2nd Targeted Protein Degradation Conference in Japan

Date: 26-27th July 2023

Venue: Shonan iPark (Fujisawa, Kanagawa)

Day 1

7:45 Registration
Networking & Breakfast

8:30 **Opening Remarks**
Yusuke Tominari, Co-founder & CEO, FIMECS

Chair: *Yusuke Tominari*, Co-founder & CEO, FIMECS

Virtual Session

8:35 **Keynote Presentation**
A 'TAC for Every Disease: The Future of Heterobifunctional Modalities
Craig M. Crews, Malone Professor of MCDB; Prof of Chem; Prof of Pharm, Yale University
- History of the PROTAC field; Development of RIPTACs; Novel Modalities using Induced Proximity

9:20 **Characterizing Degraders and Bringing Them to the Clinic**
Danette L. Daniels, Vice President, Degrader Platform, Foghorn Therapeutics
- Targeted protein degradation as a therapeutic modality has experienced an explosion in research the past several years resulting in advancements of many degraders to the clinic as well as opening possibilities in terms of targets and disease indications.
- In this talk the important biological considerations for initiation of a degradation project, our platform approach for therapeutic degrader development, and the approaches we apply to functionally characterize these compounds in relevant cellular context.
- We will also present our discovery and advancement of several new preclinical degraders, including data from our most recently selective CBP and selective EP300 programs.

9:45 **Autophagy-dependent Degradation as A Novel Therapeutic Approach**
Nan Ji, CEO, PAQ Therapeutics
- Ubiquitin-proteosome system vs autophagy system
- PoC Studies of proximity-induced, autophagy-dependent degradation
- Potential of autophagy-based, targeted degradation

10:10 Networking & Coffee Break

Chair: *Jose S. Santos*, Senior Director, DEL&Protein Sciences, Nurix Therapeutics

10:55 **Discovery of Novel E3 Ligands for Targeted Protein Degradation**
Michael Plewe, SVP – Medicinal Chemistry Cullgen
- Human cells express more than 600 E3 ligases.
- Discovery of ligands to novel E3 ligase represents a significant opportunity and major challenge for targeted protein degradation (TPD)
- The Cullin-RING family of E3 ligases is particular suitable for TPD.
- Discovery of novel E3 ligands for TPD at Cullgen

11:20 **PinGLUE: A Platform for Bifunctional and Molecular Glue Degrader Discovery**
Byron DeLaBarre, Head of Platform, Pin Therapeutics
- Our combined universal E3 ligase ligand discovery platform, a novel degron display approach, and phenotypic screening to discover both new bifunctional and molecular glue degrader molecules
- Strategies for therapeutic discovery outside well researched E3 proteins
- Synergy from combined bifunctional and molecular glue efforts

11:45 **Exploring E3 Ligases for Targeted Protein Degradation by Phenotypic-First Approach**
Kanae Gamo, Co-founder, CSO, FIMECS
- RaPPIDS^{TM} platform which allows synthesizing and evaluating a number of degraders rapidly based on the diversity-oriented synthesis with high productivity
- Generation of validated filtering procedures toward the distribution of physicochemical properties and degradation activity enabling an efficient degrader development
- Expanding the landscape of E3 ligases by function-first approach that make the process of degrader discovery more efficient

12:10 **Partner's Presentation**
Drug Discovery Solutions for Targeted Protein Degradation
Meng Ling Choong, Partnership Director (APAC), Eurofins Discovery (on behalf of Cosmo Bio)
- Identify and characterize new, potent, and selective ligands that bind and reprogram E3 ligase substrate specificity with our E3scanTM ligand binding assays.
- Develop, characterize, and validate the warhead end of novel PROTACs with our KINOMEscan®, BROMOscan®, and BCL2scan assay panels
- Enable sensitive quantitation of PROTAC-mediated degradation of targets using Enzyme Fragment Complementation (EFC)-based cellular biosensor cell lines which combine EFC detection technology with CRISPR genome editing in our SPRINTer™ Protein Turnover Biosensor Assays.
- Evaluate the impact of target inhibitors and degraders on efficacy and safety-related translational biomarkers with our BioMAP phenotypic platform.

12:20 Short Break

12:30 **Luncheon Seminar**

DMPK Optimization of Proteolysis-Targeting Chimeras

Genfu Chen, Executive Director, ADME/DMPK, WuXi AppTec

- Challenges in the ADME evaluation of PROTACs
- Strategies and solutions for overcoming those challenges
- Experience and expertise

13:00 Networking & Coffee Break

Chair: *Manfred Koegl*, Scientific Director, Cancer Research, Boehringer Ingelheim

13:30 **Keynote Presentation**

Clinical Translation of Degraders and Building the Next Pipeline of Drugs

Juliet Williams, Senior Vice President, Head of Research, *Kymera Therapeutics*

- Preclinical to clinical translation has now been demonstrated across multiple degrader programs
- Target selection comes first; targeted protein degradation modality enables targeting of highly credentialed targets
- Building a portfolio of revolutionary medicines includes drugging the undruggable, identifying novel E3s, and exploring molecular glues

14:15 **Keynote Presentation**

The Arvinas Discovery Engine: advancing discovery of PROTAC® targeted degraders as potential therapies for cancer and neurological diseases

Miklos Bekes, Associate Director of Platform Biology Arvinas

- Overview of Arvinas' PROTAC portfolio of targeted protein degraders & the Arvinas PROTAC Discovery Engine platform
- Highlights & learnings from our PROTAC degraders across oncology & neuroscience
- Employing classical and novel E3 ligases at Arvinas

15:00 Networking & Coffee Break

Chair: *Philip Chamberlain*, Co-Founder President and CEO, Neomorph

16:00 **PROTACs for neurodegenerative disorders**

Minoru Ishikawa, Professor, Tohoku University

- PROTAC
- Neurodegenerative disorders
- IAP

16:25 **A targeted protein knockdown with the power of plants**

Masato Kanemaki, Professor, National Institute of Genetics/The University of Tokyo

- We employed a plant-specific degradation pathway for developing the auxin-inducible degron (AID) technology
- An improved version, AID2, enables sharp protein knockdown in many eukaryotic species Including mice
- A comparison with other PROTAC-based degrons will be discussed

16:50 **Protein control using targeted degradation approaches to advance oncology drug discovery**

Behnam Nabet, Assistant Professor, Fred Hutchinson Cancer Center

- Development of in vivo-compatible degraders for applications in cancer.
- Development of the dTAG technology platform for cancer drug target validation.
- Advancement of the dTAG technology platform for protein control in murine models.

17:15 **Partner's Presentation**

In Vitro POI Ubiquitination Assay Solution and Application

Lingbing Sun, Senior Director, HD Biosciences

- Introduce a kinetic reading solution to biochemical POI ubiquitination evaluation
- Introduce an universal clean pull-down system for cellular POI ubiquitination evaluation
- Introduce other capabilities and research strategies under TPD platform at HD Biosciences

17:25 Short Break

17:35 **Reception Party**

19:35 Venue Closing

Day 2

8:00 Registration
Networking & Breakfast

8:30 **Opening Remarks**
Masahiko Hayakawa, Vice President, Head of Targeted Protein Degradation, Astellas

Chair: *Masahiko Hayakawa, Vice President, Head of Targeted Protein Degradation, Astellas*

8:35 **Inducing protein degradation for precision medicine against cancer.**
Mikihiko Naito, Project Professor, The University of Tokyo
- Protein degradation by SNIPERs recruiting IAP ubiquitin ligases
- Ubiquitin chain elongation induced by PROTACs and SNIPERs
- Degradation of an oncogenic protein by DUB inhibition

9:00 **Recent Advances in the Thalidomide and CRBN study**
Takumi Ito, Visiting Associate Professor, Tokyo Medical University

9:25 **Resistance mechanism of protein degrader ; lessons learn from Multiple Myeloma patients**
Ryosuke Shirasaki, Senior lecturer, Teikyo university of medicine
- Multiple myeloma treatment has advanced over the years.
- Key drugs for myeloma treatment are IMIDs and proteasome inhibitors.
- E3 ligase CRBN is the most reported resistance mechanism for IMIDs treatment.
- In addition to CRBN itself, other mechanisms of resistance caused by CRL complex have been reported in recent years.

9:50 **Partner's Presentation**
Integrated bioresearch services in Protein Engineering
Takahiro Iwasaki, Protein Purification Group Leader, TechnoPro Inc.
- The research services elevate your projects in protein preparation, screening, cell based research, molecular and biochemical research.
- Our technologies can realize to synthesize hard-to-express proteins with wheat germ cell-free protein expression system.
- PhD researchers are your partners at TechnoPro R&D.

10:00 Networking & Coffee Break

Chair: *Michael Plewe*, SVP – Medicinal Chemistry, Cullgen

10:45 **Discovery of the first clinical KRAS (G12D) degrader ASP3082**
Tomohiro Yoshinari, Associate Director, Research Fellow, Astellas
- A clinical KRAS (G12D) degrader ASP3082 was identified
- ASP3082 induces selective degradation of KRAS (G12D) protein
- ASP3082 potently inhibits KRAS downstream signaling and cell growth
- ASP3082 exhibits anti-tumor activity in KRAS G12D mutated xenograft models

11:10 **Targeted Protein Degradation for the Treatment of Hematologic Malignancies: Addressing both the Enzymatic and Scaffolding Functions of BTK using NX-5948 and NX-2127 in the Clinic**
Jose S. Santos, Senior Director, DEL&Protein Sciences, Nurix Therapeutics
- Potent and Selective Degradation of BTK or a Combination of BTK and IKZF1/3 Provides Superior Efficacy in Preclinical Models of B-cell Lymphoma
- Detailed Analysis of BTK Inhibitor Resistance has Revealed a Previously Unappreciated Scaffolding Function of BTK that Contributes to Oncogenesis.
- Nurix Clinical Stage Degraders are Effective at Eliminating both the Enzymatic and Scaffolding Functions of BTK and Show Clinical Activity Across Mutation and Disease Types.

11:35 **Destruction with a purpose: Targeted protein degradation in oncology drug discovery**
Manfred Koegl, Scientific Director, Cancer Research, Boehringer Ingelheim
- PROTACs and glues open novel opportunities in drug discovery
- Serendipitously isolated glues cause oligomerization of BCL6
- SMARCA2 can be degraded in vivo using VHL based PROTACs
- There are many pitfalls in the search for targeted degraders

12:00 **•Partner's Presentation**
AI-driven de novo PROTAC design and synthetic planning
Hideyoshi Fuji, Senior External Advisor, Iktos SA
Overview and use cases of Iktos' proprietary AI platform (Makya, Spaya, and DockAI) for drug design and discovery.
- Makya – the ligand and structure-based de novo drug design platform for chemical space exploration and Multi-Parametric Optimization (MPO) of lead compounds in line with Target Candidate Profile (TCP).
- Spaya – the data-driven retrosynthetic analysis AI which performs an exhaustive analysis of all possible synthetic routes for a given compound.
- DockAI – the new technology that combines docking with a state-of-the-art active learning methodology to significantly improve the efficiency and effectiveness of an ultra-large scale virtual screening.

12:10 Short Break

12:20 **Luncheon Seminar**

Bifunctional Degrader Modeling and Design with the Schrödinger Platform

Agustina Rodriguez-Granillo, Sr Principal Scientist, Schrödinger

- Overview of the Schrödinger platform and its application to bifunctional degrader design

12:50 Networking & Coffee Break

Chair: *Byron DeLaBarre*, Head of Platform, Pin Therapeutics

13:20 **Druggable Genome Expansion Through Novel Molecular Glue Discovery**

Philip Chamberlain, Co-Founder, President and CEO, Neomorph

- Molecular glues enable the degradation of 'undruggable' targets with broad proteome coverage
- The thalidomide analogs offer a deep case-study in molecular glue mechanism of action
- The discovery of neosubstrate degrons has enabled prospective glue target searches
- A systematic survey for new glues has yielded novel ligase/substrate systems
- Structure-based efforts are showing promise for rational optimization of novel glue systems

13:45 **Intramolecular Bivalent Molecular Glue: A Novel Mechanism for Targeted Protein Degradation**

Tasuku Ishida, Senior Scientist, Eisai

- The sulfonamide-based PROTAC does not use DCAF15 for BRD4 degradation
- BRD4 degradation is highly dependent on DCAF16
- The BRD4BD1 and BRD4BD2 tandem structure is essential for the degradation
- This PROTAC-like molecule binds bivalently to BRD4 and induces the formation of the BRD4-compound-DCAF16 ternary complex as a molecular glue

14:10 **Panel Discussion**

Present and Future of Targeted Protein Degradation; Target, Technology, Challenges, and External Collaboration

Facilitator: *Yusuke Tominari*, Co-founder & CEO, FIMECS

Panelist: *Philip Chamberlain*, Co-Founder President and CEO, Neomorph
Masahiko Hayakawa, Vice President, Head of Targeted Protein Degradation, Astellas
Manfred Koegl, Scientific Director, Cancer Research, Boehringer Ingelheim
Juliet Williams, Senior Vice President, Head of Research, Kymera Therapeutics

14:55 Networking & Coffee Break

Chair: *Mikihiko Naito*, Project Professor, The University of Tokyo

15:55 **Ubiquitin and deubiquitination to study TPD and TPS**

David Komander, Professor, Walter and Eliza Hall Institute of Medical Research (WEHI)

- Protein ubiquitination is at the core of all TPD applications.
- We are providing key methods and approaches to study ubiquitination and bolster MOA studies for TPD modalities.
- Deubiquitinases/DUBs are key regulators of protein stability. DUB inhibitors are emerging anti-cancer agents.
- Targetted protein stabilisation through DUB recruitment promises to be an exciting new modality to interfere with protein function.

16:20 **Targeting Selective Autophagy by AUTAC degraders**

Hirokazu Arimoto, Professor, Tohoku University

- AUTAC (autophagy-targeting chimera) technology enables the selective degradation of proteins and mitochondria by harnessing autophagy.
- In this presentation, I will discuss the current understanding of the mechanism by which AUTAC degraders selectively target proteins for degradation.

16:45 **TPD² - Dual-Precision Targeted Protein Degradation by Antibody Delivery**

James Palacino, Head of Oncology/Biology, Orum Therapeutics

- Orum's Dual-precision targeted protein degradation (TPD²) approach increases the safety window and improves drug delivery of TPDs by combining the catalytic approach of TPDs with the precision of tumor targeting therapeutic antibodies.
- Two lead molecules applying the TPD² approach leverage a highly potent and selective GSPT1 molecular glue conjugated to a HER2/3 targeting antibody for ORM-5029 (in Phase 1), and a CD33-targeting antibody for ORM-6151.
- ORM-5029 and ORM-6151 have demonstrated superiority to traditional TPDs in terms of efficacy, safety profile, and pharmacokinetics.
- Orum's TPD² approach also enables the conjugation of heterobifunctional degraders to antibody, demonstrating superior potency and specificity compared to traditional small molecule degraders, holding promise to target a vast number of proteins of interest and indications.

17:10 **Partner's Presentation**

Comprehensive Protein Analysis using AI and Innovative Two-Dimensional Electrophoresis Method

Hiroshi Sakai, Chief Strategy Officer, aiwell.inc

- Advanced Two-Dimensional Electrophoresis: Achieving High Reproducibility and Precision in Comprehensive Protein Analysis
- Cost-effective and Time-efficient Compared to Other Proteomics Modalities
- Proficient in Analyzing Protein Chemical Modifications

17:20 **Closing Remarks**

Mikihiko Naito, Project Professor, The University of Tokyo

WiFi

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Transportation

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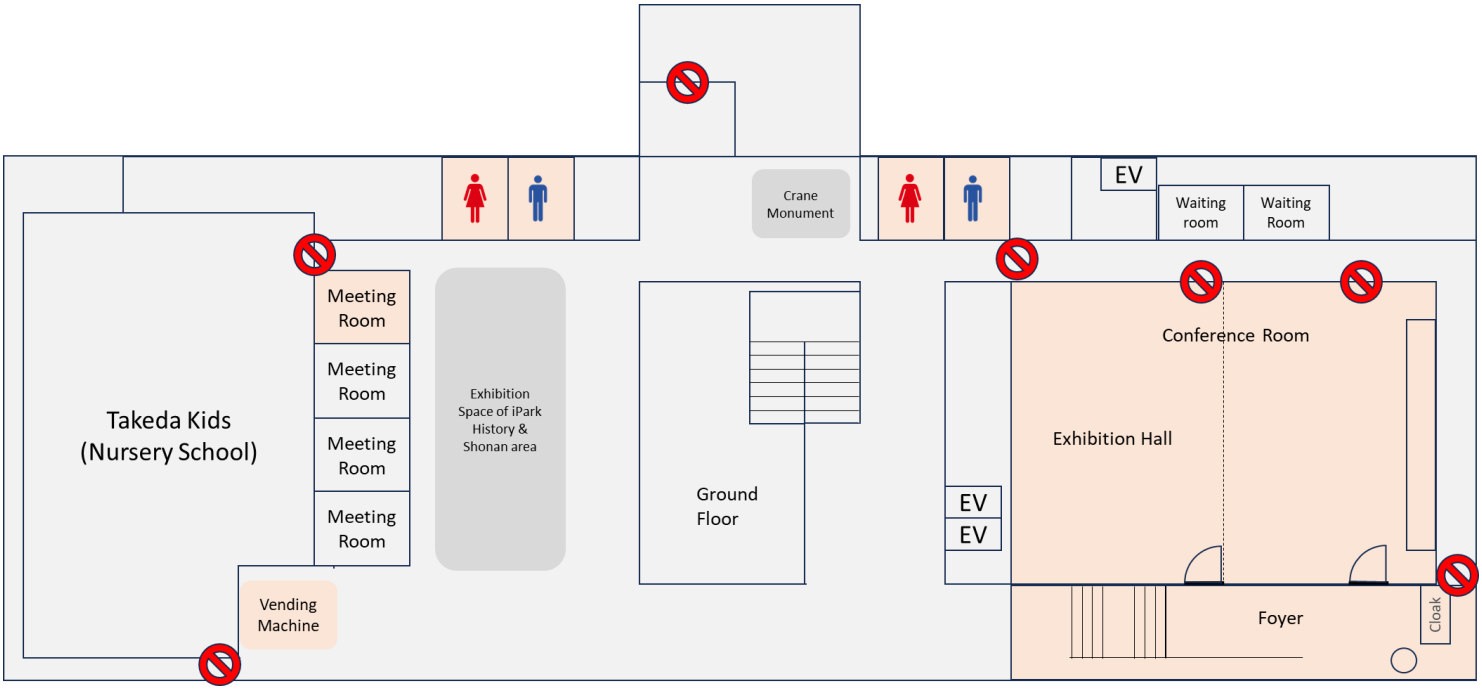

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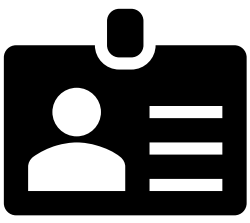

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