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Northeastern Section
American Chemical Society
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Webinar

"The Discovery of Sotorasib (AMG 510), a First-in-class Covalent Inhibitor of $KRAS^{G12C}$"

By **Brian Lanman, Amgen**

Organized by the Medicinal Chemistry Section
of the Northeastern Section, American Chemical Society (NESACS)

Thursday – January 21st, 2021
4.00 pm

Register for the January Webinar meeting at:

https://american-chemical-society.zoom.com/webinar/register/WN_f7lbcbQnQRG-PSkXoQsPJQ

SPEAKER

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Brian Lanman
Director of Research, Amgen

Bio: Brian Lanman received his A.B. in Chemistry from Harvard University (1998), where he performed undergraduate research on the total synthesis of Taxol® in the labs of Yoshito Kishi. He subsequently completed doctoral studies at Harvard as an NSF research fellow under the guidance of Andy Myers, receiving A.M. (2000) and Ph.D. (2004) degrees for his work on the solid-supported synthesis of tetrahydroisoquinoline antitumor antibiotics. In 2004, he joined Larry Overman's group at UC Irvine as an NIH postdoctoral fellow, where he developed methods to access the architecturally complex bis-guanidine marine natural product palau'amine and contributed to its structural revision. Brian joined the medicinal chemistry department at Amgen in 2006, where he has since led chemistry and discovery research efforts on projects in the inflammation, oncology, and cardiovascular therapeutic areas. Most recently, Brian led the medicinal chemistry team that discovered sotorasib (AMG 510), Amgen's first-in-class $KRAS^{G12C}$ inhibitor, which is currently in phase 2 clinical trials for the treatment of $KRAS^{G12C}$-mutant non-small cell lung cancer.

Abstract: *KRAS* is one of the most frequently mutated oncogenes in human cancer. Despite more than three decades of research, indirect approaches targeting *KRAS* mutant cancers have largely failed to show clinical benefit, and direct approaches have been stymied by the apparently 'undruggable' nature of KRAS. Cysteine-12 of $KRAS^{G12C}$ has emerged as a unique vulnerability in *KRAS*-mutant cancers. I'll describe our efforts to identify cysteine-reactive molecules capable of selectively inhibiting $KRAS^{G12C}$. Through iterative screening and structural biology efforts, we identified novel Cys12-reactive inhibitors that derived their potency from occupancy of a previously unknown cryptic pocket induced by side-chain motion of the His95 residue of KRAS. We leveraged knowledge of this cryptic pocket to design a series of inhibitors that demonstrated significantly enhanced potency relative to prior tool compounds. Extensive optimization of these leads led to the identification of a highly potent, selective, and well-tolerated covalent inhibitor, sotorasib (AMG 510), which has become the first direct $KRAS^{G12C}$ therapeutic to enter human clinical testing.

Symposium Organizing Committee: Brian Aquila, Mark Ashwell, Scott Edmondson, Dan Elbaum, Jeremy Green, Paul Greenspan, Adrian Hobson, Blaise Lippa, Lisa Marcaurelle, Min Lu, Kap-Sun Yeung, Andrew Scholte, Raj (SB) Rajur (Chair)

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