Universität Basel

Research Project

ExploDProteins

Third-party funded project

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Organisation / **Research unit**
Departement Chemie / Organische Chemie (Gillingham)
Department
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Here I propose to use small molecules to degrade proteins specifically around sites of DNA damage by using the damage itself as a homing signal. The approach will create new ways to study DNA damage, but will also offer translational possibilities in cancer. Cancer cells are often acutely sensitive to DNA damage because they have one or more faulty DNA damage response pathways – a feature that makes them highly dependent on their remaining DNA repair systems. We will pioneer two novel and related chemical approaches for selectively degrading proteins by modulating DNA damage response pathways with bifunctional DNA damaging molecules. We will do this by reprogramming E3 ligases. E3 ligases are multi-protein complexes that catalyse the formation of polyubiquitin chains on its substrates, leading to their degradation in the protein recycling station known as the proteasome. A recent revolutionary advance in chemical biology is to use small molecules to change the specificity of E3 ligases, leading to the degradation of user-defined proteins. By degrading proteins instead of inhibiting them, these small molecules achieve levels of functional modulation typically only possible with genetic techniques. We are inspired by this new protein degradation technology, but will take it in a new direction. Chemical damage of DNA recruits E3 ligases as well as critical DNA damage response proteins in preparation for DNA repair. We will invent a new generation of small molecule protein degradation catalysts and reagents by repurposing these natural responses to DNA damage.

We will accomplish our goal with three aims:

Aim 1: Use DNA damage as a homing signal for induced protein degradation

Aim 2: Use direct repair of DNA damage by the repair protein methylguanine methyltransferase (MGMT) to promote the degradation of other proteins

Aim 3: Promote pleiotropic protein degradation by recruiting broadly acting E3 ligases to sites of DNA damage

I propose an ambitious project that will create conceptually novel ways to study the DNA damage response and potentially build new medicines.

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