Lecture Series – Modern Drug Discovery

Binding characterization of DNA-encoded-library (DEL) compounds in tripartite protein complexes

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Abstract: To start off, I will give a brief introduction to Amgen Research Copenhagen (ARC), its capabilities and focus into its DNA Encoded Library Small Molecule platform (DEL). (https://www.youtube.com/watch?v=8jLIgTBJmdU) Targeted protein degradation and the use of heterobifunctional small molecules to create tripartite protein complexes has risen to be one of the new paradigms within drug discovery. By harnessing the cells' own proteolytic system, instead of classically inhibiting a target difficult to drug, targets can be removed by this process. Recently, this non-natural complex formation has been extended to include a myriad of new avenues to 'inhibit' cellular functions. E.g., complementing the popular PROTACs, PhosTACs recruit phosphatases, LYTACs are lysosome targeting molecules, and ReloTACs relocate proteins to different compartments of the cell, among others. What they all have in common is the ability to introduce a Ternary Complex induced by the small-molecule. Traditional small molecule drugs exhibit a simplistic 2-body interaction problem with a range of technologies at our disposal. In contrast, the 3-body problem when using hetero-bifunctional molecules to form Ternary Complexes introduces a much more less easily deduced system. A wide range of assays, their limitations and need to re-design is presented to properly understand the Ternary Complex formation, a prerequisite for their quantitative assessment and optimization for drug discovery.

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If you wish to meet the speaker, please contact Prof. Rasmus Linser (rasmus.linser@tu-dortmund.de).