HESI PROTACs and Molecular Glues Safety Workshop

Workshop Dates: October 14-15, 2021

Problem Statement: Although the volume of Proteolysis Targeting Chimeras (PROTAC) and targeted protein degrader-based therapeutic development programs has grown over the past several years, there is limited public discussion or scientific consensus on the application of rigorous, consistent, and effective methods for assessment of their clinical safety. As a result, the progress of these programs and their ability to support critical patient populations safely and efficiently has opportunity to be enhanced.

Null Hypothesis: To aid with ensuring the clear outcome of the workshop we will structure the meeting around a null hypothesis. The null hypothesis we will be testing is "the nonclinical safety evaluation of PROTAC/Molecular Glue based therapeutics does not differ from that of small molecules in any systematic way (for oncology and/or non-oncology indications)".

Meeting Goal: The goal of this workshop is to discuss the preclinical and translational safety assessment of proteolysis targeting chimeras (PROTACs) and molecular glues, focusing on 6 topics as described based on sessions below. To this end, we have recruited speakers and attendees from institutions working actively in the area of PROTACs and molecular glues. The participants who have thus far agreed to help develop each of these sessions are listed here although the actual speaker list is not yet confirmed. It is anticipated that most of the session will be reserved for discussion rather than presentation.

Anticipated Attendance: This think-tank style meeting will be invitational and will engage representatives from the organizations sponsoring the event, those academic, clinical, and government scientists involved in the event design and other invited experts and stakeholders. At present there are approximately 40 scientists (from academia, government, and industry) involved in the planning and design of this event. Total attendance is anticipated to be approximately 250 attendees.

Workshop Outputs: The event will be summarized in a short summary white paper and/or other communication materials for the participants. If feasible, a manuscript highlighting key workshop recommendations, gaps and opportunities will be developed and submitted for peer-review. This workshop may be a single time event or could result in the recommendation to create an ongoing forum for discussion and scientific resolution of the issues that are raised during the event.

Regulatory Panel: In the last session we will have a panel of regulators familiar with the assessment of PROTACs and Molecular Glues. Panelists will provide their opinion (not necessarily that of their organizations) on key questions and challenges that have arisen in the meeting.

Point of Contact: For more information about the event please contact the program lead, Connie Mitchell (cmitchell@hesiglobal.org), HESI Scientific Program Manager or Dr. Syril Pettit, HESI Executive Director (spettit@hesiglobal.org)

Thursday October 14, 2021	Topic
10:00-10:15	**Welcome and Opening Remarks:** Dr. Ruth Roberts, ApconiX, and Dr. Syril Pettit, HESI
10:15-11:00	**Background and Biology:** definitions, scope, de-risking molecules versus de-risking targets **Speaker:** Dr. Lyn Jones, Dana Farber Cancer Institute
11:00-12:30	**Screening and Applied De-Risking Strategies** **Rapporteur:** Dr. Mira Pavkovic, Bayer ***Case Studies***
11:00-11:10	**Leveraging pharmacology experiments for safety data** – Dr. Mira Pavkovic, Bayer
11:10-11:20	*Discussion/Q&A*
11:25-11:35	**A Proteomic Platform to ID Off-Target Proteins Associated with Therapeutic Modalities that Induce Protein Degradation/ Gene Silencing** – Dr. Fan Fan, Amgen,
11:35-11:50	*Discussion/Q&A*
11:50-12:05	**Teratogenic Effects of IMiDs across species and discovery of SALL4 as a target** – Dr. Katie Stamp, BMS
12:05-12:15	*Discussion/Q&A*
12:15-12:30	**Session Discussion and Summary**
12:30-12:40	**Break**
12:40-15:30	**Assessment of ADME, Solubility, PD, and other Considerations** **Rapporteur:** Dr. Laurie Volak, Janssen ***Case Studies:***
12:40-12:55	**Tissue distribution of PROTACs in mice** – Dr. Andreas Reichel & Dr. David Banczyk, Bayer
12:55 -13:10	*Discussion/Q&A*
13:10-13:25	**DMPK optimization challenges for degraders** – Dr. Matthias Wittwer & Dr. Carina Cantrill, Roche
13:25-13:40	*Discussion/Q&A*
13:40-13:55	**Insights into ADME Issues for PROTACs** – Dr. Matthew Hoffman, BMS,
13:55-14:10	*Discussion/Q&A*
14:10-14:20	**Break**

14:20-14:35 14:35-14:50 14:50-15:05 15:05-15:20 15:20-15:30	**ADME Methods to Overcome Technical Challenges in the in vitro Assays for TPD Molecules** – Dr. Dapeng Chen, Kymera *Discussion/Q&A* **ADME Challenges** – Dr. Laurie Volak & Dr. Meghan Pryor, Janssen, *Discussion/Q&A* *Session Discussion and Summary*
15:30	**Adjourn Day 1**

Friday October 15, 2021	**Topic**
10:00-10:10	**Welcome and Day 1 Recap** Ms. Connie Mitchell, HESI
10:10-12:00 10:10-10:35 10:35-10:50 10:50-11:05 11:05-11:20 11:20-11:35 11:35-11:50 11:50-12:00	**Role of Different e3 ligases** **Rapporteur:** Dr. James Sidaway, ApconiX ***Case Studies:*** **Role of different E3 ligases – a case study to exploit tissue selective E3 ligases** - Dr. Hakryul Jo, Kymera *Discussion/Q&A* **E3 ligases and PNS effects** – Dr. Natasa Zamurovic, Novartis *Discussion/Q&A* ***In vivo* tox comparison of dog vs NHP using cereblon mediated degrader** – Dr. Michelle Hemkens, Pfizer *Discussion/Q&A* Combined Discussion and Summary
12:00-12:10	**Break**
12:10-14:00 12:10-12:30 12:30-12:45 12:45-13:00 13:00-13:15	**Species Selection and Selectivity** **Rapporteur:** Dr. Madeline Fort, Amgen ***Case Studies:*** **How to select a pharmacologically relevant species for cereblon modulators** – Dr. Katie Stamp, BMS *Discussion/Q&A* ***In vitro* shifts in potency across species** – Dr. Andrew Burdick, Pfizer *Discussion/Q&A*

13:15-13:30 13:30-13:45 13:45 – 14:00	**Computational approaches in early safety assessment of protein degraders** – Dr. Mohan Rao, Janssen *Discussion/Q&A* Combined Discussion and Summary
14:00-14:10	**Break**
14:10-14:55	**Regulatory Science Panel Discussion and Key Summaries** **Moderator**: • Dr. Jim MacDonald, Synergy Medicines **Panel:** • Dr. Ian Waterson, MHRA • Dr. Jeff Summers, FDA • Dr. Brad Enerson, Kymera
14:55-15:30	**Final thoughts/ Discussion** What does this evaluation of the null hypothesis tell us about how we can move forward as a community to advance safety and development? How do we best support critical patient populations safely and efficiently for PROTACs and Molecular Glues? **Moderators:** Dr. Ruth Roberts, ApconiX and Dr. Lise Loberg, AbbVie
15:30	**Meeting Adjourn**