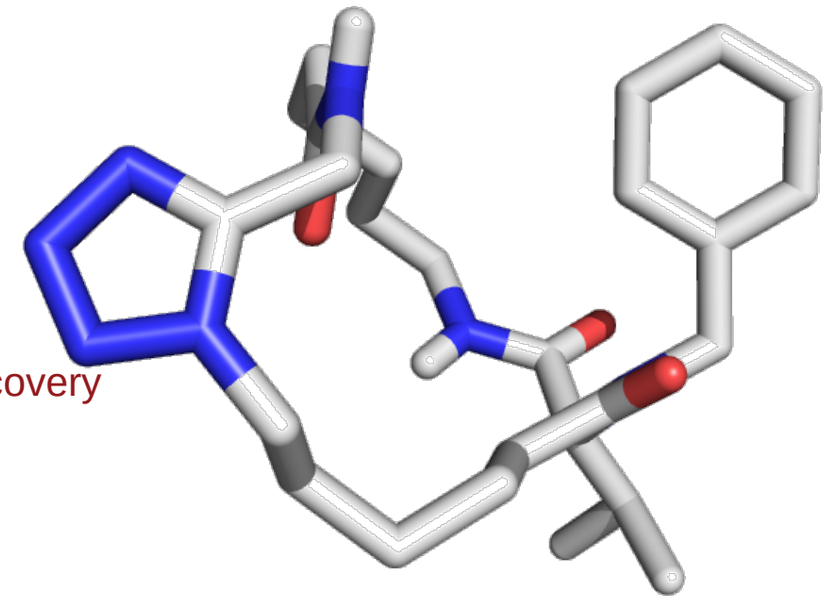
H.F.R.I.
Hellenic Foundation for Research & Innovation

Description of the funded research project

2nd Call for H.F.R.I. Research Projects to Support Post-Doctoral Researchers



Title of the research project: Artificial Macrocycles: (R)evolution of Drug Discovery

Principal Investigator: Constantinos Neochoritis

Reader-friendly title: Macrocycles in drug discovery

Scientific Area: Physical Sciences

Institution and Country: University of Groningen, The Netherlands

Host Institution: University of Crete

Collaborating Institution(s): University of Groningen, The Netherlands

Project webpage:
http://www.chemistry.uoc.gr/neochoritis/page2.html

Budget: 164,000 €

Duration: 36 months

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Research Project Synopsis

While immense progress in individual whole genome sequencing for personalized medicine has provided a wealth of novel drug targets, very few small molecule drugs for post-genomic identified targets are currently in development. Current chemical space of screening libraries is not sufficient to deliver small molecular weight leads in areas of difficult post-genomic targets that are often involved in protein-protein interactions. Synthetic macrocycles have recently emerged as a novel class of drugs that lie between biologics and traditional small molecules, potentially combining the best of both worlds. However, for the regular use of synthetic macrocycles in drug discovery, three main problems have to be solved, which we will address in our project: The difficult access towards a large and diverse macrocyclic chemical space which we will solve by the design of pathways for the convergent synthesis of multiple macrocyclic (MC) classes using modular multicomponent reaction chemistries and a mix-and-match approach including classical organic reactions; the majority of MCs does not show sufficient passive membrane permeations, a prerequisite to discover molecules for intracellular targets and to have the option to develop oral medications with drug-like properties. We will thoroughly investigate the conformational and chemical property space of the above MC scaffolds to build predictive models for passive penetration; the potential chemical space of MC is poorly reflected in the current screening collections in terms of numbers and diversity. We will address this issue by screening large macrocyclic MCR libraries against selected difficult-to-drug with traditional small molecules protein targets. It is envisaged that the herein elaborated macrocycle technology platform will provide a valuable alternative to currently screened small molecule, peptide and biologics drug space to discover new disease treatments in areas of unmet medical need.

Project originality

Nowadays, our understanding of more complex biological systems, which is constantly increasing, provides a range of exciting novel biological targets. Their modulation may enable novel therapeutic options for many diseases. These targets involve protein-protein (PPIs) and protein-nucleic acid interactions, which are however, often refractory to classical small-molecule approaches. Therefore, other types of molecules are required to address these targets, which it has led several academic research groups and pharmaceutical companies to increasingly use the concept of so-called "new modalities". Currently, pharma industry has employed successfully, a portfolio of small molecules, biologics, and peptide-based drugs. However, they cannot be applied effectively to all biological targets. For example, target classes with PPIs or transcription factors, are difficult to be approached with small molecules. In addition, biologics are usually not amenable to target intracellular proteins due to poor membrane permeability and peptides suffer from poor plasma stability as well as cell permeability. This consists of a unique opportunity and a great driving force for the modern organic and medicinal chemist to offer his knowledge on the design and synthesis of these new modalities. The current proposal targets one of the most promising "new modality", the design and synthesis of artificial macrocycles (MCs).

Expected results & Research Project Impact

Our strategy to access the macrocycle chemical space is based on a three-pronged approach with clearly defined aims and modules. First of all, we will establish and identify new synthetic methods for the preparation of macrocycles. To date, the majority of these methods have focused on sequential multi steps peptide synthesis followed by stapling via disulfide bridges, cysteine-based cross linkers, click chemistry and so on. These strategies are not suitable for the elaboration of medium-sized rings to macrocycles with unnatural (non-amino acid) side chains and additional ring hetero-atoms. We are introducing here a general synthesis concept for the fast assembly of macrocycles of different size and shape, side-chain and functional-group content. The pharmaceutical industry is under growing pressure, experiencing major losses of revenue owing to patent expirations, increasingly cost-constrained healthcare systems and more demanding regulatory requirements. Performance indicators reveal the most significant challenge for pharmaceutical R&D is innovation and productivity decline. Of all newly discovered targets for drug discovery only a very small fraction is currently progressed by pharmaceutical industry because of the unsuitability of currently used discovery technologies, specifically screening libraries. In times of reduced productivity coupled with increasing costs within the pharmaceutical industry, "reductionistic" small molecule- and biologics-based drug discovery has come under pressure and new chemotype-based discovery has gained momentum. Therefore, there is a great need for alternative drug discovery technology platforms. This project has the prospect to unravel the preclinical R&D process by focusing on an innovative 'sweet spot' of early drug discovery which will help to strongly improve R&D productivity by spotting and targeting novel unprecedented target and inhibitor classes, decreasing preclinical cycle times and thus reducing development times and costs. Most importantly the project provides a basis for a future new quality and quantity of drug pipeline to provide patients with novel treatment options.

The importance of this funding

H.F.R.I. funding of my research project came to the exactly right moment in my career, establishing all the necessary sources to run an ambitious project in Greece. Today, fortunately or unfortunately, research, especially the high quality research needs funding. The H.F.R.I funding is one of a very few funding sources in Greece. Therefore, I can bring back to my home country the acquired knowledge and start my individual, academic career. This funding will give a first class opportunity to hold my own research team and coordinate this project, which is absolutely applicable in the organic chemistry labs of the Chemistry Department in the UoC. It will refill the "missing gap" of my CV and will prove my academic independence.

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COMMUNICATION

185 Syggrou Ave. & 2 Sardeon St. 2
171 21, N. Smyrni, Greece
+30 210 64 12 410, 420
communication@elidek.gr
www.elidek.gr