**The Pan African Conference on Crystallography (PCCR2)**
**and**
**The African Light Source Conference (AfLS2)**

# Structure-guided Fragment-based Drug Discovery for Cancer and Tuberculosis: Fighting the Emergence of Resistance

*Wednesday, 30 January 2019 09:00 (1 hour)*

Knowledge derived from genome sequences of humans and pathogens has the potential to accelerate diagnosis, prognosis and cure of disease. We are moving quickly into an era of precision medicine, not only in familial diseases where a mutation in a human gene is important, but also for understanding somatic mutations in cancer. Equally important, the genome sequences of pathogens, for example in tuberculosis or leprosy, can give clues about the choice of existing drugs, repurposing of others, and the design of new ones to combat the increasing occurrence of drug resistance. High-throughput X-ray crystallography using synchrotron sources plays a major role in assessing the druggability of candidate targets identified from the genome sequences.

One approach is to exploit state-of-the-art methods to bring new drugs for different targets to the market, but this will be difficult to finance if patient populations are small. Structure-guided fragment-based screening techniques have proved effective in lead discovery not only for classical enzyme targets but also for less "druggable" targets such as protein-protein interfaces. Initial screening involves small fragments with very low, often millimolar affinities, and biophysical methods including X-ray crystallography are used to explore chemical space of potential ligands. The approach involves a fast initial screening of a library of around 1000 compounds, followed by a validation step involving more rigorous use of related methods to define three-dimensional structure, kinetics and thermodynamics of fragment binding. The use of high throughput approaches, with X-ray synchrotron sources playing a major role, does not end there, as it becomes a rapid technique to guide the elaboration of the fragments into larger molecular weight lead compounds. I will discuss progress in using these approaches for targets in cancer and in mycobacteria tuberculosis, abscessus and leprae infections, focusing on the applications of X-ray crystallography. I will include discussion of collaborations with the Institute of Infectious Disease & Molecular Medicine in Cape Town, South Africa.

I will also review our computational approaches using both statistical potentials (SDM) and machine learning methods (mCSM) for understanding mechanisms of drug resistance. These are dependent X-ray crystallographic and comparative modeling to define structures. We have demonstrated that resistance does not only arise from direct interference of the resistance mutation to drug binding but can also result allosteric mechanisms, often modifying target interactions with other proteins. This has led to new ideas about repurposing and redesigning drugs.

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