PHD PROPOSAL IN CANCER RESEARCH SAMPLE

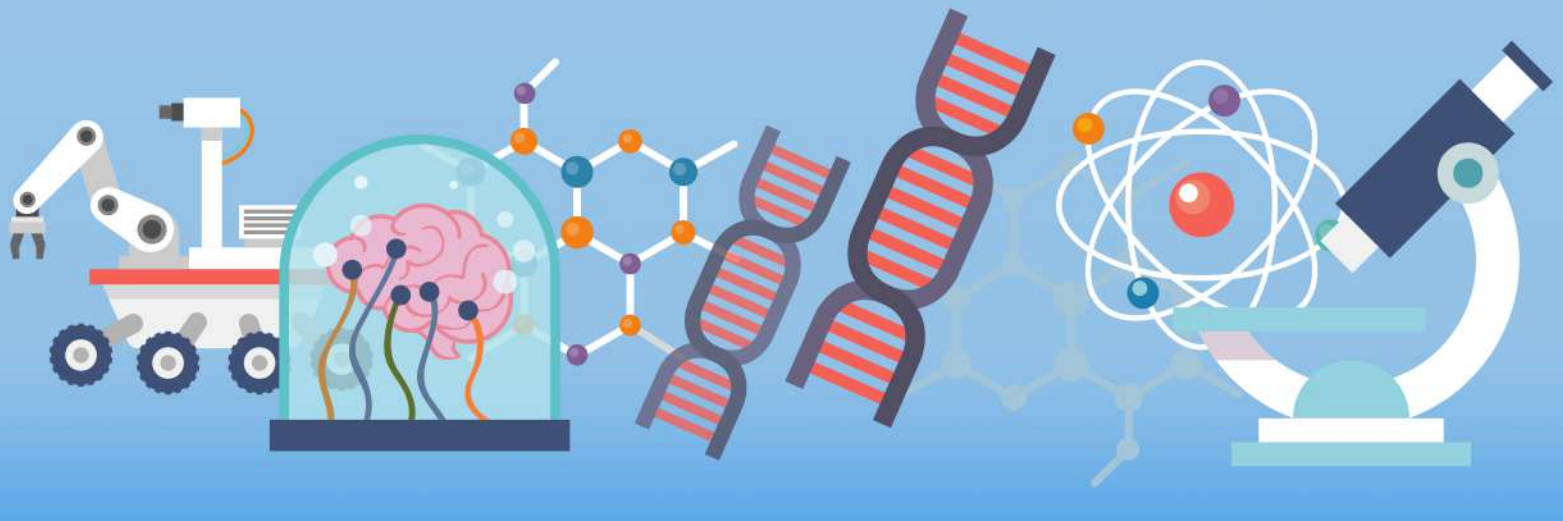
Project Details

Proposed Title: Creation and synthesis of bifunctional degrader libraries for the discovery of possible cancer targets.

Background of the Project

The success of the target discovery of cancer drug is highly dependent on the determination of protein targets which can be modulated using small molecules, thus producing anti-cancer effects. The purpose of this project is to possibly apply the use of synthetic organic chemistry, combined with medicinal chemistry to the creation and synthesis of a library of different compounds which can promote protein degradation. After, these will be used in identifying protein targets which will then be used in the discovery of new cancer drugs.

Bifunctional degrades are a newly discovered molecule class wherein an E3 ubiquitin ligase binding compound is connected to a warhead which binds its therapeutic target. In contrast with other conventional smaller molecule drugs which bind and blocks the action of their protein targets, these bifuncitonal degraders work by catalyzing the formulation of a complex in between an E3 ligase, as well as a target protein, thus allowing for ubiquitination, thus resulting to the irreversible and rapid degradation of the potential target.



This concept will be applied to target finding, by creating and synthesizing libraries of bifunctional degraders, screening them using assays in the cellular level. The process of chemoproteomics will be used in order to identify the targets which will be degraded. The primary benefits of this approach in target identification include the understanding that identified targets are druggable, hitting compounds which have the potential to effectively represent cellular probes, thus serving as starting points for chemistry.

The student who will be conducting this research will be given support by a supervisory team with both industrial and academic expertise in both medicinal and synthetic chemistry, chemoproteomics and cancer biology. The student will also be mainly placed in the 4th Group of the Medicinal Chemistry team, along with Dr. Strauss Meyer. The candidate will also be provided with the opportunity to spend some time with the Molecular Therapeutics team and Target Evaluation group.

Aims of the Project

Overall purpose:

To create a new target identification method which explores the different libraries of bifunctional degraders while presenting some proof of concept.

Steps required:

Discover and develop the right synthetic routes to allow for the preparation of different bifunctional degraders.

Use various physicochemical properties, as well as expertise in the field of medicinal chemistry in order to allow for the design of bifunctional degraders which crosses cell membranes.

Synthesize validation sets of different compounds, which will then be followed by the preparation of 200-compound degrader library.

Test compounds using a series of cellular assays, along with the development and the application of different chemoproteomic methods in order to identify different targets.

Research Proposal

Synthetic routes development to bifunctional degrader libraries

During the project's initial phase, the student will work on applying synthetic routes, combined with some in-house expertise in order to prepare degraders which will be used during the initial validation. The development of new or altered synthetic routes will be undertaken, so as to establish the parallel synthesis for bigger compound sets. This will allow the candidate to start on their current practical and theoretical knowledge or organic synthesis, while developing skills in purification and parallel synthesis. All of these will be done under the guidance of experienced synthesis within the team, as well as the chemistry department.

Use of principles in medicinal chemistry in the cell-permeable compound design

The compounds should be membrane-permeable so that the activity on the cellular assays will be visible. The student will also use accurately measured and calculated physicochemical properties, including permeability data in order to establish an enhanced understanding of different factors which impacts permeability for these molecule classes, and using this to design different compounds with various properties.

Outcomes

Certain outcomes involved in this project serve as validated and new approach for potential target discovery, serving as design criteria for the possible synthesis of enhanced extensive libraries. This project may also deliver chemical probes, thus discovering new cancer targets. The relevance and novelty of this work for cancer therapy will allow the publication of dependable journals.

References

Olsen, G., & Matthews, G. (2016). Chimeras: Proteolysis Targeting: Protein Degradation for Therapeutic Strategy. ABC Chem. Science, 12(2), 234-245.

Luy, G., Tian, Q. & Palmer, G. (2017). E3 Ubiquitin Ligase Hijacking to Efficiently Target the Formation of BRD4. Chemical World, 22(3), 123-145.

Daubian, E., & Spot, G. (2009). Enrichment of Kinase-Selective Compounds Enabling Quantitative Phosphoproteomics. Molecular Cell Biology, 12(2), 456-478.