Protein Degradation & Targeting Undruggables Congress
EUROPE

An interview with:

Adam Gilbert, Executive Director, Head of Design and Synthesis Sciences, Pfizer

Good day, Adam. It is such a privilege to have the opportunity to talk to someone as successful and such a developed medicinal chemistry background as you. Your career has been very focused and as you approach almost 30 years with Pfizer working to develop areas such as Hit to Lead/Lead Optimization, novel and experimental design chemistry and now into Innovative Design and Synthesis, what brought you to the field? What are some of your fondest memories or past achievements?

My fondest memories really focus on the amazing scientists that I've had the privilege of working with during my career. I remember starting my career and feeling like I knew very little. Supportive and generous colleagues have really helped me learn to be a good drug discovery scientist, and how to develop cutting-edge modalities/approaches such as covalent inhibition and protein degradation.

Given your current role which involves consolidating chemistry-based techniques and technologies to interrogate, study, identify, design and synthesise drugs for therapeutic benefit, as well as having worked with modalities such as covalent inhibitors, kinase inhibitors, cyclic peptides just to name a few, targeted protein degradation seems to be of increasing interest these days. What is gravitating you towards this modality? What is your motivation working in this field?

My gravitation toward TPD is being driven by helping find treatments for diseases with high unmet medical need. While TPD is a fascinating mechanism of action for a drug modality, my scientific drive is really about finding ways to engage high validated drug targets that have been resistant to previous drug discovery efforts such as transcription factors, E3 ligases, DUBs, and viral targets.

> "With any new scientific advance in the drug discovery arena...one needs to quickly find out where the new technology will be effective and where it won't be."

Despite having almost two decades since the first report of PROTACs in literature, the field of protein degradation as a therapeutic is still relatively young with the first clinical proof-of-concept for PROTACs

realised just two years ago. There is an increasing number of compounds in and entering the clinic, exemplifying the promise in the space. What would you say is sparking this surge of investment and rush to the clinic?

The surge is due to the potential to access biological scaffolding effects of proteins that we can currently functionally inhibit as well as proteins where we have good target binding molecules that are functionally inactive. There are also potential PK/PD advantages of degrading a protein as well as potential safety advantages – advantages that could lead to superior patient treatment options compared to the current standard of care options.

Of the number of approaches that constitute degraders, PROTACs and Molecular Glues take centre stage. Arguably, progress in the field of PROTACs have been more advanced; however, roadblocks remain, particularly exhibiting favourable PK profiles and general drug-like properties. Do you share this notion? In this respect, which challenges need to be overcome to move past?

With any new scientific advance in the drug discovery arena (structure-based design, combinatorial chemistry, RNA therapeutics, TPD etc...), one needs to quickly find out where the new technology will be effective and where it won't be. I'm truly excited about the potential of TPD for future therapies but PK/exposure limitations will likely limit what heterobifunctional moieties can deliver to patients for certain biological targets/diseases due to the properties of these molecules. Thus, I think the recent advances in more rational molecule glue approaches to tough targets being driven by companies like Monte Rosa, Proxygen, Orionis (to name but a few companies) may provide superior clinical tools with superior efficacy since their properties may allow higher free drug exposures in patients. I like that there is strong investment in both approaches – each TPD modality will have its niche.

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Some would say that despite having protein degradation as an end result, PROTACs and molecular glues could not be more distinct. Unlike PROTACs, glues have the immediate advantage of having these favourable PK properties, as well as systemic distribution, CNS penetration and manufacturing scalability among others. Despite these, it has been an uphill battle finding and characterising new glues. Where does the industry need to focus to advance?

The molecular glue field has made and continues to make huge advances towards a way to develop degradation therapies more rationally for targets of our choosing. The days of screening large compound collections in cells and looking for evidence of protein degradation are over and companies are discovering new E3/glue systems and new protein degrons for existing systems (i.e. CRBN). Companies are finding new endogenous E3/protein interactions and identifying compounds to improve this interaction affinity to catalyze degradation. The more we learn in this space, the more rationally we'll be able to identify biological targets that are "gluable".

Building from the last question and involving all modes of degradation in mind, leveraging advanced technologies such as AI and ML have proved useful in instances such as mapping the target degradability landscape, PK profile

prediction, and positive ternary complex effectors to improve degradation, to name a few. Do you see further advantages in using these technologies in the pursuit to optimise translation to the clinic?

Yes – AI/ML to help stratify patient selection for degrader modalities we take into the clinic will be very important. AI/ML approaches in the discovery space will continue to improve as we build more robust data sets to interpret for predictive use.

What developments are you most excited about in TPD, and perhaps the coming decade? Which companies or research groups are doing exciting approaches these days?

I've been most excited about the advances in the molecule glue space in the past year. Many high-value protein targets don't have binding sites that can be liganded by small molecules – a requirement for PROTAC development. Molecular glue systems can get around this requirement making traditionally "non-druggable" targets accessible (i.e., the CRBN glue system). I view companies like Monte Rosa, Orionis, and Proxygen being leaders in this space. I've also been very excited by newly formed companies, like Triana, who are going into a completely novel glue space.

You will be one of our key speakers at the 4th Annual Protein Degradation & Targeting Undruggables Congress in Basel this October – we are certainly looking forward to you proposing a translational PKPD roadmap for degraders. Are there any insights you'd like to share prior to the event?

Everything is PK/PD. Seriously, any modality you dose in vivo will drive biology based on its PK/PD. For TPD, we need to evolve our understanding of what PK is possible given the properties of the modality we are dosing in order to generate the efficacious response we want in patients. Still a lot to learn here but we have the scientific tools and expertise in hand to start sorting this out.

Join us at the 4th Annual Protein Degradation & Targeting Undruggables, as we continue these discussions. Discover opportunities in addressing optimal target classes, optimising drug-like properties, reducing resistance potential and achieving cellular and tissues selectivity to boost clinical translation.

We are looking forward to hearing Adam speak on how to best leverage recent methodologies and align priorities towards successful clinical translation and exploring a facilitated targeted protein degrader rational design workflow.

Book your place now to hear from, meet, and connect with over 150+ executives from across the industry.

View the Agenda Here

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