NAME, PH.D.
Postdoctoral Fellow
Harvard University
Department of Chemistry and Chemical Biology
The Broad Institute of MIT and Harvard
415 Main St. Cambridge, MA 02142

UNIVERSITY X
Department of Chemical Biology

Dear Members of the Faculty Search Committee,

I am writing to apply for the position of Assistant Professor of Chemical Biology, as advertised online by Chemistry and Engineering News. My curriculum vitae, research experience summary, future research interests summary and detailed research proposals, as well as a statement describing my teaching philosophy are enclosed. PROFESSOR A at Vanderbilt University, PROFESSOR B at Harvard University and the Broad Institute, PROFESSOR C at the Broad Institute, and PROFESSOR D at Harvard Medical School and Massachusetts General Hospital have agreed to submit letters of recommendation on my behalf, and their contact information is also enclosed.

I am currently a postdoctoral fellow in the laboratories of PROFESSOR B at Harvard University and the Broad Institute, where I use insights from patient-based genetics to reveal cellular pathways that are associated with disease occurrence, synthesize small molecules to probe these pathways, and aim to discover novel therapeutic mechanisms for treating diseases. I have recently identified small molecules that enhance autophagy, a vital component of innate immunity which has been implicated in the pathogenesis of Crohn's disease (CD), and I plan to study this critical pathway in CD and other diseases in which defective autophagy has been implicated, such as cystic fibrosis, infectious diseases, neurodegenerative diseases, and cancer. Presently, I am working to identify the cellular targets responsible for the observed autophagy enhancement and to study the role of these targets in disease biology. We are currently preparing two manuscripts describing (1) the discovery and cellular activities of novel, mTOR-independent autophagy enhancers and (2) the discovery of a potent, small molecule inhibitor of lysosomal acidification with significant anticancer activity.

As a graduate student under the guidance of PROFESSOR A at Vanderbilt University, I primarily focused on the total synthesis of two polypyrrole natural products with anticancer activity, tambjamine K and marineosin A. The total synthesis of tambjamine k and synthesis of unnatural analogs led to an investigation of the biological activity of these small molecules in viability, proliferation, and invasion assays where an unnatural analog possessed greater activity in and selectivity for cancerous cells. I also achieved the synthesis of a densely functionalized model core as well as a highly advanced intermediate of marineosin A. Finally, I developed methodology to rapidly prepare small molecules to test for M1 muscarinic acetylcholine receptor antagonism as a potential treatment for dystonia.

My independent research program is inspired by both my graduate and postdoctoral studies and will investigate topics at the interface of synthetic chemistry and immunology with a focus on human health and disease biology. A major aspect of my program will be the development of synthetic methods to access complex "unnatural products" as a starting point to discover novel immunomodulatory probes. Chemical biology efforts in my lab will investigate the role of the autophagy machinery in protein misfolding diseases (e.g. cystic fibrosis), unconventional protein trafficking pathways, and bacterial infection. Additional projects will focus on risk and protective alleles in inflammatory diseases, especially ulcerative colitis (UC). The RNF186 A64T variant is associated with an enhanced risk of UC and may be responsible for an increase in endoplasmic reticulum stress and an inability to properly respond to bacterial infection. The lymphoid tyrosine phosphatase (LYP) R620W variant is actually a protective allele in UC. LYP WT is sequestered and inactivated by C-terminal Src kinase (CSK); however, LYP R620W is unable to interact with CSK, resulting in a chronically active LYP, which dampens T-cell signaling in response to antigen presentation. In addition to biochemical and genetic methods of perturbation, my lab will discover and optimize small molecules to probe these biological pathways and potentially identify novel therapeutic mechanisms to treat inflammatory and infectious diseases.

As an educator, I am especially interested in teaching courses in organic and bioorganic chemistry, biochemistry, advanced organic synthesis and reaction mechanisms, and chemical biology. Eventually, I would like to develop a course at the interface of chemistry and immunology that investigates the role of small molecules in innate and adaptive immunity and how these small molecules can lead to a better understanding of human diseases. I am also comfortable working as a team with other professors to develop a highly collaborative and interdisciplinary course that could discuss chemical biology and molecular medicine in the context of different diseases or biological systems.

The exceptional academic and research environment at the UNIVERSITY X will provide the perfect setting in which to establish my independent research career, and I am confident that I will be able to build an innovative, externally funded program at UNIVERSITY X. I believe my research experience and future plans in chemical and biomedical research would greatly complement your highly interdisciplinary department. The superb biomedical research community at UNIVERSITY X and in the greater CITY area will provide many exciting opportunities for collaborative, translational research, and I am enthusiastic to become a part of this community. Please contact me with any questions you may have, and thank you for considering my application.

Sincerely,

SIGNATURE
NAME