Mike Payne Celebratory Symposium

Protein dynamics and structure prediction in biological networks

Ashok Venkitaraman

The Ursula Zoellner Professor of Cancer Research & Director, Medical Research Council (MRC) Cancer Unit at the University of Cambridge

MRC | Cancer Unit

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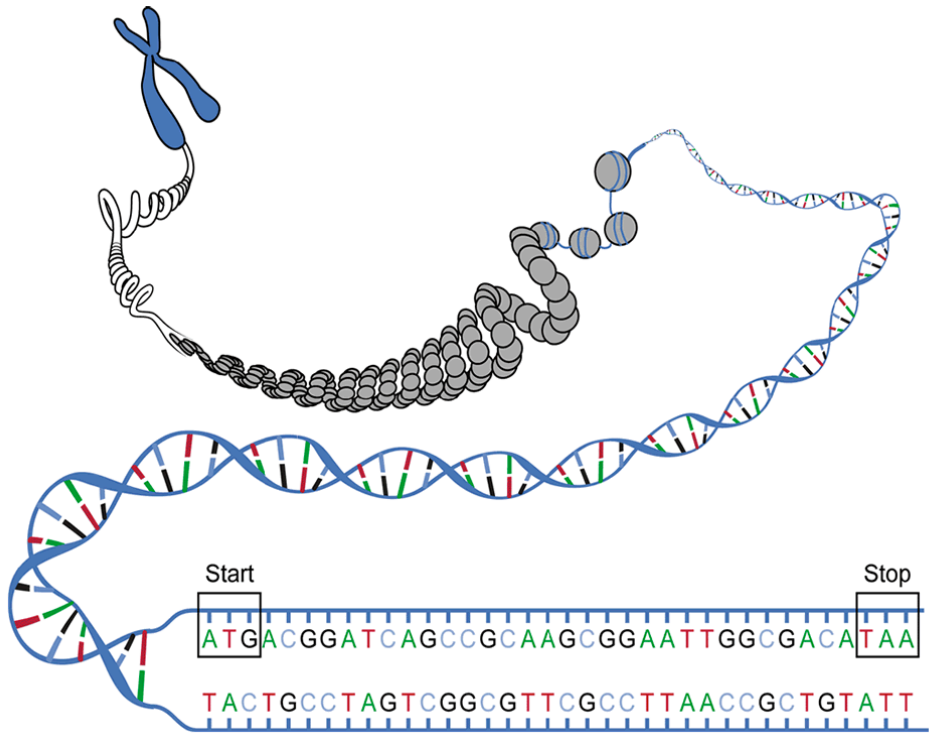
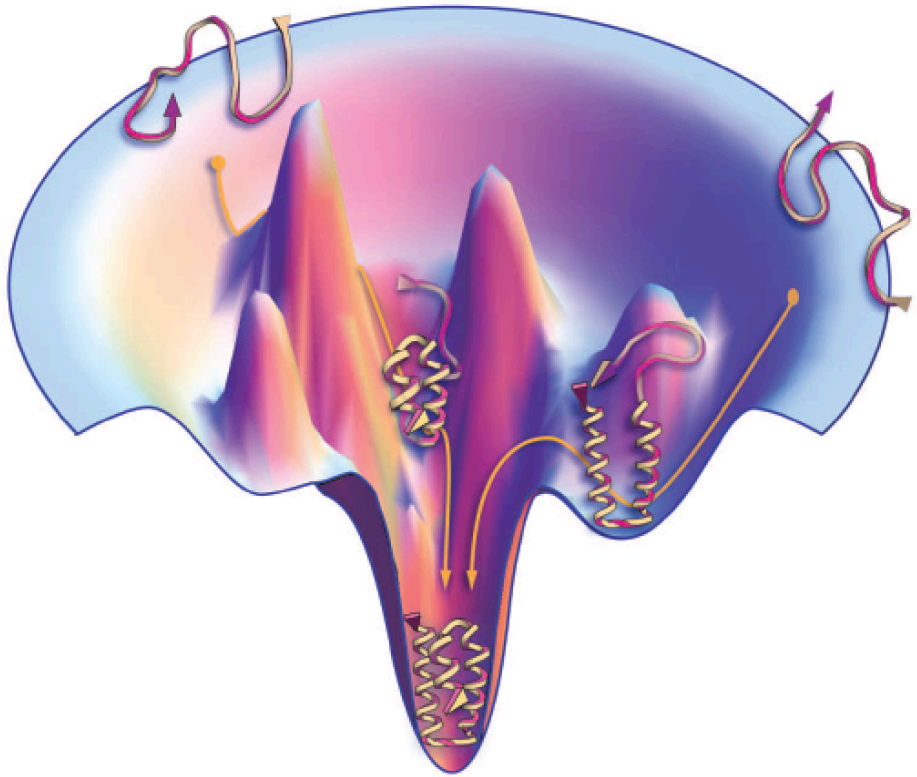
Biological perspectives: protein structure & dynamics



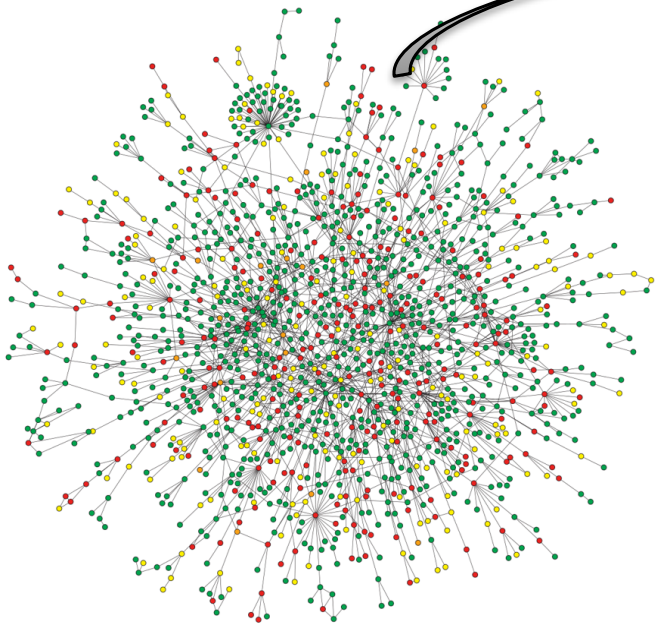
The human genome: ~25,000 genes
Potentially encoding >100K protein species

Low-resolution structure of Myoglobin
Kendrew & Perutz

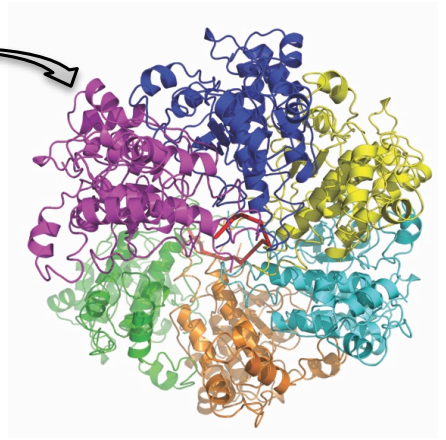
Biological perspectives: protein structure & dynamics



The energy landscape of protein folding:
Many unfolded structures, a few low-energy folded states
Dill & MacCallum, Science (2012)



S. cerevesiae protein interaction network
(Jeong et al., *Nature* (2011))



Short, Venkitaraman et al (2016))

Macromolecular interactions alter protein structure dynamics & mediate function

Mike Payne (c. 2005) ….. 18 months of learning over lunches!

Quantum Mechanical Calculations

(= ab initio = first principles)

Atomic Numbers

↓

Solve the quantum mechanical equations for the **electrons**

Predict physical and chemical properties of systems

Impact of Disruptive Hardware and Software

Quantum mechanical atomistic simulations:
2 atoms in 1981, 400 atoms in 1991.

Increase in computational effort of this calculation using 1981 techniques at least 10^8.

Increase in power of hardware in this period ~100.

Hence, disruptive software technologies increased efficiency of calculation in this period by at least 10^6.

Hardware improvement has been continuous (Moore's Law) - software improvements are not continuous.

Mike Payne (c. 2005)

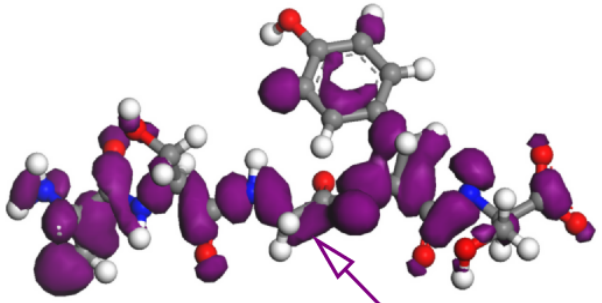
ONETEP
Linear scaling quantum mechanical calculations

Peter Haynes
Arash Mostofi
Mike Payne
Cavendish Laboratory

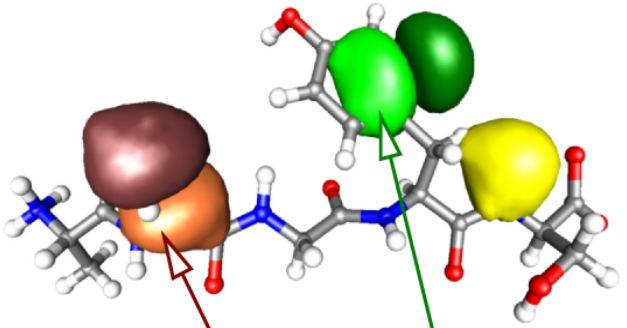
Chris Kriton Skylaris
University of Southampton

ONETEP - Linear Scaling Density Matrix DFT

Molecular orbitals (MOs)



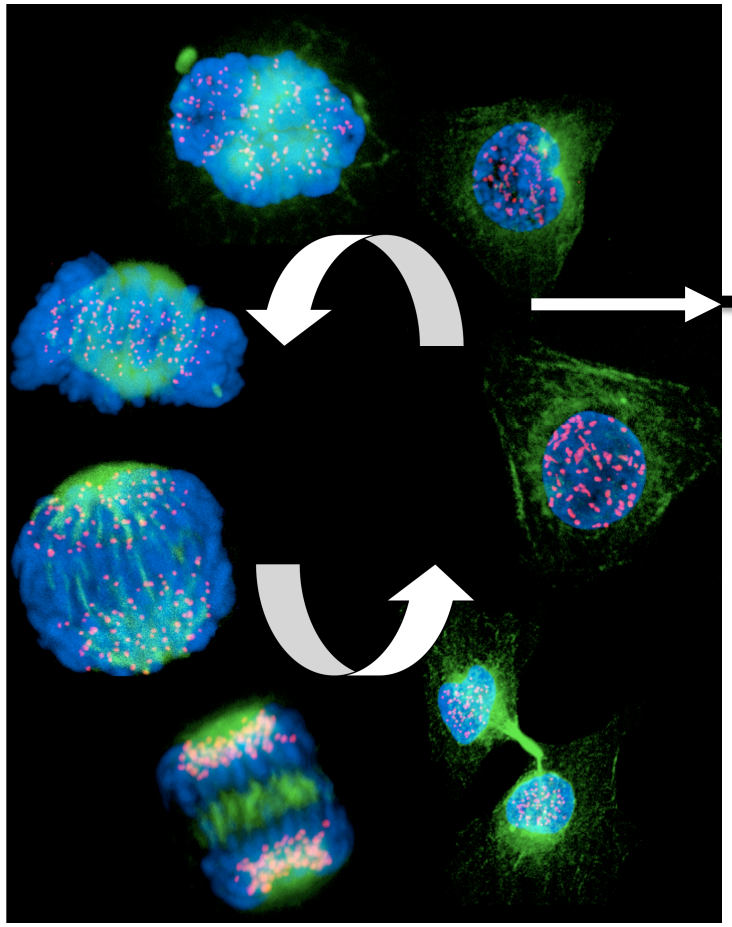
Non-orthogonal Generalised Wannier Functions (NGWFs)



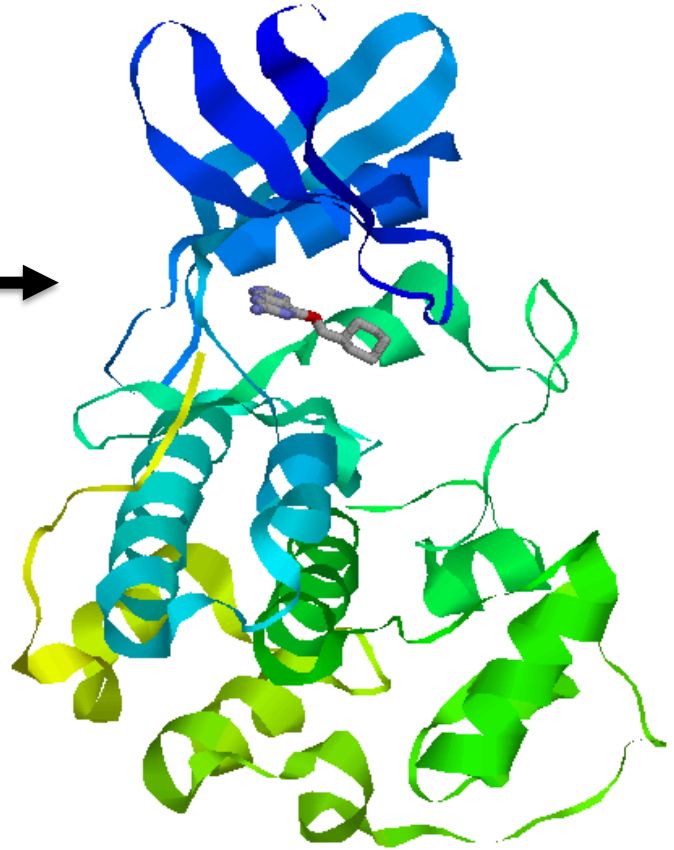
$$\rho(\mathbf{r},\mathbf{r}') = \sum_n f_n\,\psi_n(\mathbf{r})\,\psi_n^*(\mathbf{r}') = \sum_{\alpha\beta}\phi_\alpha(\mathbf{r})\,K^{\alpha\beta}\,\phi_\beta^*(\mathbf{r}')$$

- Optimise non–orthogonal localised functions $\{\phi_\alpha(\mathbf{r})\}$ instead of orthogonal extended wavefunctions $\{\psi_n(\mathbf{r})\}$ } linear scaling
- Aim: to achieve the same accuracy as traditional plane–wave methods

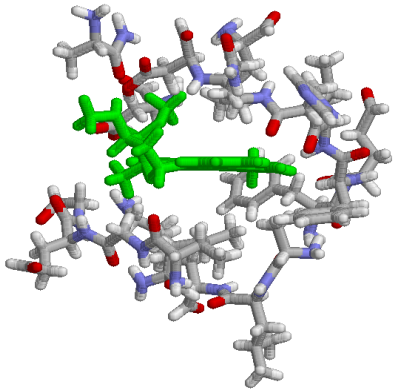
Controlling DNA synthesis initiation – inhibitors of CDK2/CDK4



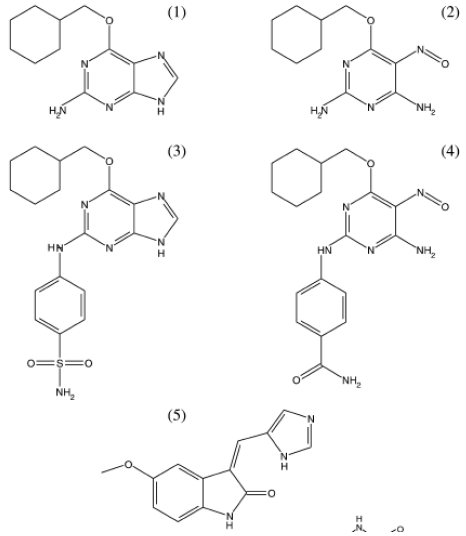
Visualizing the cell division cycle
Daniels & Venkitaraman (c. 2003)



Cyclin dependent kinase (CDK) structure



ATP-binding catalytic site



Controlling the cell cycle – inhibitors of CDK2/CDK4

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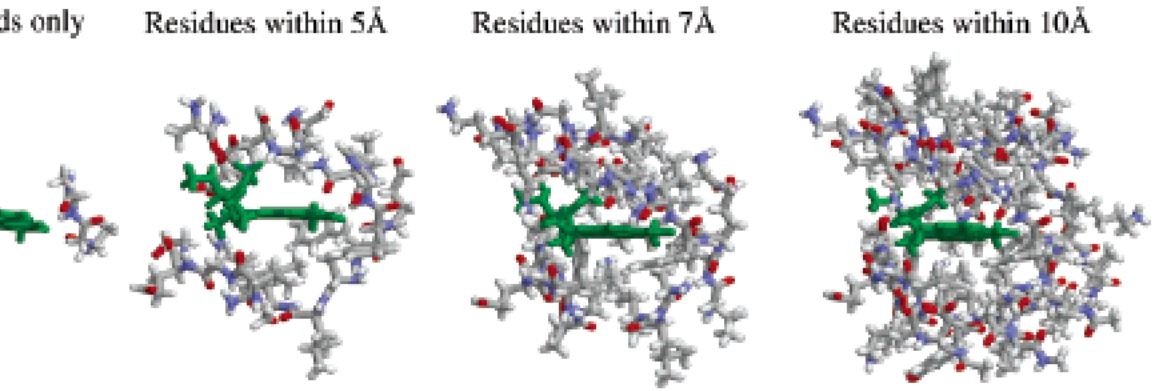
Novel Structural Features of CDK Inhibition Revealed by an ab Initio Computational Method Combined with Dynamic Simulations

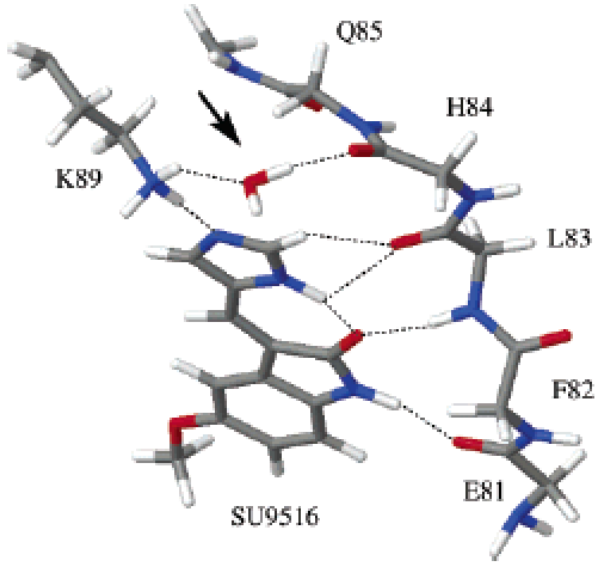
Lucy Heady, Marivi Fernandez-Serra, Ricardo L. Mancera, Sian Joyce, Ashok R. Venkitaraman, Emilio Artacho, Chris-Kriton Skylaris, Lucio Colombi Ciacchi and Mike C. Payne

View Author Information



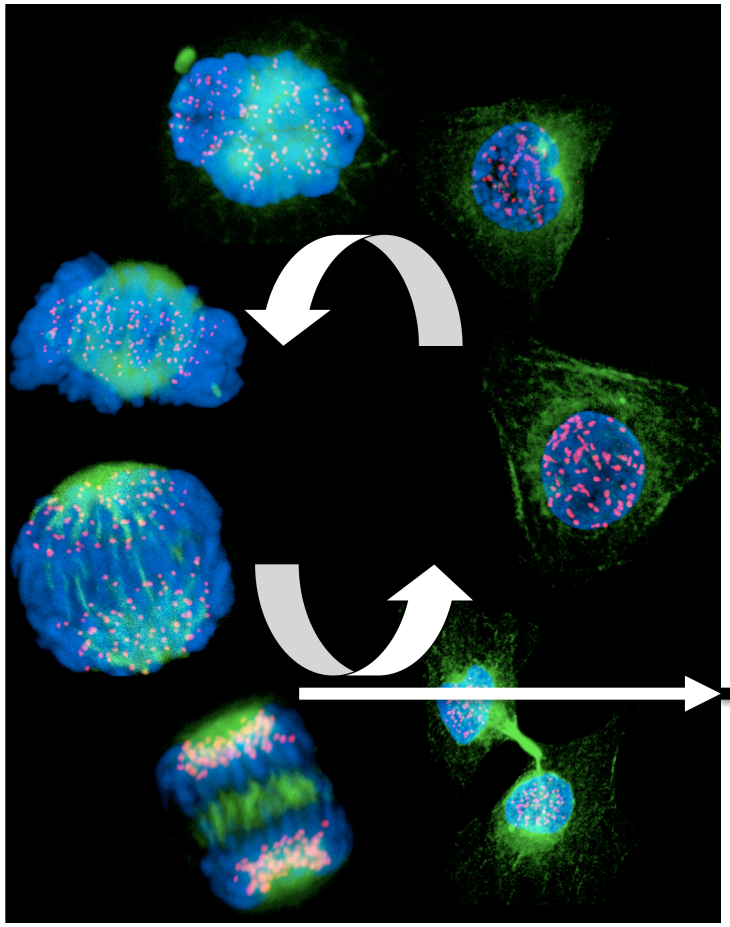
SIESTA	32.22	37.40	39.59	39.46
ONETEP	32.38	38.88	40.59	40.47

Convergence of binding energy values (kcal/mol) with increasing CDK fragment size using ONETEP

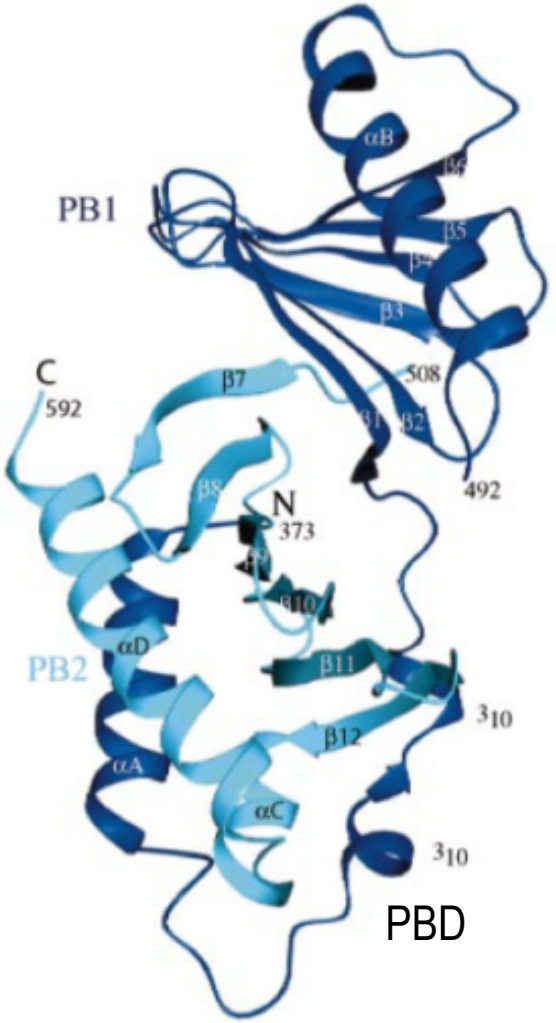


The K89 residue in CDK2 forms H-bonds with SU9516, but T89 in CDK4 cannot

Directing enzyme activity – substrate binding to PLK1



Visualizing the cell division cycle
Daniels & Venkitaraman (c. 2003)



The substrate-binding Polo Box domain
(PBD) of PLK1

How does a single substrate-engaging structure engage multiple binders?

Directing enzyme activity – substrate binding to PLK1

PLOS | COMPUTATIONAL BIOLOGY

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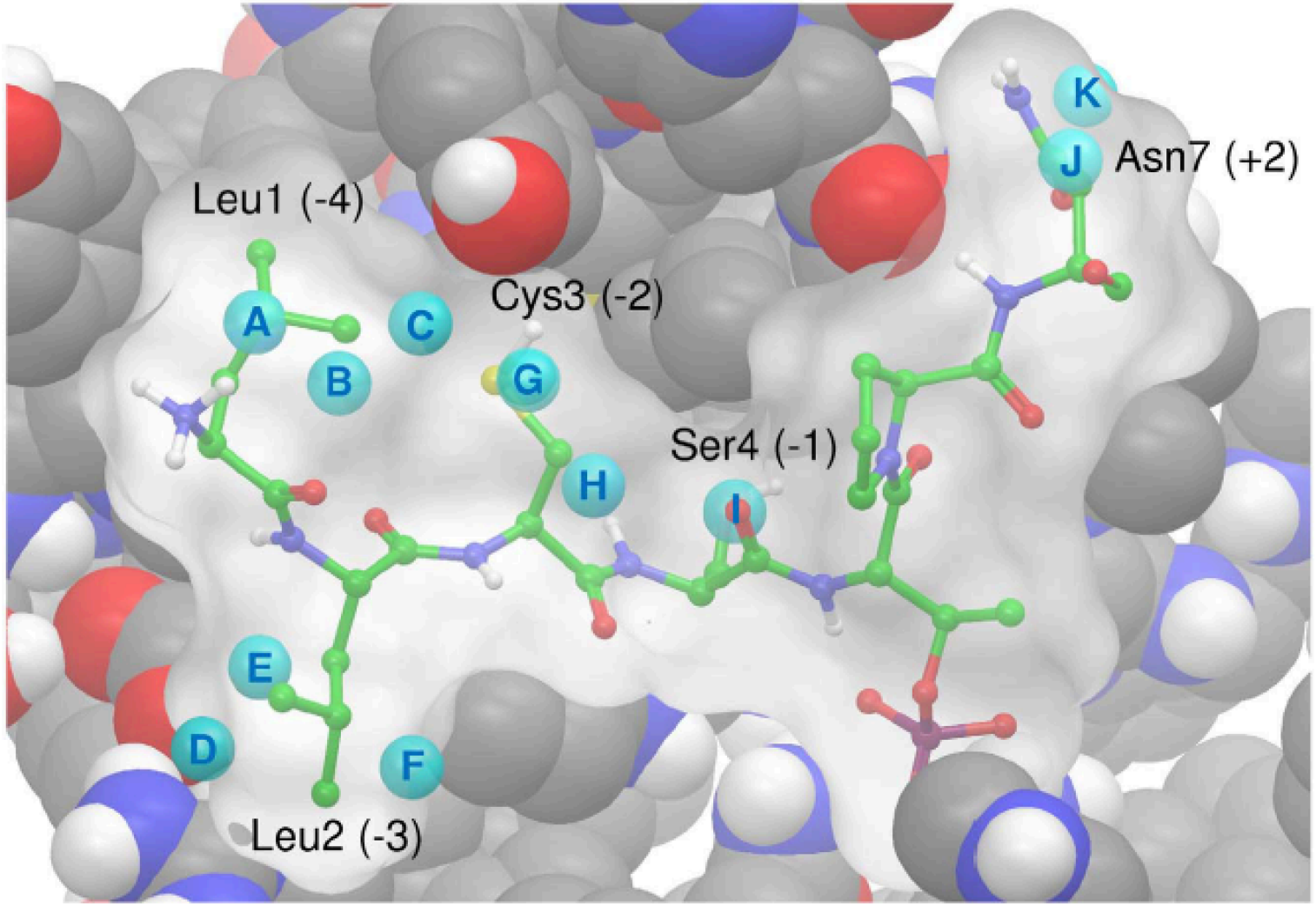
RESEARCH ARTICLE

Computational Analysis of Phosphopeptide Binding to the Polo-Box Domain of the Mitotic Kinase PLK1 Using Molecular Dynamics Simulation

David J. Huggins, Grahame J. McKenzie, Daniel D. Robinson, Ana J. Narváez, Bryn Hardwick, Meredith Roberts-Thomson, Ashok R. Venkitaraman, Guy H. Grant, Mike C. Payne

Directing enzyme activity – substrate binding to PLK1



Stabilization or displacement of a dynamic network of water molecules (A-K) modulates the binding affinity of different PLK1 PBD substrates

Allosteric control of enzyme activity – the BRCA2 / RAD51 interaction

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RESEARCH ARTICLE

Interrogation of the Protein-Protein Interactions between Human BRCA2 BRC Repeats and RAD51 Reveals Atomistic Determinants of Affinity

Daniel J. Cole, Eeson Rajendra, Meredith Roberts-Thomson, Bryn Hardwick, Grahame J. McKenzie, Mike C. Payne, Ashok R. Venkitaraman, Chris-Kriton Skylaris

Future impact: delivering the clinical impact of personalized medicine

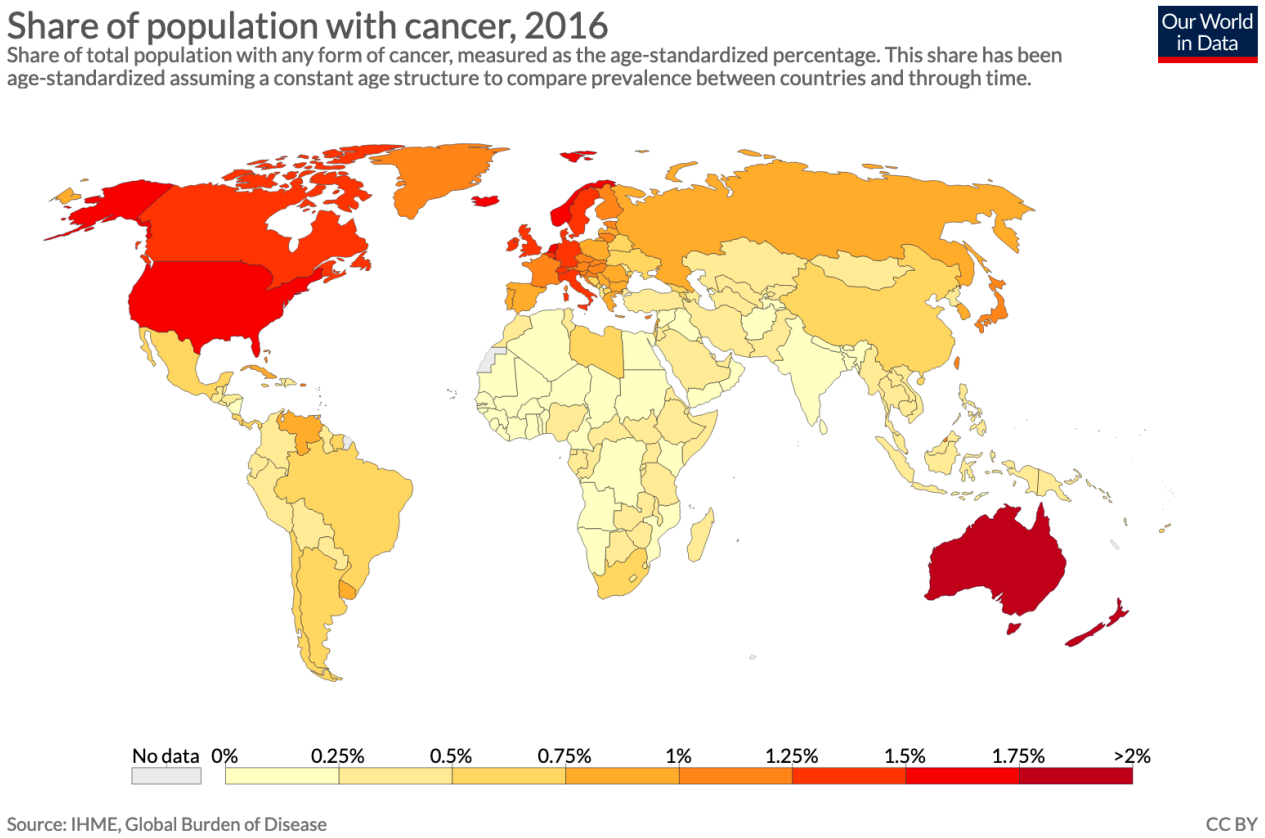
- Formulation of a new taxonomy of human diseases, based on the integration of their molecular and clinical features
- Discovery and validation of robust, clinically applicable biomarkers to individualize patient management
- **Creation of an enhanced repertoire of drugs and clinical interventions suited to individual patients**

The *status quo* is not an option

- The cost of bringing a new medicine to market is estimated by pharma companies to exceed $1BN. The time taken exceeds 10 years. Yet, the failure rate may approach 70-90%.

- *The status quo is not an option* ….We need to more rapidly and cheaply develop ‘next generation’ drugs to fuel the personalized treatment of diseases like cancer.

The global unmet need is acute



Accelerating next-generation medicines – our work at the MRC Cancer Unit in Cambridge

New genetic tools to identify rate-limiting steps

Structure-guided chemical lead discovery as a starting point for new drugs

Systems microscopy to reveal how new drugs work

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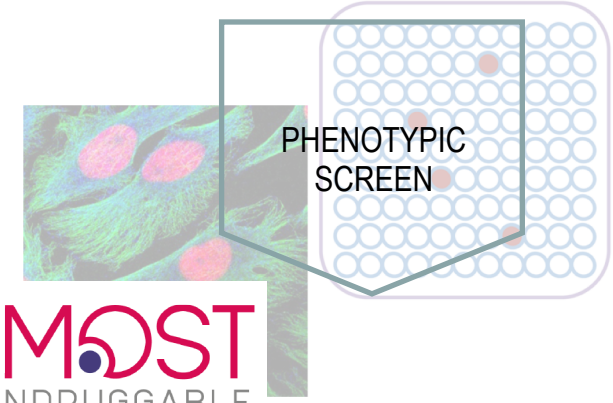

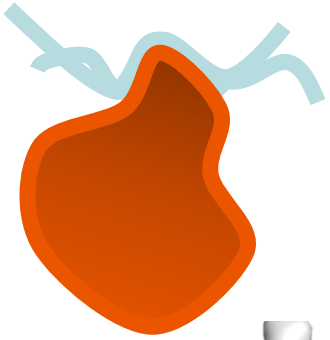

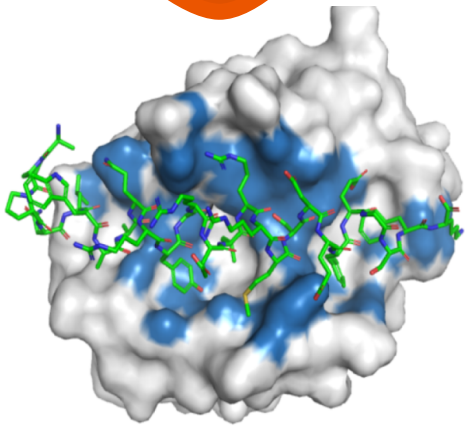

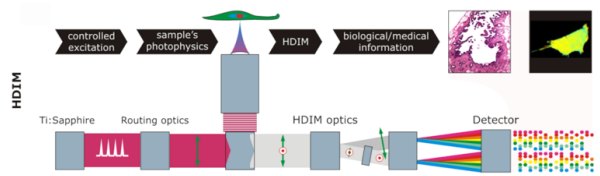

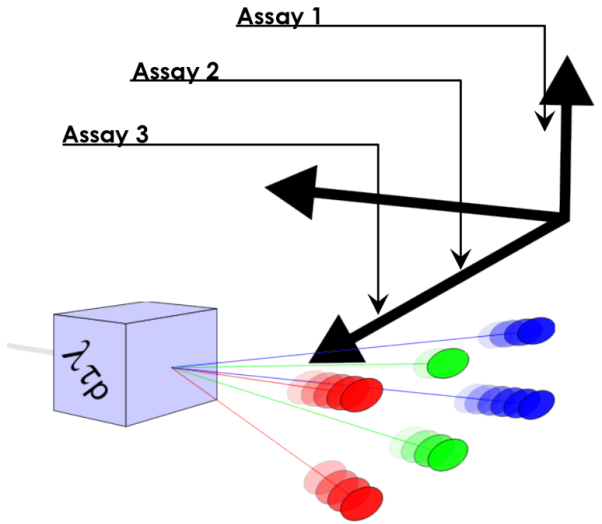

PHORECAST
DRUGGING THE UNDRUGGABLE

Many happy returns, Mike!