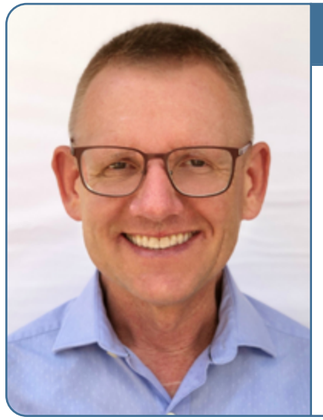
UBIQUITIN MEDIATED SMALL MOLECULE INDUCED TARGET ELIMINATION (USMITE) FOR CANCER



MICHAEL PLEWE, Vice President – Medicinal Chemistry, **Cullgen Inc.**

Michael Plewe is Vice President – Medicinal Chemistry at Cullgen Inc., a company dedicated to the development of novel approaches for targeted protein degradation in oncology and immune disease. Before joining Cullgen in 2018, he was the Head of Chemistry at Arisan Therapeutics, a start-up focused on developing novel treatments for neglected viral diseases. Prior to Arisan, he was an Associate Research Fellow and project leader at Pfizer Inc. working in multiple therapeutic areas including oncology, ophthalmology, diabetes, and infectious diseases such as HIV. He was a medicinal chemist at Agouron and Vical, a gene therapy company. Dr. Plewe completed his postdoctoral training at the University of California at Irvine and earned his Ph. D. and Diploma in organic chemistry from the University of Konstanz in Germany.

Over the past five years, big pharma companies and biotech firms began utilizing targeted protein degradation as a mechanism to discover new drug candidates. This new approach offers drug developers a mechanism to create small molecule drugs against targets previously considered “undrugabble” or against targets that are not ideally suited for inhibitors.

Most of the small molecule targeted protein degraders were discovered empirically. Medicinal chemists in the pharmaceutical industry are now forging a new set of rules on how to rationally build drugs that consistently and selectively degrade proteins. While the momentum of these activities is building, drug companies are confronted with a few critical issues, including delivery mechanisms, dosing, target selectivity and safety.

Cullgen is a leading targeted protein degradation company that utilizes the ubiquitin proteasome system to degrade disease-causing proteins. We discussed with Michael Plewe, Vice President of Medicinal Chemistry, Cullgen the opportunities, challenges and how targeted protein degradation promises to be the future of drug discovery.

Plewe will be presenting research on targeted protein degradation strategies utilizing the ubiquitin proteasome, the human body’s existing system for the disposal of unwanted or malformed proteins. Cullgen’s degrader molecules contain two operative ends— one, a ligand (or warhead) that binds to the protein targeted for degradation, and the other, an E3 ligand that binds to an E3 ubiquitin ligase. These two ligands are connected by a linker moiety. The degraders bring the targeted protein and the E3 ligase in close proximity to allow catalytic transfer of ubiquitin to the target protein, triggering its degradation by the 26S proteasome. Due to the high degree of specificity and catalytic nature of the ubiquitin proteasome system, Cullgen’s small molecule degraders can specifically and efficiently eliminate any disease-associated target protein from the cell. The degraders can repeat the tagging and elimination process in an iterative fashion before eventually being metabolized or eliminated from the cell. The permutations of this system, adds Plewe, allow for a potentially vast number of drug candidates to be researched.

Q&A Session with Michael Plewe

What is your current role at Cullgen and what are your current activities in protein degradation?

I am the Vice President for Medicinal Chemistry responsible for overseeing the medicinal chemistry efforts at Cullgen. We are currently focusing on two areas: developing novel targeted protein degraders for treatment of cancer and identifying novel ligands for E3 ligases for which no known E3 ligand exists, and thus far have not been used for targeted protein degradation. Currently only four E3 ligases are commonly being used to develop targeted protein degraders, and they all come with certain limitations. Certain ImIDs have been shown to cause peripheral neuropathy. It has also been reported recently that drug resistance to degraders is emerging as a result of the deletion of the non-essential genes for CRBN and VHL. We believe that through the use of new E3 ligands we can develop degraders which reduce toxicity, alleviate drug resistance, provide tissue and subcellular compartment selectivity, expand the substrate spectrum, and ultimately make drugs that are safer.

Are there clinical candidates you are working on for protein degradation?

Yes. We are actively working on six internal degrader programs. For our most advanced programs, we expect IND-enabling studies will start soon.

What are the current challenges?

Developing orally bioavailable degraders was initially quite a challenge, but by optimizing the warhead, linker and E3 ligand we have been able to routinely achieve very good oral bioavailability in animals. Our next big challenge is demonstrating safety by conducting in vivo toxicity studies in animals. We currently do not know what toxicities we might see with this new modality.

Opportunities in protein degradation for Cancer?

I really believe that the opportunities for protein degradation are endless, not only in the cancer field but for many other therapeutic areas. In cancer we are focusing on epigenetic proteins with scaffolding functions, as well as transcription factors.

What is your aim in attending the Drug Discovery summit?

This summit brings together leaders from different areas of drug discovery. I am looking forward to meeting with colleagues from other companies and academia, and discussing cutting edge advances in new technologies for targeted protein degradation.