Special Organic Colloquium

The development and targeting of epigenetic drugs for therapeutic benefit

Abstract: The talk will comprise two interconnected parts describing the development and targeting of epigenetic drugs for the treatment of disease.

The development of bromodomain ligands for the treatment of disease
Bromodomains, protein modules that 'read' of lysine acetylation state, have emerged as important therapeutic targets for indications including oncology. I will describe our work on the design and synthesis of inhibitors for the BET and CREBBP/EP300 bromodomains, their biological effects, and their role as leads for cancer drug discovery.

While the function of some human bromodomain-containing proteins (BCPs) has been heavily investigated, little is known about the role of these proteins in other species. I will describe work to identify 22 BCPs in *Schistosoma mansoni* (schistosomiasis/bilharzia). We have annotated one of these proteins as *Sm*BRD3, in analogy to human BRD3, a member of the BET bromodomain family. I will discuss the design, synthesis, and validation of high affinity ligands for *Sm*BRD3 and the use of these ligands in phenotypic studies on *S. mansoni*.

Targeting and imaging tumour hypoxia
Tumor hypoxia (low oxygen) is associated with therapy resistance and poor patient prognosis. Hypoxia-activated prodrugs, which target oxygen-deficient cells, represent a promising treatment strategy. We have demonstrated the pre-clinical efficacy of NI-Pano, a novel hypoxia-activated pro-drug of the clinically used lysine deacetylase inhibitor, panobinostat. NI-Pano is stable in normoxic (21% oxygen) conditions and undergoes NADPH-CYP-mediated enzymatic bioreduction to release panobinostat in hypoxia (<0.1% oxygen). NI-Pano exhibited growth delay effects as a single agent in mouse tumor xenografts. Pharmacokinetic analysis confirmed the presence of panobinostat in hypoxic mouse xenografts, but not in circulating plasma or kidneys. Our preclinical results provide a strong mechanistic rationale for the clinical development of NI-Pano for selective targeting of hypoxic tumors. Work to develop complementary imaging agents for hypoxia will also be discussed.

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& via Zoom

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