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Drug Discovery

GOING FOR GOLDILOCKS :

INNOVATIVE MOLECULES FIND THEIR WAY TO NEW TARGETS

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CYCLOINFORMATICS: A PLATFORM FOR RAPID PRODUCTION OF MEDIUM-SIZED MACROCYCLES AS PROTEIN-PROTEIN INTERACTION PROBES

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AND $250K FROM MARS INNOVATION

A NEW CLASS OF CYCLIC PEPTIDE STRUCTURES CALLED MACROCYCLES COULD REACH INTRACELLULAR DRUG TARGETS TO MODULATE PROTEIN-PROTEIN INTERACTIONS CURRENTLY INACCESSIBLE TO MOST PHARMACEUTICAL AGENTS. THE POTENTIAL TO REACH AN UNTAPPED GOLDMINE OF NEW TARGETS HAS ATTRACTED A GREAT DEAL OF INTEREST AND EXCITEMENT IN BIOPHARMACEUTICALS. ENCYCLE THERAPEUTICS, A TORONTO-BASED START-UP, HAS USED A PLATFORM TECHNOLOGY DEVELOPED AT THE UNIVERSITY OF TORONTO IN COLLABORATION WITH UNIVERSITÉ DE SHERBROOKE TO CREATE A LIBRARY OF SUCH MACROCYCLES AND DEVELOP THEM AS NEW MEDICINES.

INVESTIGATORS

Andrei Yudin,
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Encycle Therapeutics Inc.
Éric Marsault,
Université de Sherbrooke

Jeff Coull,
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THE CHALLENGE

Drug “targets” — the binding sites on various cells where drug molecules attach themselves — come in a wide range of sizes and locations.

Smaller molecules can penetrate cellular membranes to reach sites inside a cell, but these agents require specialized binding sites such as hydrophobic pockets.

Larger molecules, such as biologic compounds or protein therapeutics, can mediate protein-protein interactions over a wider number of receptors, but these agents are generally too large to penetrate cell membranes.

These two types of binding strategies cover the mechanism of action of most drugs used today, yet they account for about 20 % of the potentially “druggable” targets in the human body.

THE SOLUTION

University of Toronto chemist Andrei Yudin developed an innovative method using aziridine aldehyde as an amphoteric reagent, capable of either accepting or donating electrons. This reagent is used to bind the ends of long linear peptides, transforming them into a mid-sized circular form known as a macrocycle.

Éric Marsault, a medicinal chemist specializing in macrocycle drug discovery at Université de Sherbrooke, further adapted this method to synthesize these macrocycles in parallel, and begin building a library of these molecular probes.

These probes, named nacellins, are large enough to retain the extensive binding characteristics of the original peptide, yet small enough to cross cell membranes and access hard to reach intracellular targets. Such a structure has the potential to initiate drug interactions at entirely new sites within cells that existing products have been unable to reach. In addition, nacellins are chemically sturdy enough to become orally delivered agents.

MAIN ACCOMPLISHMENTS

This collaboration between investigators in Ontario and Quebec has led to the development of a powerful chemistry platform for more efficiently **designing and synthesizing nacellins**, a new type of macrocycle derived from peptides with enhanced potential for cell permeability and oral bioavailability.

This unique technology has allowed the creation of Encycle Therapeutics, a dynamic biotechnology start-up founded in 2012 by Andrei Yudin in partnership with MaRS Innovation which helped incubate and finance the company, and recruit its current President and CEO, Jeff Coull.

The firm, in collaboration with the laboratories of professors Yudin and Marsault, has already generated a **library containing some 1,400 nacellins**. Comprehensive ADME and PK evaluations have been performed on various scaffolds from the library. Encycle has also developed a **computational tool** for analyzing protein interactions that could be disrupted using nacellins, which provides an important indication of drug potential.

That potential is now being explored with the beginning of a new research initiative on the company’s first macrocycle drug, which targets the integrin α4ß7 receptor, paving the way for a new oral treatment for inflammatory bowel diseases.

IMPACT

Funding of this project resulted in the maturation of a unique and promising technology to develop orally administered therapeutics that cannot only inhibit extracellular proteins, but also target the hitherto “undruggable” intracellular protein-protein interactions. Encycle’s library of nacellins should be able to identify entirely new types of treatments based on drug interactions at sites within cells that existing drugs cannot reach. Such progress would dramatically improve existing treatments for multiple diseases, while perhaps making it possible to address medical conditions that until now have remained untreatable.

While most leading pharmaceutical companies are actively exploring the new market opened up by macrocycles, this collaboration with Encycle has also provided our pharmaceutical members with exclusive, state-of-the-art access to this highly competitive field. CQDM’s unique mentorship program has fostered a strong partnership between the researchers and senior scientists from Pfizer, Merck, AstraZeneca and GSK who have provided guidance and resources to ensure steadfast progress. One pharma member, for instance, tested the druggability of the nacellins developed and shared the results with the other members of the consortium.

CQDM pharma members were also granted the right to screen Encycle’s library with a limited number of therapeutic targets of their choice. The discovery of “hits” from this screening effort would open the door to long-term strategic partnerships between Encycle and CQDM’s pharmaceutical members.

BRIDGING THE GAPS

Encycle’s ongoing endeavour is a prime example of how CQDM’s collaborative model bridges strategic development gaps by funding risky yet translational research. CQDM provided non-dilutive funding that allowed Encycle to accomplish significant proof-of-concept work and validate the platform with the assistance of major pharmaceutical companies, generating both direct and indirect benefits to all participants, and positioning Encycle very favourably to raise venture capital.

MENTORS

Scott Cowen, AstraZeneca
Spiros Liras, Pfizer
Graham Simpson, GSK
Yusheng Xiong, Merck

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