Contemporary Targeted Protein Degradation (TPD) & Induced Proximity - Key Strategies & Priorities to Enable Successful Therapeutic Discovery: A Training Course

Outline - May 2024

Course can be given to any group size, in a lecture room or smaller room or via video link. The course content is applicable to all drug discoverers including medicinal chemists, disease biologists and pharmacologists/drug metabolism scientists. Some sessions may be more relevant to eg medicinal chemists.

Course is intended to be interactive with frequent questions posed to audience to stimulate discussion.
A chemistry design workshop option is also included (in session 4) which is most applicable to medicinal chemists.

Exact content and format to be agreed with client. Example format 4 x 2h sessions (8h total time) shown below. Options for more condensed courses (topics tba) of 2-6h also available.

Any section below can be expanded or removed to create a custom training programme to fit the needs of your scientists.

Example session contents:

Session 1 - TPD fundamentals

1a - Why would you want to degrade a target and how can you do it? (30mins)

- Advantages of degradation over inhibition of a target
- PROTACs
- Molecular glues
- Other degrading approaches (AbTACs, LYTACs, AUTACs etc)

1b - Basic bifunctional TPD concepts and implications for PROTAC design (45mins)

- What needs to be optimised to give an active degrader?
- Ternary complex and octonary complex architecture
- Mathematical considerations
- Kinetic factors including Dmax
- Hook effect

- E3 ligase vs PoI stoichiometry
- Glues vs PROTACs - design approaches, pros and cons

1c - *Assay set up and data interpretation* (45mins)

- Assay types (WB, HiBit, FRET, NanoBRET etc)
- Use of functional assays
- Cell type choice
- Controls
- Data interpretation - what is a real hit? Potential for false positives
- Considerations setting up a screening cascade
- Optional Workshop - data interpretation class

Session 2: *Medicinal chemistry & DMPK optimisation considerations for designing PROTACs*

2a - PROTAC med chem design for efficient degraders (60mins)

- Target selection (sub-cellular location, half-life, PROTACtability)
- Linker design
- Choice of E3 ligase (CRBN/VHL/other E3 pros & cons)
- POI ligand choice
- Optimisation strategies
- Synthetic chemistry strategies
- Computational methods

2b - PROTAC DMPK properties (60mins)

- Available dosing routes
- Metabolism considerations
- Properties to get oral availability
- Using and interpreting in vitro ADME assays
- In vivo studies
- Species differences
- Biodistribution
- CNS penetration

Session 3 - Assessing PROTAC in vivo efficacy, safety & other development considerations;

3a - Assessing degrader efficacy (60mins)

- Role of primary cells

- Animal models - issues of rodent CRBN
- PD studies
- Differentiating inhibitor vs degrader-based efficacy
- Role of Dmax to drive efficacy
- Free drug hypothesis
- AUC vs Cmax driven efficacy
- In vivo hook effect

3b - Assessing degrader safety & development (60mins)

- How to assess selectivity
- Interfering role of cytotoxicity
- Role of CRBN neosubstrates
- In vivo safety
- Considerations leading up to GLP tox studies
- Chemical scale up and physical form

Session 4 - PROTAC interactive design workshop & Emerging applications of bifunctional agents

4a - PROTAC interactive design workshop - developing an optimisation strategy for degraders of an exemplar target (75mins - split into teams of 6-8 to devise a chemistry optimisation plan based on a dossier of provided information)

4b - Other emerging induced proximity-based approaches beyond PROTACs and glues (45mins)

- Degrader antibody conjugates
- DUBTACs
- Using alternative effectors - recruiting kinases, glycosylases etc
- Cellular redistributors