2021 lecture series

238th IBB Seminar

“Taking a Bead on HIV: Developing HIV-1 Integrase Inhibitors that Are Broadly Effective Against Resistant Viruses”

~ the 2019 ACS Hillebrand Prize ~

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National Cancer Institute (NCI)/National Institutes of Health (NIH)

日時：令和 3 年 1 月 12 日（火）9:00～10:30

開催方法：Zoom によるオンライン開催

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Abstract: HIV-1 encodes three enzymes that are essential for viral replication. Drugs that target these three enzymes are widely used in the combination anti-retroviral therapies (cART) that have dramatically improved patient outcomes. Yet, developing clinically relevant inhibitors of the third viral enzyme, integrase (IN) has been much more difficult. It wasn’t until 2007 that raltegravir (RAL) became the first IN inhibitor to receive FDA approval. However, the high mutation rate of HIV-1 means that there are some drug-resistant variants already present in a patient when therapy is initiated. Understanding the resistance mechanisms and developing drugs that are broadly effective against the known resistant variants is an important and ongoing objective of HIV research. In a more than 25-year collaboration we have worked to develop therapeutically relevant IN inhibitors. Our work has culminated in the discovery of potent IN inhibitors that retain greater antiviral potency against known drug resistant mutants than the best FDA-approved IN inhibitors. X-ray crystal structures of our inhibitors bound to the prototype foamy virus integrase and, more recently, cryo-EM structures of our inhibitors bound to HIV-1 IN, have greatly improved our understanding of what makes a broadly effective IN inhibitor. Our findings will inform the design of new IN inhibitors, which may be able to better retain efficacy against resistant mutant forms of IN.

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