

Expanding Natural Product Drug Discovery at the University of Michigan

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Executive Summary

Background: The University of Michigan has developed an effective academic drug discovery enterprise over the past 15 years. This effort was originally born from an initiative by Dr. Alan Saltiel and the medical school (Pharmacology) in 2003, which provided resources to develop robotic small molecule high throughput screening at the Center for Chemical Genomics, and protein x-ray crystallography at the Center for Structural Biology. Following Pfizer's closure in Ann Arbor, and the resulting opportunity to recruit outstanding local medicinal chemists (Drs. Scott Larsen and Hollis Showalter), the College of Pharmacy opened the Vahlteich Medicinal Chemistry Core, and a few years later with the recruitment of Prof. Duxin Sun, the Pharmacokinetics Core facility was established. Moreover, Professor Shaomeng Wang has grown a strong cancer therapeutics discovery and development program at the UM North Campus Research Center, and these combined activities have enabled remarkable success competing for NIH grants, publishing prestigious papers, filing patents and negotiating licensing agreements relating to pharmaceutical discovery and development projects.

The year 2003 could not have been better to initiate academic drug discovery at Michigan. As large pharmaceutical companies have diminished their internal early stage drug discovery efforts, academic institutions have rapidly begun to fill the void. Michigan's early, strong position has made it highly attractive as a partner for public-private partnerships with large pharmaceutical and biotechnology companies. Academic drug discovery projects at UM have driven a new culture of entrepreneurial activity with a growing number of start-up companies, licensing agreements, and filed/issued patents. Strong return on investment from academic drug discovery and development at Michigan provides a convincing rationale for continued institutional commitment to these activities. Based on current track record, increasing momentum, and high faculty enthusiasm, it is reasonable to expect that these returns will multiply as research activities expand, and royalty income from intellectual property and licensing agreements continues its upward trend. There is clearly a strong future for research, and student training in drug discovery and development at the University of Michigan.

Current Challenge: Academic drug discovery is now recognized as a "must have" enterprise at research intensive universities. Not only does it facilitate the drive to identify new disease targets, it also offers a fantastic opportunity to build sustainable funding sources through licensing of technology and high value molecules. Access to small molecules that offer potential to generate strong composition of matter intellectual property is a cornerstone of a sustainable drug discovery program. *This Biosciences Synergy Initiative proposes to expand and fill important gaps in an already unique strength at Michigan, its one-of-a-kind natural products drug discovery capabilities.* To do so, we envision adding three new faculty lines, and a state-of-the-art Natural Products Discovery Core that will provide effective, responsive and high value access to new chemical matter, positioned readily for downstream transformation into unique, bioactive, patentable small molecules.

Current Strengths: Over the past decade the University of Michigan has gained a leadership position in a broad scope of natural product sciences. This includes microbial and natural products discovery (Sherman, Tripathi), separations technology and structural characterization of new metabolites (Tripathi, Sherman), function and structure of enzymes involved in natural product assembly and tailoring (Smith, Sherman, Narayan), genome mining, and annotation of biosynthetic gene clusters from individual genomes, and metagenomes (Dick, Sherman), and big-data artificial intelligence-driven discovery of natural product molecules (Rao, Tripathi, Sherman). Moreover, the Center for Chemical Genomics hosts a 40,000-sample (and growing) library of natural product extracts derived from a unique collection of diverse marine- and terrestrial derived pure culture actinomycetes, fungi and cyanobacteria developed by the Sherman group. To fill gaps in research and technology, expand Michigan's capabilities, access to novel chemical matter, and improve speed and identification of biologically active pharmaceutical quality natural products a number of key faculty hires are envisioned. Moreover, expansion of the nascent Natural Products Discovery Core at the Life Sciences Institute will relieve identified bottlenecks in the discovery pipeline and provide access to a broader scope of internal and external collaborators, and industrial partners.

Pathway to Synergy: To achieve greater scope in basic research in natural product sciences, while strengthening translational opportunities, three additional faculty hires are proposed. One will focus on the exciting and rapidly growing arena of *plant natural products*, which currently has no substantive representation at Michigan. The greatest impact will come from an individual with strong interests in plant genomics/genome mining, pathway discovery involving dispersed genetic systems, and synthetic biology approaches to pathway design and heterologous expression to create new bioactive molecules. This individual could be attractive to the College of Pharmacy Department of Medicinal Chemistry, the LS&A Department of Plant Biology under the recently launched Green Life Sciences Initiative (<https://sites.lsa.umich.edu/green-life-sciences>), or the Department of Chemistry, or Biological Chemistry. Another deep synergy with current strengths would be achieved by recruiting an individual with expertise in *natural product discovery from complex microbiomes*, and its relationship to human/animal diseases. The individual would find a natural home in the Department of Microbiology & Immunology (Medical School) with a robust research community in the UM Center for Microbial Systems, and the Michigan Microbiome Project. A third way to enhance synergy in the current Michigan community of natural product researchers would involve recruiting an expert in chemical or biochemical engineering and *synthetic biology of complex secondary metabolite pathways*. A natural home for this individual is the Department of Chemical Engineering or Biomedical Engineering. The ideal individual will have deep interests and expertise in design/refactoring of pathways de novo from big data genome sequencing projects, and engineering suitable microbial or plant cell hosts to synthesize complex bioactive metabolites with drug lead potential.

Natural Products Discovery Core: In this Biosciences Synergy Initiative, we propose to augment an already strong natural product discovery effort and create a formal Core (NPDC) that includes state-of-the-art infrastructure, expanded scientific talent and a sustainable business model. Natural products drug discovery currently includes twelve active projects in varying stages of development. The majority of projects include UM collaborations with LSI, Medical School, Pharmacy and LS&A investigators. These initiatives for drug discovery to improve human health include targets in infectious diseases (Collins, Mobley, Xi, Yonath), cancer (Dou, Mapp, Ohi, Garner), inflammatory (Colgate-Palmolive), metabolic (Cone), cardiovascular (Lawrence), neurodegenerative diseases (Gestwicki), and others. In addition, a project involving phase II development of oral biofilm inhibitors is currently under negotiation with Colgate-Palmolive following a highly successful phase I program. Our objective is to create a Core that enables strong collaborations based on NIH grant funding opportunities, public-private partnerships, foundation-supported projects and internal pilot programs involving early stage identification of active natural product extracts and pure molecules from the Core library. Moreover, a recharge rate is envisioned to capture revenue for consulting services, performing scale-up fermentation and downstream processing, complex separations, and MS/NMR/small molecule x-ray-based structure determination activities. Although the current effort managed by Dr. Ashootosh Tripathi continues to acquire necessary infrastructure, specific items are required to catalyze essential improvements. One critical gap demands acquisition of a robotic colony picker that will enable rapid processing of mutant bacteria for selection of improved strain titers of bioactive natural products identified from high throughput screening campaigns. Additional robotic infrastructure relating to front end sample handling for high throughput LC/MS and sample collection will also represent game-changing improvements. We also propose to add two critical staff scientists to provide expertise and continuity for project flow, management and technical skills. One individual will add deep microbiological experience to lead strain improvement and microbial pathway engineering capabilities. Another individual will be recruited to provide additional structure elucidation expertise, as this aspect of natural product discovery can be particularly challenging and time-consuming.

Synergy with other Bioscience Initiatives and Current Centers: We anticipate the NPDC will have extensive interactions with each of the current cores comprising the CDN. Robust relationships already exist between natural products discovery efforts by Sherman/Tripathi, the Center for Chemical Genomics, Center for Structural Biology, and VMCC. In addition, we envision growing interactions with the UM NMR Core and Cryo-electron microscopy facility to expand biocatalyst engineering efforts. These interactions will become increasingly important as natural products are identified and unnatural forms are generated by total synthesis, semi-synthesis, pathway engineering, and in vitro or whole cell biocatalysis. This step is essential to gain composition of matter intellectual property at the earliest possible stage of discovery, and to facilitate identification of leads for on-going drug development projects. Taken together, we believe this Synergy Initiative will position UM as the premier source of high value natural products and allied resources for academic drug discovery.