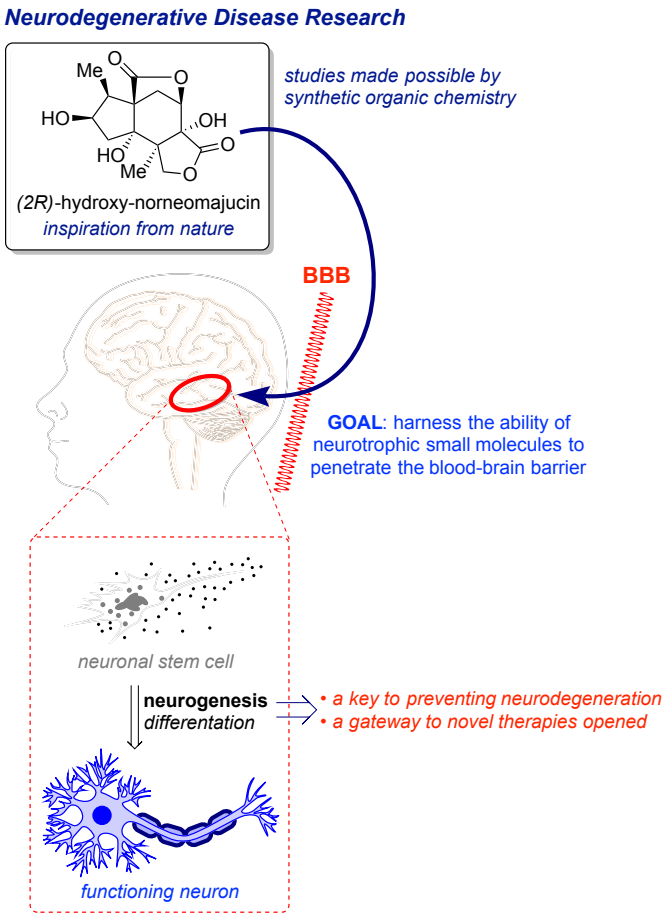
There has been an alarming escalation in the prevalence of neurodegenerative diseases worldwide, such as Alzheimer's, Parkinson's and Huntington's disease, over the past century. To put this epidemic in perspective, approximately 26 million people suffer from Alzheimer's disease today worldwide. In Europe alone, almost 1.2 million people are estimated to have Parkinson's disease, with about 75,000 new cases diagnosed every year. Nearly every person is related to and/or knows someone who has suffered from these diseases. A main reason for this epidemic happening now and to such an extent is the global increase in average life expectancy. As a result, a *significant* financial and social burden is placed on both the patients and their families. The scary reality is that there are *still no cures for these disorders* and current therapeutics are only palliative, meaning that they only treat the symptoms. These illnesses are caused by inflammation of cells of the nervous system ("neuronal" cells, the process is called neuritic atrophy), which often leads to pain and/or a loss in the ability of these neuronal cells to communicate (loss of synaptic function). Previously, these diseases have been treated with "neurotrophic" proteins that promote the growth of new neuronal cells, such as nerve growth factor (NGF). However, this type of treatment isn't really viable, because these proteins have poor pharmacokinetics, in the sense that they don't distribute well in the body to the problematic areas, mainly the brain and nervous system, and therefore they don't work well. They don't distribute well due to a protective membrane to these systems called the blood-brain barrier, or BBB, that only allows very small objects or hydrophilic (water-loving) molecules to pass through it. Therefore, an ideal way to treat these diseases would be to *use small molecules that mimic these neurotrophic properties* of the neuronal growth-promoting proteins (like NGF), which would be able to cross the BBB. To find such small molecules, we often turn to Mother Nature, who is the best chemist around. From soil samples to sponges in the sea to samples from plants, animals and fungi, we can extract natural product molecules with remarkable biological activities, which we would like to then harness for suitable treatments. Nearly half of all of the chemical entities introduced in the last 30 years in the pharmaceutical industry were based on natural products, underscoring their importance in drug development. Consequently, we became interested in a natural product (*2R*)-hydroxy-norneomajucin, which was isolated in 2012 from fruits of the plant, *Illicium jiadifengpi*. The scientists who isolated it found that it exhibited excellent neurite outgrowth-promoting activity in the primary cultures of fetal rat cortical neurons at concentrations ranging from 1 to 10 μmol/L. However, they were only able to isolate 1.2 mg of the natural product from 3.5 kg of the fruits; an approximate 0.00003% yield (w/w). This means that extraction of this potential therapy from natural sources for further biological investigations or even use as a drug was an impractical option. This is where it becomes necessary to use synthetic organic chemistry as the tool to make this natural product compound from scratch, which would otherwise be inaccessible from its plant source. We can thereby produce enough material to allow us to perform more thorough biological evaluations and even enough for treatments (pharmaceutical production). We can also use synthesis to



modify the structures with an aim to improve the selectivity, potency, stability or pharmacokinetics of these therapies.

Therefore, in our multidisciplinary project, we aimed to *(1) complete the first total synthesis of (2R)-hydroxy-norneomajucin, (2) confirm the neurotrophic activity of this natural product and evaluate advanced intermediates, and also (3) initiate investigations into the biological target and pathways affected by this compound*.

Toward this end, we have completed the **successful development and optimization of the first 12 steps of our total synthesis** *in an excellent 18% overall yield*, putting us about halfway through our synthetic sequence (aim 1). Details of our novel strategy and all of the synthetic obstacles encountered and overcome will be disclosed in a full paper as it is completed. In addition, we have **successfully implemented the neurite outgrowth assays** (aim 2). Through these efforts, we were able to *learn about and prepare the neuronal cell culture, then design and execute the neuronal differentiation assays, complete the cell imaging and counting, and finally perform statistical analysis of the neurite outgrowth abilities* of several standard and unknown compounds. This cell work will be published during the late summer/fall of 2016. We also published an enlightening review in the esteemed scientific journal, Angewandte Chemie, highlighting the importance of natural product fragments in drug discovery (References: **Crane, E. A**.; Gademann, K. “Capturing Biological Activity in Natural Product Fragments by Chemical Synthesis,” *Angew. Chem. Int. Ed.* **2016**, *55*, 3882-3902. DOI: 10.1002/anie.201505863 and **Crane, E. A**.; Gademann, K. “Synthetisch gewonnene Naturstofffragmente in der Wirkstoffentwicklung,” *Angew. Chem.* **2016**, *128*, 3948-3970. DOI: 10.1002/ange.201505863). All of the aforementioned work has been disseminated by the fellow at 6 symposia to both academic and industrial audiences, in Switzerland and in the USA, and will be presented in a plenary lecture during the Medicinal Chemistry and Chemical Biology session of the Swiss Chemical Society Fall Meeting at the University of Zürich on September 14, 2016.

Our efforts on the synthesis are ongoing and, upon completion, we will be able to wrap up the neurite outgrowth analysis of the natural product and advanced intermediates (finish aims 2 and 3). Future work would involve performing structure-activity relationship (SAR) studies to improve the activity of the compound, and identifying where (*2R*)-hydroxy-norneomajucin is binding in the body to cause this neuroprotective effect. By identifying these biological targets of the natural product in the body, we open ourselves up to additional therapies as we discover other molecules that target these same areas. *The overarching aim of this proposal was to utilize a multidisciplinary combination of organic synthesis and chemical biology to develop novel therapeutics for the advancement of neurodegenerative disease research.* In this way, our efforts throughout this project have added to the solid foundation of basic research, which will contribute to better understanding of and finding cures for these widespread degenerative disorders.