Focus on Faculty #63
Jian Hui Wu

I obtained a B.Sc. degree in Chemistry at Sichuan University, China and a M.Sc. in Chemistry at the Chinese Academy of Sciences. I then worked as a researcher at the Fujian Antibiotic Corporation for two years before pursuing a Ph.D. in structure-based drug design at the University of Essex, UK. As a result of my training and work experience I developed an interest in drug discovery. In 2001 I was recruited by the McGill Department of Oncology and am currently an Associate Professor at McGill and a Senior Investigator at the Lady Davis Institute, Jewish General Hospital. My laboratory is multidisciplinary in nature, involving structure-based drug design, medicinal chemistry and biological assays. I am particularly interested in studying the impact of mutations on the structure and function of a drug target and designing novel chemical compounds to overcome this impact.

My research program, funded by multiple grants from CIHR and Prostate Cancer Canada, focuses on androgen receptor (AR) which is a driver of prostate cancer in the early stage, advanced stage and even at the castration-resistant stage. The AR protein is comprised of three domains: the N-terminal domain, the DNA-binding domain and the ligand-binding domain. As AR signaling is activated by the binding of androgen to the ligand-binding domain, compounds were developed to target the ligand-binding domain and inhibit AR activation. Such ligand-binding domain-targeting compounds are referred to as antiandrogens and include enzaluamide, apalutamide and bicalutamide. My research focuses on the identification of novel compounds that can overcome the mechanisms underlying the development of resistance to antiandrogens:

1. Mutations at the ligand-binding domain
A major objective of this project is to develop novel compounds that remain as the full antagonists not only for the AR wild-type, but also for multiple clinically-relevant mutants.

2. Emergence of AR splice variants lacking the ligand-binding domain
AR splice variant AR-v7 lacks the ligand-binding domain and is constitutively active even in the absence of androgen. All of the currently FDA-approved antiandrogens were designed to target the ligand-binding domain thus making it impossible to directly inhibit AR-v7**.** The objective of

this project is to develop chemical inhibitors of AR-V7 by targeting the N-terminal domain of the Androgen Receptor. We have discovered several novel AR-v7 inhibitors that showed potent *in vivo* efficacy against the 22Rv1 xenograft in mice. As the N-terminal domain is intrinsically disordered, it is very challenging to identify inhibitors that target this domain.

3. Androgen Receptor-GATA2 transcription factor feedback loop

The therapeutic effects of all of the FDA-approved AR-targeting agents are short-lived. The burning question is why is the AR so quickly reactivated in Castration-Resistant Prostate Cancer (CRPC) cells despite castration, and how can we effectively and permanently inhibit it? We discovered a critical feedback loop between AR and GATA2 that results in the rapid emergence of resistance to castration and antiandrogens. To date, we have discovered a novel selective GATA2 inhibitor. We demonstrated a dramatic synergistic effect between our GATA2 inhibitor and the antiandrogen enzalutamide.

My laboratory recently joined the fight against COVID-19 with a CIHR-funded project to repurpose FDA-approved drugs for COVID-19.

Over the years I have established many exciting collaborations with several outstanding researchers, including Dr Gerald Batist at McGill and Dr Anne-Marie Mes-Masson at CHUM. I am particularly proud that, together with Dr Batist's laboratory, we were able to discover compounds to repair a broken protein-protein interaction and thereby selectively sensitize tumor cells to chemotherapy (manuscript submitted for publication). This is in contrast to many other projects that aim to discover compounds to disrupt a protein-protein interaction.

Once spring arrives I like to spend time working on my flower garden. I enjoy reading marshal arts novels and time travel novels, particularly those back to the Tang Dynasty.