CRBS

Special Seminar Announcement

Chemical biology of drug resistance

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I will discuss how the analysis of resistance, which is generally considered to be a limitation of molecularly targeted therapeutics, can be leveraged to address major challenges in chemical biology. First, characterizing chemotype-specific resistance can help deconvolve a chemical inhibitor's mechanism of action in human cells and achieve 'gold standard' validation of its direct target, i.e. when a silent mutation in the target suppresses drug activity in cell-based and biochemical assays. Second, examining resistance can help with the use of chemical inhibitors as probes of cellular mechanisms. In particular, phenotypes due to target inhibition can be identified as those observed in wildtype cells, across a range of inhibitor concentrations, but not in matched cells with a silent resistant-conferring mutation in the target. Finally, I will highlight our recent efforts to design new chemical inhibitors for AAA+ (ATPases associated with diverse cellular activities) proteins. Our approach, named RADD (Resistance Analysis During Design), involves testing selected chemical scaffolds against constructs with engineered silent mutations. Identifying mutations that confer resistance lead to robust inhibitor-target binding models that guide improvements in inhibitor potency and selectivity. These data can also help develop chemical strategies to overcome or delay the emergence of resistance.

Wednesday, Feb. 2nd, 2022
12:30 pm EST, via ZOOM

Zoom Link:
https://mcgill.zoom.us/j/81472776630?pwd=bFJVeGVoWjU0VXpPWTFUeHRFcW15Zz09

Meeting ID: 814 7277 6630
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