**CASE STUDY 1: PROTACs – Building Chemical Libraries to support PROTAC R&D**

Degraders (e.g. PROTACs™, SNIPERs etc) are bifunctional small molecules that harness the Ubiquitin Proteasome System (UPS) to selectively degrade target proteins within cells. They represent an exciting new modality, repurposing small molecule ligands to achieve selective degradation (knock-down) of target proteins.

Currently, predictions regarding the optimal nature of each component cannot be done a priori and empirical effort is required to guide the development process.°

We are building a library of Degrader Building Blocks to support new researchers entering this field. The Building Blocks consist of different E3 Ligase Ligands and Linkers, ready to conjugate to a chosen Target Ligand.

The Degrader Building Blocks range now contains ~50 combinations that are enabling researchers’ early stage Degrader discovery projects. To further aid researchers entering this field, we are building a set of medicinal chemistry principles to help guide the design of new Degraders in this new area of chemical space:

**Beyond the Rule of 5 – Degrader Chemical Space**

Degraders occupy a new area of beyond rule of 5 (bRo5) chemical space. To understand the properties required for a cell permeable Degrader and inform further development, we have compiled a database of ~400 Degrader structures from the peer reviewed literature. All Degraders were classified according to their effectiveness (Degrader Score – a single measure of efficacy taking into account DC50, ERP, and Degrader incubation time) and physicochemical properties.

**CASE STUDY 2: Optical Tools for Integrin Biology**

The α4β1 and α9β1 receptors share some common ECM ligands, and have been shown to promote both cell migration in a number of cell types in vitro and wound healing in vivo. However, their relative contribution in maintaining epidermal homeostasis and potential contributions to pathological processes in the skin remain unclear. To further elucidate the role of these integrins in epithelial cell migration, we are developing chemical tools to probe their function.

We report the development of a new fluorescent probe for studying integrin-dependent control of keratinocyte migration. The compound is based on Janelia Fluor® 549 coupled to a dual inhibitor of α4β1/α9β1 Integrins.

**No-wash time course experiment with Janelia Fluor® 549-BOP**

Addition of a single methyl group is sufficient to ‘cage’ activity of BOP. Further work is underway to add a photocaging group at this position to enable 2-photon uncaging of BOP.