UCDAVIS HEALTH | SCHOOL OF MEDICINE

Medical Microbiology & Immunology
MMI 291 Seminar Series
Emerging Challenges in Microbiology and Immunology

MMI 291 Seminar Series

Current Theme: Interdisciplinary Research
Fall Quarter 2021 – CRN 41611

Friday Seminar – 12:10-1 PM

MICROBIOLOGY GRADUATE GROUP EXIT SEMINAR

"Broad Spectrum Antiviral Activities of Recombinant Enhanced Antiviral Restrictors (REAVRs)"

Research / Bio

Most virus families produce double-stranded (ds) RNA during their lifecycles, which can be sensed by multiple dsRNA-dependent innate immune sensors, including two potent host restriction factors OAS/RNase L and PKR. PKR mainly restricts replication of viruses that are dependent on eIF2, and RNase L inhibits viral replication via degradation of host and viral RNAs. However, while PKR is directly activated by dsRNA, RNase L activation depends on the OAS to both bind dsRNA and synthesize 2'-5' oligoadenylate (2-5A). We hypothesized that engineering proteins to combine the dsRNA sensor domain of PKR with the effector domain of RNase L would bypass the need for OAS activation, making them less susceptible to inhibition by viral molecules, and preserve their potent antiviral activity. To test this, we generated Recombinant Enhanced Antiviral Restrictors (REAVRs) by combining dsRNA-binding domains of PKR from different species with the effector domain of human RNase L. We show that REAVRs led to RNA degradation and decreased the activity of a luciferase reporter, suggesting the REAVRs are functionally active. To investigate whether REAVRs could restrict viral replication, we generated T-REx 293 cells containing a single REAVR copy under the control of a doxycycline-inducible promoter. Some REAVRs exerted potent antiviral activities against five tested viruses: vaccinia virus, dengue virus, Zika virus, SARS-CoV-2, and vesicular stomatitis virus. Importantly, these REAVRs were also effective against viruses that are resistant to PKR activation, for example, SARS CoV-2 and flaviviruses. This study provides proof-of-concept that REAVRs are active in vitro and exhibit antiviral effects on various families of viruses.

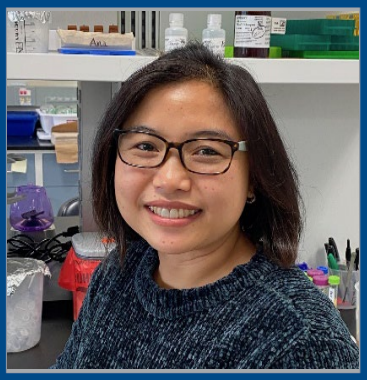
Publications

Megawati D, Peng C, Stoian A, Banerjee S, Brennan G, Rothenburg S. Broad Spectrum Antiviral Activities of Recombinant Enhanced Antiviral Restrictors (REAVRs). *In preparation*

Megawati D, Stroup JN, Park C, Clarkson T, Brennan G, Rothenburg S. Inhibition of Primate Protein Kinase R (PKR) by Yatapoxvirus K3 Orthologs. *In preparation*

Megawati D, Ryan C. Bruneau Brennan G, Rothenburg S. Diverse strategies used by viruses to evade PKR and OAS/RNase L pathways. *In preparation*

Nov
19



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Nov 19, 2021
12:10 – 1 PM
ZOOM Meeting

Medical Microbiology
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We hope to see you there!