

Mentor-Postdoc Spotlights Series 2019



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With over 35 years of research experience, Dr. Alan Engelman received a PhD in Molecular Biology and Microbiology from Tufts University School of Medicine under the guidance of Dr. Naomi Rosenberg. He is now a tenured Professor of Medicine in the Department of Cancer Immunology and Virology at the Dana-Farber Cancer Institute and at Harvard Medical School.

After completing his Masters in Life Science Engineering at Tufts University, Dr. Engelman studied the relationship between Abelson murine leukemia virus protein tyrosine kinase activity and the transformation of pre-B cells at the Sackler School of Graduate Biomedical Sciences, which is part of Tufts University School of Medicine. Dr. Engelman performed postdoctoral studies under the mentorship of Drs. Robert Craigie and Kiyoshi Mizuuchi at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH, where he focused on HIV integration. Their work determined that (1) HIV integrase cleaves and joins DNAs via one-step transesterification reactions, (2) a protease resistant central domain of integrase, which they called the catalytic core domain (CCD), harbored an invariant D,D-35-E motif that comprised the enzyme active site, and (3) integrase functioned as a multimer, with the N-terminal domain of one integrase molecule working in trans with the CCD of a separate integrase protomer within the multimer. Dr. Engelman has continued to focus on HIV integration since starting his own laboratory, expanding his approaches to include structural biology and genome-wide mapping of integration sites within chromosomal DNA. Such efforts have yielded novel X-ray crystal, NMR, and single-particle cryo-EM structures, elucidated the roles of virus-host interactions in determining sites of HIV-1 integration, and shed light on the mechanism of action of the novel class of HIV-1 inhibitors called the allosteric integrase inhibitors (ALLINIs). In collaboration with his postdoctoral trainee Dr. Peter Cherepanov, Dr. Engelman solved the 3-dimensional structure of the prototype foamy virus integrase-DNA complex or intasome, which for the first time revealed the architecture of the active nucleoprotein complex and explained the mechanism of action of the clinical strand transfer inhibitors. Additional intasome structures have revealed a common integrase-DNA structure at the heart of the retroviral machines, which Dr. Engelman and Dr. Cherepanov have termed the conserved intasome core (CIC).

With more than 175 publications to his credit, Dr. Engelman currently focuses on: 1. Virus-host interactions in HIV-1 pre-integration trafficking and nuclear import, 2. mechanism of HIV DNA integration,

3. structural biology of retroviral intasomes and virus-host interactions, 4. mechanisms of action of HIV integrase inhibitors.

Notable publications from Dr. Engelman's lab that influenced the HIV field are:

1. Engelman A, Mizuuchi K, Craigie R. HIV-1 DNA integration: mechanism of viral DNA cleavage and DNA strand transfer. *Cell* 1991 67:1211-1221.
2. Hare S, Gupta SS, Valkov E, Engelman A, Cherepanov P. Retroviral intasome assembly and inhibition of DNA strand transfer. *Nature* 2010 464:232-236.
3. Achuthan V, Perreira JM, Sowd GA, Puray-Chavez M, McDougall WM, Paulucci-Holthauzen A, Wu X, Fadel HJ, Poeschla EM, Multani AS, Hughes SH, Sarafianos SG, Brass AL, Engelman AN. Capsid-CPSF6 interaction licenses nuclear HIV-1 trafficking to sites of viral DNA integration. *Cell Host Microbe* 2018 24:392-404.e8.

Dr. Engelman fondly recalls his Ph.D. mentor Dr. Rosenberg's classification of postdoctoral training as the "golden era" of one's scientific career, when researchers are generally relieved from responsibilities associated with graduate school education and tenure track positions. E.g., in graduate school, one must qualify for PhD through the completion of coursework and examination, write reports and attend regular thesis committee meetings, and then write and orally defend the PhD thesis. Of course, responsibilities further burgeon when one sets up one's own lab, as one has to assume Administrative and Mentorship caps, in addition to ongoing experimentation and likely some formal classroom teaching. Hence, Alan's key advice to postdocs is, "**take full advantage of the golden era of your research career, work hard, stay focused on research goals, and reach out to your mentors for advice and support.**"

Check out the lab's webpage: <http://engelmanlab.med.harvard.edu/people.html>



Dr. Vasudevan Achuthan obtained his PhD from University of Maryland in 2016 under the mentorship of Dr. Jeffrey J. DeStefano. His doctoral thesis focused on the topic "*HIV Reverse Transcriptase fidelity and inhibition are modulated by divalent cations in a concentration-dependent manner in vitro*". After his Ph.D., Dr. Achuthan joined the Engelman lab at Harvard Medical School.

With a decade worth of research experience, Dr. Achuthan has 7 publications in renowned journals to his credit.

Please read the Achuthan *et. al.* manuscript titled "Capsid-CPSF6 interaction: Master regulator of nuclear HIV-1 positioning and integration" published in this inaugural issue of *JoLS, Journal of Life Sciences*.