SAPIENZA
UNIVERSITÀ DI ROMA

Dipartimento di Chimica
e Tecnologie del Farmaco

AVVISO DI CONFERENZA

Si comunica che il giorno 4 luglio 2019, alle ore 11, nell'Aula A "R. Giuliano" della Facoltà di Farmacia e Medicina (Edificio CU019) dell'Università Sapienza, il

Prof. Mamuka Kvaratskhelia

(Division of Infectious Diseases, University of Colorado School of Medicine, Aurora, CO, USA)

terrà una conferenza sul tema

"Allosteric HIV-1 Integrase Inhibitors"

La S.V. è invitata ad intervenire.

Il Proponente
Prof. Roberto Di Santo

Allosteric HIV-1 integrase (IN) inhibitors (ALLINIs) are a promising new class of antiretroviral agents that disrupt proper viral maturation by inducing hyper-multimerization of IN. ALLINIs potently inhibit HIV-1 replication during virion maturation by inducing hyper- or aberrant IN multimerization but are largely ineffective during the early steps of viral replication. We have synthesized the highly active pyridine-based (-)-KF116 enantiomer, which displayed EC50 of ~7 nM against wild type HIV-1 and ~10-fold higher, sub-nM activity against a clinically relevant dolutegravir resistant mutant virus suggesting potential clinical benefits for complementing dolutegravir therapy with pyridine-based ALLINIs. Mechanistic and structural studies demonstrated that KF116 exhibits striking selectivity for IN tetramers versus lower order protein oligomers. IN structural features that are essential for its functional tetramerization and HIV-1 replication are also critically important for KF116 mediated higher-order IN multimerization. Live cell imaging of single viral particles revealed that KF116 treatment during virion production compromises the tight association of IN with capsid cores during subsequent infection of target cells. Viral genotyping in the presence of KF116 uncovered an unexpectedly complex mechanism for the evolution of drug resistance to KF116 with the stepwise emergence of the triple substitutions in IN. These findings highlight a relatively high genetic barrier exerted by KF116 and argue for extending efforts for potential clinical application of these compounds.

Recent Publications:

1. Koneru PC, Francis AC, Deng N, Rebensburg SV, Hoyte AC, Lindenberger J, Adu-Ampratwum D, Larue RC, Wempe MF, Engelman AN, Lyumkis D, Fuchs JR, Levy RM, Melikyan GB, Kvaratskhelia M. (2019) HIV-1 integrase tetramers are the antiviral target of pyridine-based allosteric integrase inhibitors. Elife. PMID 31120420
2. Passos DO, Li M, Yang R, Rebensburg SV, Ghirlando R, Jeon Y, Shkriabai N, Kvaratskhelia M, Craigie R, Lyumkis D. (2017) Cryo-EM structures and atomic model of the HIV-1 strand transfer complex intasome. Science. 355(6320):89-92. PMID: 28059769.
3. Kessl JJ, Kutluay SB, Townsend D, Rebensburg S, Slaughter A, Larue RC, Shkriabai N, Bakouche N, Fuchs JR, Bieniasz PD, Kvaratskhelia M. (2016) HIV-1 integrase binds the viral RNA genome and is essential during virion morphogenesis. Cell 166, 1257-1268. PMID: 27565348.
4. Sharma A, Slaughter A, Jena N, Feng L, Kessl JJ, Fadel HJ, Malani N, Male F, Wu L, Poeschla E, Bushman FD, Fuchs JR, Kvaratskhelia M. (2014) A new class of multimerization selective inhibitors of HIV-1 integrase. PLoS Pathog. 10(5):e1004171.
5. Jurado KA, Wang H, Slaughter A, Feng L, Kessl JJ, Koh Y, Wang W, Ballandras-Colas A, Patel PA, Fuchs JR, Kvaratskhelia M, Engelman A. (2013) Allosteric integrase potency is determined through the inhibition of HIV-1 particle maturation. Proc Natl Acad Sci USA 110(21):8690-5.