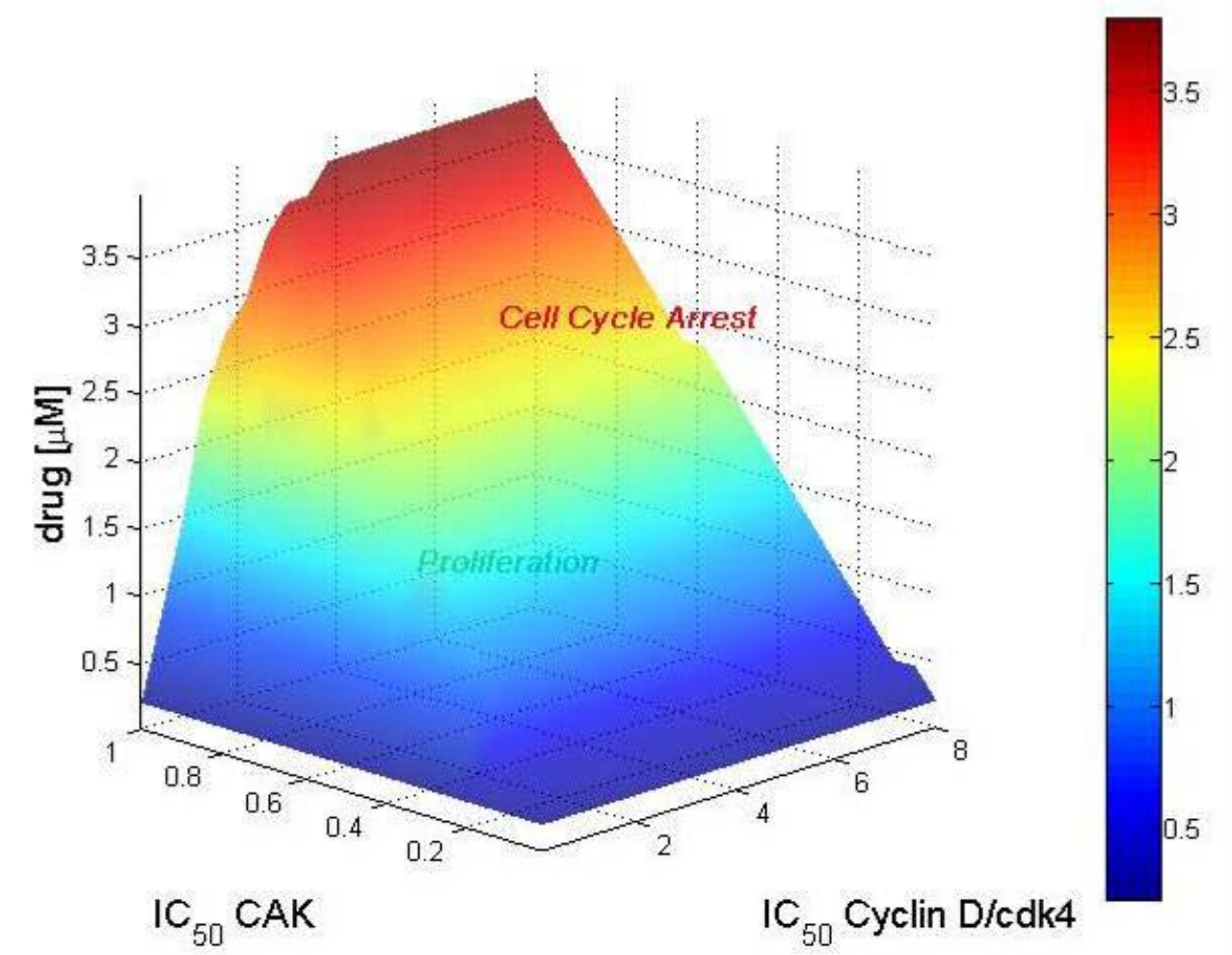
…giving dose response prediction



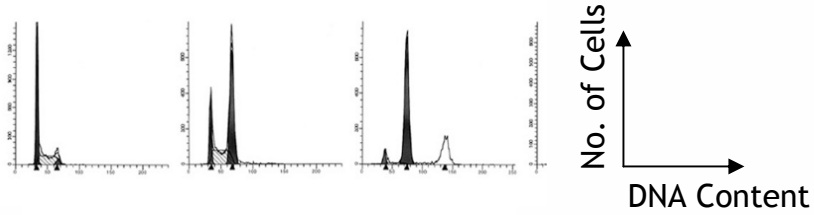
The cytotoxicity assay yields a dose-response curve for the phase II drug (Seliciclib).

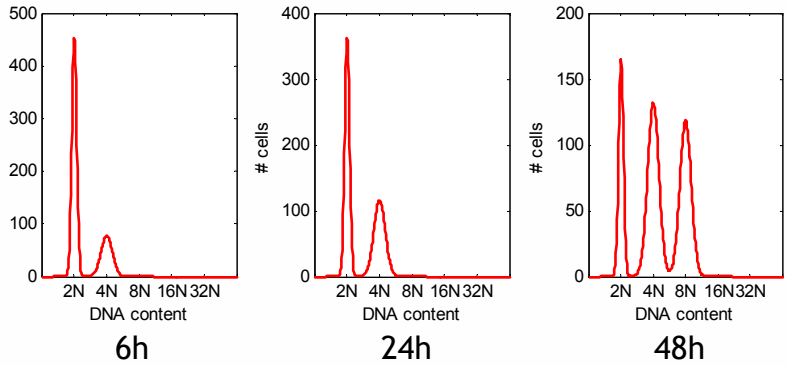
→ There exists only a narrow window where cell cycle time prolongation is observed.

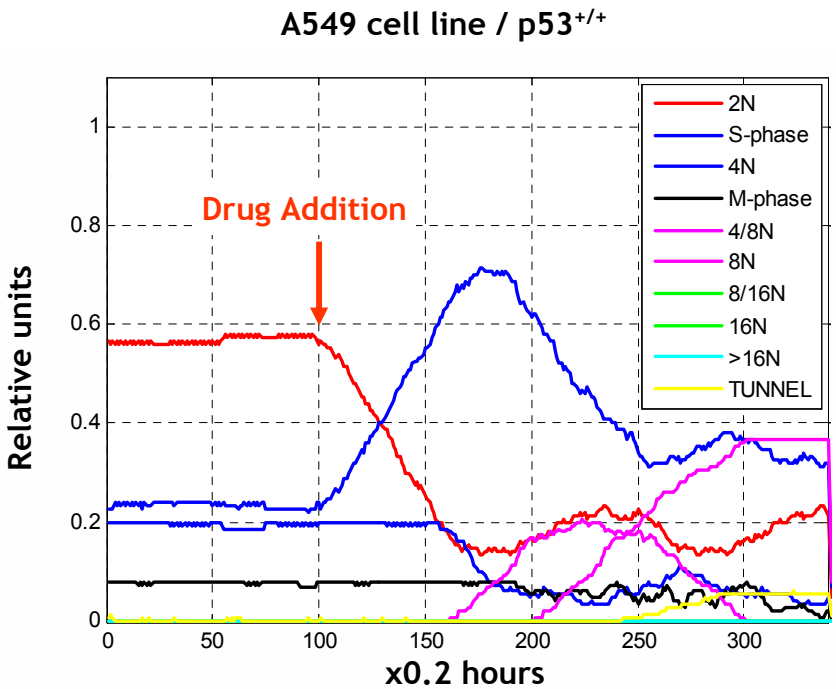
Going further: dual pure inhibitor scan CyclinD-cdk4 - CAK (CycH/cdk7)

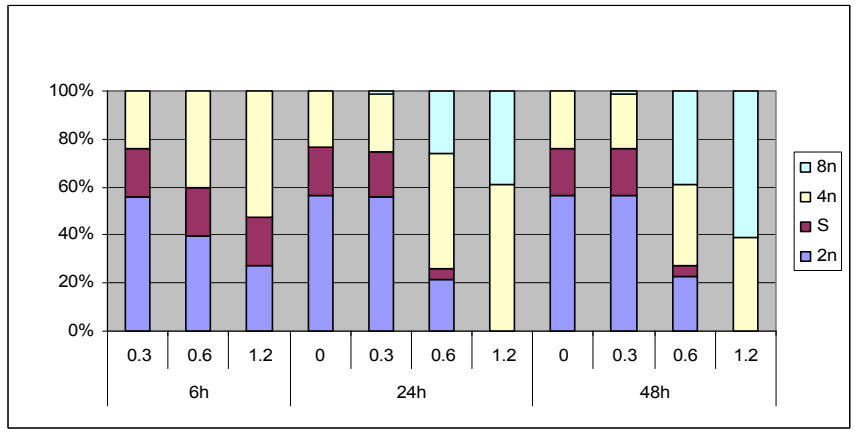


Virtual FACS Modelling Aurora Kinase Inhibitor Response Phenotypes (P53+/+)

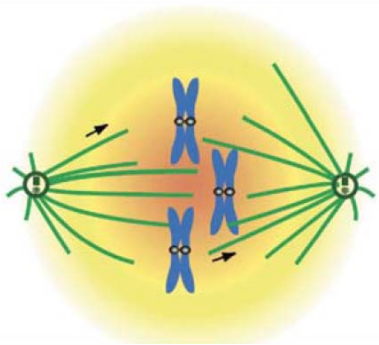








Combination Therapy Design



Mitotic poison (i.e. Taxol)

Spindle Checkpoint

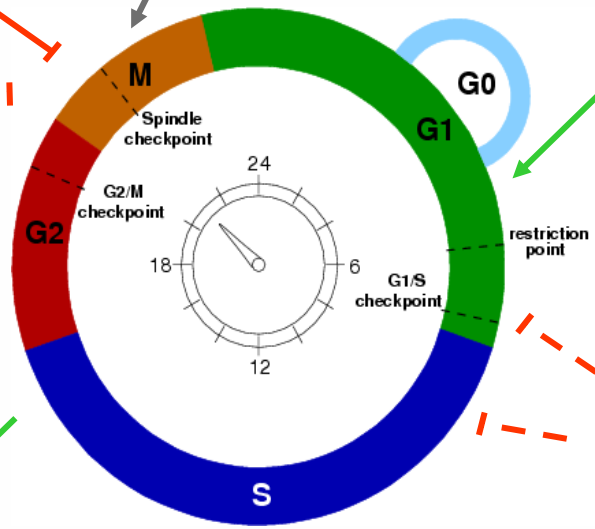
Aurora kinase inhibitors

Circadian clock

CDK inhibitors

Growth factor

MAPKinase pathway inhibitors



Pro-apoptotic drugs

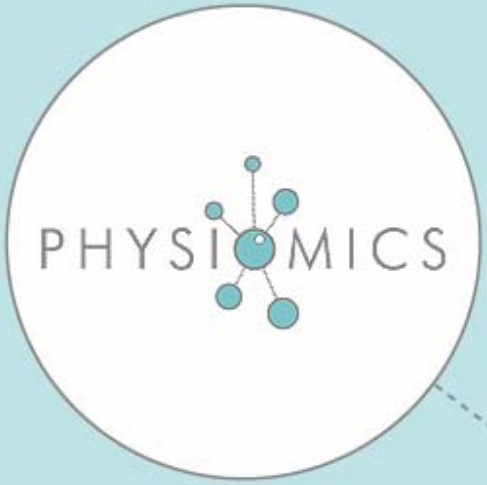
Apoptosis

Nucleoside analogs

CDK inhibitors

Conclusion – Service Offering

- **Qualitative outputs:**
  - Target prioritization
  - Validation of mechanism of action
  - Multi-target drug: synergy/antagonist, sensitivity analysis
- **Quantitative outputs:**
  - Compound ranking (virtual Screening)
  - Pharmacodynamic module based on mechanism of action
- **Drug combination assessments:**
  - E.g. CDK or AK inhibitor plus existing anti-mitotic drug such as Taxol or Nocodazole
  - Optimal therapeutic strategies for tumours according to specific molecular phenotype
- **"Clinicophore":**
  - PK/PD integrated technology with Bayer Technology services
  - Whole body ADME simulation **(PK-Sim®)**



Thank You

dfell@physiomics-plc.com