Profile of an Early-Career Researcher

Dr Brian Lanman

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This issue's Early Career Profile highlights Dr. Brian Lanman, a Principal Scientist in the Medicinal Chemistry department at Amgen in Thousand Oaks, California, USA. Brian leads cross-functional teams in the discovery and pre-clinical development of new therapies, principally in the oncology therapeutic area. A synthetic organic chemist by training, Brian also directly supervises a team of medicinal chemists in the design of new lead molecules, relying extensively on structure-based design, computational modeling, and state-of-the-art high-throughput experimental platforms. Most recently, Brian led Amgen's chemistry efforts investigating covalent inhibitors of KRAS(G12C), coordinating efforts across an international team in the identification of AMG 510 (pINN sotorasib), the first investigational KRAS(G12C) inhibitor to enter human clinical trials. Brian received his A.B. in Chemistry from Harvard University (1998), where he performed undergraduate research on the total synthesis of Taxol® in the lab of Yoshito Kishi, and had his first exposure to pharmaceutical research as a summer intern at Schering-Plough Pharmaceuticals. Brian subsequently completed his doctoral studies at Harvard as an NSF research fellow under the guidance of Andrew Myers, receiving A.M. (2000) and Ph.D. (2004) degrees for his work on the solid-supported synthesis and biological characterization of tetrahydroisoquinoline antitumor antibiotics. In 2004, Brian joined Larry Overman's group at UC Irvine as an NIH postdoctoral fellow, where he developed new synthetic methods to access the architecturally complex bis-guanidine marine natural product palau'amine and contributed to its structural revision.

Brian joined Amgen's medicinal chemistry department in 2006. His early research focused on the optimization of sphingosine-1-phosphate receptor-1 (S1P1) agonists for the treatment of multiple sclerosis, leading to the identification of the investigational agent AMG 369. Brian subsequently began work in the oncology therapeutic area, contributing to research on PI3Kα and PIM kinase inhibitors. This work, which leveraged unique kinase structural features to impart kinome selectivity and led to the identification of the investigational PI3Kα inhibitor AMG 511, initiated a long-standing research focus on structure-based drug design.

After a brief foray into cardiovascular research—exploring lipid conjugation as a strategy for the half-life extension of APJ agonist peptides—Brian returned to oncology research to lead medicinal chemistry teams focused on the disruption of protein-protein interactions. During this time, Brian contributed to the discovery of AMG 397, Amgen's investigational oral Mcl-1 inhibitor, and led chemistry efforts in the development of covalent β-catenin/TCF4 inhibitors for the potential treatment of colorectal cancer.

Brian became involved with KRAS inhibitor efforts in 2013. Following an initial exploration of published non-covalent binders in the design of Cys12-reactive covalent inhibitors and the identification of several promising starting points from in-house screening efforts, research efforts accelerated in 2015, when new hits from focused covalent inhibitor libraries were found to occupy a previously unknown cryptic pocket on the KRAS protein. Binding to this “H95-pocket” significantly enhanced inhibitor potency, and kick-started an intense period of research, during which Brian led efforts to optimize early leads and, subsequently, to leverage knowledge of this new pocket to develop novel inhibitor scaffolds with improved pharmacokinetic properties. By 2017, optimization efforts had overcome multiple pre-clinical development hurdles (e.g., atropisomer configurational stability, metabolic liabilities, moderate permeability, and poor aqueous solubility) to culminate in the identification of the clinical development candidate AMG 510. Ph1 studies of AMG 510 were initiated in August 2018, and initial clinical results in KRAS(G12C)-mutant NSCLC and CRC were first reported in June 2019. Ph1 combinations studies (with select MAPK-pathway inhibitors as well as anti-PD-1 immunotherapy) have recently been initiated and are currently enrolling. A Ph2 trial investigating AMG 510 as a monotherapy in NSCLC is also currently underway.

The aforementioned research has led to Brian’s co-authorship of more than 25 peer-reviewed publications, to his role as a co-inventor on over 25 patent applications and issued patents, and to multiple national and international invited lectures. In his current role at Amgen, Brian continues to lead international cross-functional teams with the aim of integrating world-class capabilities in genomic target identification, DNA-encoded library screening technology, and cutting-edge structural biology in the discovery and development of new small-molecule therapies to treat grievous disease.