Chemical biology in anticancer and antibiotic drug discovery

Modern chemical biology methods have accelerated various aspects of drug discovery, and this talk will describe use of these approaches in the development of anticancer and antibiotic therapeutics.

Hedgehog signalling regulates growth and is reactivated in certain cancers. The membrane protein Hedgehog acyltransferase (HHAT) is critical for signalling, making it an attractive therapeutic target [1]. Only one HHAT inhibitor series (termed 'RUSKIs') exists, which were analysed *in silico* [2-3], via chemoproteomics, and in signalling assays [4] to identify on-target inhibitors. Photocrosslinking RUSKIs were used to map their HHAT binding site, providing insights into HHAT's structure [5]. Inhibitor development resulted in highly-potent compound **IMP-1575**; however, intrinsic metabolic instability demonstrated the need for additional series. Novel high-throughput HHAT assays were therefore developed [6-8], and a screening campaign resulted in the most potent inhibitors to-date. Despite being a challenging integral membrane protein, chemical biology has made HHAT a tractable target for drug discovery.

The global emergence of antibiotic resistance is one of the most serious threats facing modern medicine. There is an urgent need for new drug targets and small molecules with novel mechanisms of action. Inhibiting bacterial DNA repair by the AddAB complex can sensitize bacteria to DNA damage from the host immune system or antibiotics. Rational, hypothesis-driven optimization identified **IMP-1700** as a nanomolar-potency AddAB inhibitor that sensitized methicillin-resistant *S. aureus* (MRSA) to fluoroquinolone antibiotics [8]. Subsequent optimisation led to the development of **OXF-077**, which is also capable of inhibiting the mutagenic SOS response in bacteria and can prevent the emergence of resistance. Bacterial DNA repair therefore represents a novel therapeutic target and **OXF-077** is a valuable tool molecule for development to address the challenge of antibiotic resistance.

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