

Eleventh Ewald Prize Lecture

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Crystallography, structural biology & drug design

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In the 1960s, when protein crystallography was still in its infancy, there was emerging awareness of its potential contribution to making new medicines. Those of us with Dorothy Hodgkin in Oxford often visited Eli Lilly, Wellcome Foundation and Novo, where crystalline insulin was produced for treatment of diabetes. In the late 60s, when the insulin structure was defined (1), availability of amino-acid sequences from Fred Sanger's laboratory in Cambridge stimulated our interest in design of long-lasting insulins.

However, one of the challenges to making crystallography relevant to medicine was that proteins were often selected because they could be crystallised, and not for relevance in medicine. In the 1970s, my group developed comparative modelling of clinically more relevant targets, such as relaxin, based on our insulin structures, assisted by new graphics facilities. Clinically important drug targets like renin, which regulates blood pressure, were modelled on homologues, allowing structural biology to move into big pharma. This led to our software for knowledge-based prediction (2) of protein structure: first COMPOSER in 1987, and later MODELLER, based on restraints on intramolecular distances and angles derived from homologues.

In 1978, with Jordan Tang, who determined the sequence of pepsin, we suggested that these proteases had evolved from an ancestral dimer. The questions this posed were: "Does a similar dimeric enzyme exist today and what does it do?" The answer came a few years later in the retroviral proteases, most topically in HIV protease. Crystal structures followed, allowing structure-guided drug discovery to deliver a drug.

The increasing interest in pharma in large screening libraries of drug-like compounds in the 90s moved crystallography to the role of supporting hit-to-lead optimisation. However, developments in fragment-based drug discovery allowed crystallographers in Astex back to centre stage for early drug discovery (3). A library of ~1000 small molecules (<300 Da), known as a fragment library, is screened against a target of interest using biophysical or crystallographic methods, resulting in identification of initial hits of known structure. These are then optimized into lead candidates by chemically growing or linking the fragments, thereby exploring the chemical space available for binding to the target protein.

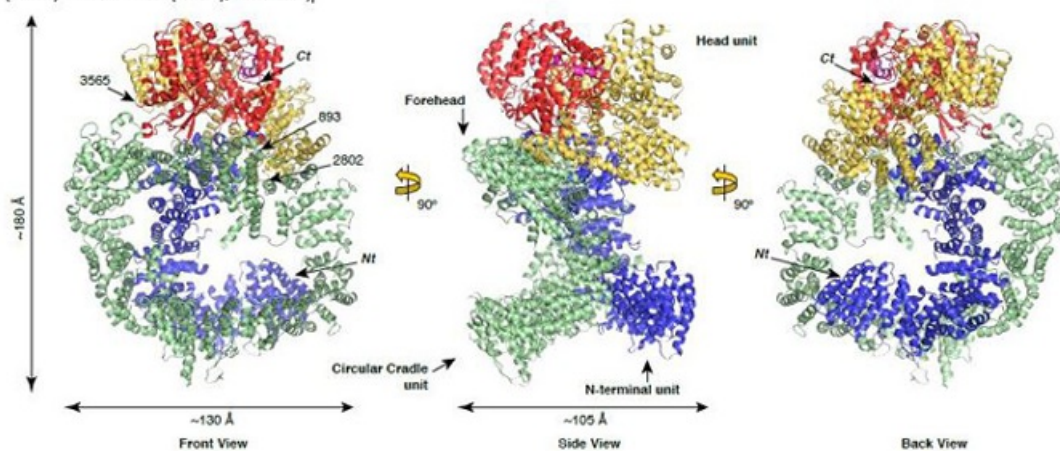
In my Ewald Lecture I will discuss recent developments in structure-guided and fragment-based approaches both to targeting multicomponent cell regulatory and signalling systems at interfacial sites, particularly relevant to cancer, and to difficult targets in infectious mycobacteria such as *M. tuberculosis*, *M. abscessus* (in cystic fibrosis) and *M. leprae* that cause many deaths and are becoming increasingly resistant to current drug therapies.

[1] Blundell TL, Cutfield JF, Cutfield SM, Dodson GG, Dodson EJ, Hodgkin DC, Mercola D, Vijayan M (1971) *Nature* 231, 506-511.

[2] Sibanda BL, Sternberg MJE, Thornton JM and Blundell TL (1987) *Nature*, 326, 347-352

[3] Blundell, T.L., Jhoti, H. and Abell, C. (2002). *Nature Reviews Drug Discovery*. 1, 45-54.

The overall structure of DNA-PKcs. Structural units of DNA-PKcs. N-terminal in blue, Circular Cradle in green, Head comprising FAT region in pink, kinase in yellow and the FATC in light pink. Also shown are the Forehead in light green and FRB (FKBP12-rapamycin-binding) in orange. (based on Figure 1, Sibanda BL, Chirgadze DY, Ascher DB, Blundell TL (2017) *Science* 355 (6324), 520-524)



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