Human Immunodeficiency Virus type 1 (HIV-1) remains a serious health issue, with over 1.5 million new infections worldwide in 2021. Untreated infection progresses to Acquired Immunodeficiency Syndrome (AIDS), but can be stalled or delayed through modern HAART treatment. Current regimes utilise a combination of antiretroviral drugs, preventing the spread of HIV-1 and delaying the onset of AIDS. Unfortunately, treatment is not without problems; it is costly, has side effects and consequently has low patient compliance and extended use can result in the development of resistance. Therefore, the development of new and effective therapeutics is necessary to increase compliance and accessibility, and combat resistance.

The HIV-1 capsid protein plays a key role in both the early and late stages of the viral lifecycle, making it an ideal target for new therapeutics. Recent advances in HIV-1 capsid protein targeting compounds, PF74 [1] and GS-6207 [2] (Gilead Sciences – Lenacapavir/Sunlenca), show great promise as a new antiretroviral therapeutic.

To further develop potential new compounds targeting the HIV-1 capsid protein, we are undertaking a structural approach to characterise the binding of 3rd generation compounds to the HIV-1 capsid hexamer [3-4]. These compounds bind to the host-factor binding pocket at the interface between two monomers of the hexamer. Active compounds share a conserved polyphenol core with many avenues to explore a large area of the binding pocket. It is hoped that this will inform the continued development of compounds in this area towards a future long-term cure of HIV-1 infection.