

Research Interests – Prof. Dr. Sarah Ellen O’Connor

Natural Product Biosynthesis

Plants are sessile organisms that cannot move. To compensate for this lack of movement, plants have evolved to become chemists: plants synthesise thousands of complex molecules called natural products. These natural products allow plants to defend themselves, to signal to other plants, and to attract pollinators. However, in addition to these roles that natural products play in plants, many natural products have pharmacological activity, and humans have long used plant natural products as medicines. For example, artemisinin from sweet wormwood is used to cure malaria, vinblastine from Madagascar periwinkle is used to treat cancer, and morphine from poppy alleviates pain. Although plant natural products play an enormously important role in human medicine, our access to plant natural products is limited, since these molecules are often produced by the plant in small amounts or by plants that are rare, endangered or difficult to cultivate.

Synthetic biology approaches are being used with increasing success to overproduce these expensive plant-derived molecules in heterologous hosts such as yeast or tobacco. However, to pursue such approaches effectively, we must first fully understand the chemistry and biology of the biosynthetic pathways that generate these molecules. Given the complexity of plants and plant genomics, this pathway discovery process has been a major bottleneck in harnessing the chemical power of plants. Our research aims to develop methods and resources to unlock the biosynthesis of complex molecules produced by plants.

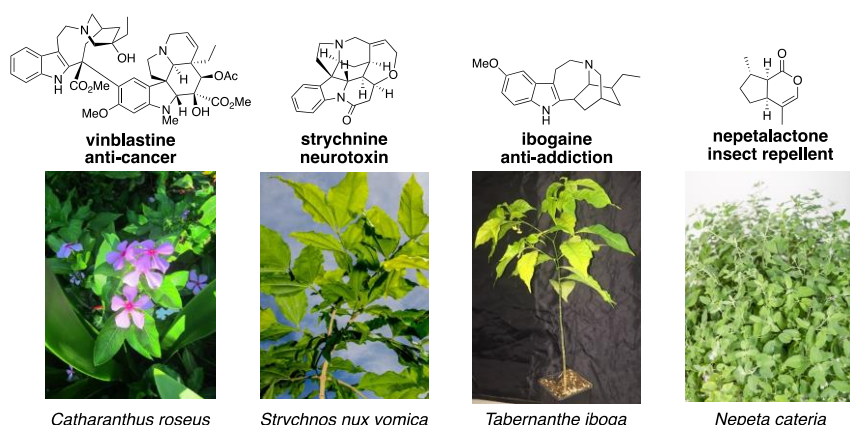


Figure: Some of the plant natural products that the O’Connor lab has studied.

We can now generate extensive “omics” datasets from plants, and then use bioinformatic approaches to mine these datasets to generate a list of gene candidates that may encode the biosynthetic pathway enzymes. These gene candidates are then subjected to a variety of biochemical assays to determine if they are involved in the biosynthesis of the natural product of interest. Using this general approach, we have discovered plant-derived enzymes that catalyse the formation of several important medicinal natural products. Recent examples include the discovery of the key cyclisation enzymes in the vinblastine pathway; the enzymes responsible for the biosynthesis of ibogaine, an anti-addiction agent; the biosynthetic genes for the neurotoxin strychnine; and the biosynthetic enzymes for nepetalactone, which, although not a medicinal product, has important biotechnological potential as a natural mosquito repellent (and is also the molecule in catnip that makes cats go wild).

Moreover, we continually look for opportunities to translate our discoveries into engineering efforts. We have developed ways to modify the structures of these natural products to make “new to nature” products; we develop new methods to streamline the reconstitution of these pathways in heterologous hosts such as tobacco; and we aim to develop methods to mix and match enzymes from different natural product pathways to further expand the chemical diversity that is observed from naturally occurring biosynthetic pathways.

Many of the enzymatic transformations in plant natural product biosynthesis are unprecedented. After discovering biosynthetic enzymes, we use our expertise in organic and biochemistry to rigorously study the mechanism of these enzymatically catalysed chemical reactions. By solving the structure of the enzymes, by isolation and structural characterisation of unstable reaction intermediates and by monitoring the incorporation of isotopic labels, we can determine the most likely molecular mechanism for many of these highly unusual enzymatic transformations.

We also try to unravel how these natural product pathways may have evolved. For example, in nepetalactone biosynthesis in *Nepeta* (catnip), using a combination of approaches, we showed how one of the enzymes of nepetalactone biosynthesis evolved from another enzyme, and we also showed how and when the gene encoding this enzyme moved from one place to another on the plant genome. More recently, we discovered how nepetalactone is synthesised by insects (aphids), and we used this discovery to compare and to contrast how two organisms, from two different kingdoms of life, synthesise the exact same molecule in different ways.

We will continue to expand our efforts in these areas, to both make the chemistry of plants more accessible to humans, and to also understand the fundamental chemical and biological mechanisms that are responsible for the synthesis and evolution of these compounds. We are committed to developing approaches that allow both deeper and faster insights into these processes, such as generating omics datasets at the single cell level, so that we can understand how the mechanics of these enzymatic pathways work in the context of the individual cellular environment.