PRINCIPE FELIPE
CENTRO DE INVESTIGACION

CIPF Seminar

Targeted protein degradation: a novel paradigm in drug development

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Date: **15/05/20- 12:30h**
Place: Salón de Actos CIPF

Abstract: Only 10-20% of all proteins are within the reach of traditional inhibitors. Since they mostly rely on occupancy of accessible pockets, the vast majority of proteins, including the most prolific cancer targets (KRAS, MYC...) are chemically inaccessible by conventional approaches. Targeted protein degradation (TPD) is a new paradigm in drug development that promises to overcome limitations of traditional pharmacology. It is based on small molecules, often called degraders, which induce proximity between an E3 ubiquitin ligase and a target protein of interest, leading to target ubiquitination and proteasomal degradation. The shift from "inhibition" to just "binding" comes with the promise to allow the targeting of proteins so far considered undruggable. We set out to systematically delineate all cellular effectors required for TPD efficacy. We found that sensitivity to degraders is mainly dictated by shared modulator networks, with some interesting, ligase-specific differences. Collectively, our study informs on regulation of E3s amenable for TPD, and outlines biomarkers and putative resistance mechanisms for upcoming clinical investigation. Downstream efforts also allowed us to develop the first rational strategy described so far to look for novel degraders of the type known as "molecular glues".

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