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Designed bispecific molecules selectively inhibiting both JAK2 and HDAC at low nanomolar concentrations

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Inhibitors of Janus Kinases (JAKs) for the treatment of myelofibrosis as well as other cancer and non-cancer indications are finding increasing utility. Following the discovery in 2005 of an activating mutation in JAK2, several JAK2 kinase inhibitors have entered the clinic with two now on the market, Ruxolitinib and Tofacitinib. Recently the macrocycle Pacritinib (SB1518), discovered in Singapore by S*BIO, successfully completed Phase 3 studies in myelofibrosis with an NDA filed this year (licensed to CTI Biopharma). S*BIO also developed the pan-HDAC inhibitor Pracinostat (SB939), currently in Phase 2 clinical trials. S*BIO showed that extension of JAK therapy through combination of Pacritinib and Pracinostat has a synergistic effect in JAK2-driven malignancies *in vivo*. Furthermore, combinations of JAK and HDAC inhibitors are now being studied in the clinic. Given the challenges of developing combination therapies and treating resistant cancers we have further developed Pacritnib and Ruxolitinib by merging them in a designed multiple ligand (DML) strategy with an HDAC pharmacophore. Following optimisation we have shown that these single molecules inhibit both JAK2 and HDACs, with distinct selectivity profiles, displaying dual activity in cells. This presentation will show it is possible for medicinal chemists to 'tune' small molecules with multiple pharmacologies for potential application in poorly treated resistant diseases.

Biography

Brian W Dymock is currently an Associate Professor at NUS and Deputy Director of the NUS Drug Development Unit (DDU). Following a PhD in organic synthesis in the UK, Brian worked as a medicinal chemist in the pharma and biotech industry for over 20 years. In Singapore, he was the Head of Chemistry at S*BIO contributing to the discovery of Pacritinib and Pracinostat. In 2012, he joined NUS Pharmacy. He has a special interest in designed multiple ligands and fragment screening and has established the first fragment screening platform in NUS. He has published over 80 papers and patents.

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