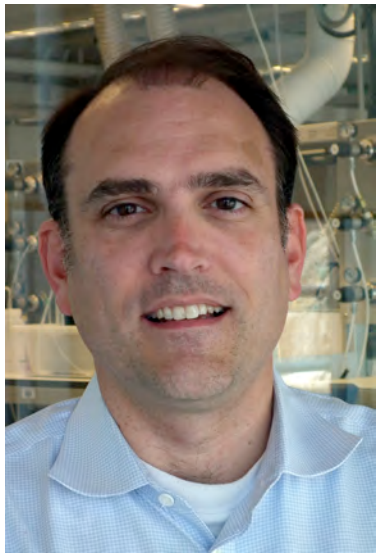

2017-2018 POCC Lecture Series

May 24, 2018, 7:30 PM

Dean G. Brown, Ph.D

AstraZeneca Pharmaceuticals

Current and future perspectives on molecular screening libraries and synthetic methods in drug discovery

Carolyn Hoff Lynch Lecture Hall
Chemistry Building, University of Pennsylvania

The Philadelphia Organic Chemist's Club

POCClub.org

Dr. Dean Brown is currently Director of External Chemistry at AstraZeneca Pharmaceuticals within the Discovery Sciences IMED Biotech Unit.

Dean received his B.S. degree in Chemistry at Abilene Christian University and a Ph.D in Organic Synthesis at the University of Minnesota under Professor Thomas Hoye. Dean joined AstraZeneca as a medicinal chemist in Wilmington Delaware in the neuroscience disease area and led chemistry efforts on multiple programs for neuropathic pain, Alzheimer's disease and psychiatry. Dean then led the CNS Lead Generation Chemistry group from 2006-2010, and was responsible for the delivery of many new programs culminating in several clinical candidates. In 2010, Dean moved to the AstraZeneca Boston Infection team with a focus of building new programs for multi-drug resistant infections and respiratory viral infections. Dean helped to rebuild the lead generation portfolio of programs and ultimately managed the project transitions for Entasis, the AstraZeneca infection spin-off company launched in 2015.

In 2015 Dean joined the AstraZeneca Neuroscience unit as a Director and Project Leader. This led to an appointment in the Discovery Sciences group where he is responsible for the neuroscience open innovation efforts, a portfolio of 20+ programs with world leading academic researchers, biotech companies and funding agencies in neurodegenerative diseases and neuropathic pain. Dean is also leading the AstraZeneca DNA-encoded library screening in partnership with XChem Pharmaceuticals. He is listed as an author and co-author on more than 50 publications and patent applications. Dean has received the AstraZeneca publication of the year award (2017) as well as the AstraZeneca team of the year award (2014) for his efforts on the structure based drug design for the GPCR, Protease-activated receptor 2 (PAR2).

Abstract: Drug discovery is both critically dependent on the types molecular libraries used to find new chemical starting points as well the types of chemistry employed to expand these initial hits. We have determined that both the selection of reagents and reactions used in library synthesis heavily favor certain functional groups (e.g. p-ClPh) and reaction types (e.g. Amide, Suzuki, SNAr). The justification for this bias does not seem to be scientific, but rather driven by historical reasons of synthetic ease. The continued accumulation of these types of compounds in screening libraries reinforces a misleading bias that these are privileged fragments and reactions types, and thus propagates further investment in these areas. Furthermore, these types of reactions result in very narrow population of chemical shape space towards linear and rod-shaped compounds. Uptake of diverse reaction types and reagents are likely needed to expand chemical diversity for the new generation of drug discovery target classes. We will discuss the pros and cons of the typical medicinal chemistry synthetic toolbox, as well as future directions and synthetic technologies where improvements are being made.