SELECTED TALK:

Dr. Lars Kruse

A bioengineered plant production system for the anti-diabetes metabolite Montbretin A

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Type 2 diabetes (T2D), the 3rd most prevalent disease in the western world, affects nearly half a billion people worldwide. Montbretin A (MbA) is a complex acylated flavonoid glycoside that is being developed as a novel treatment option for T2D. MbA selectively inhibits the pancreatic a-amylase, thereby slowing starch digestion and lowering blood glucose levels. MbA does not have the negative side effects of other T2D medications. However, development of MbA as a T2D treatment is limited by its rare supply. The only known natural source of MbA are the below-ground storage organs (corms) of the plant montbretia (*Crocosmia x crocosmiiflora*), which produce MbA in very small amounts during a short period of the year. The complex structure of MbA makes scalable chemical or chemo-enzymatic synthesis unfeasible. We are therefore exploring different heterologous bioengineered production systems as a stable and scalable source for MbA. This work builds upon our discovery of the complete MbA biosynthetic pathway including all the essential genes and enzymes. MbA biosynthesis requires five different metabolic building blocks: the flavonol myricetin, the activated sugars UDP-rhamnose (UDP-Rha), UDP-glucose (UDP-Glc), UDP-xylose (UDP-Xyl), as well as the activated phenylpropanoic acid caffeoyl-CoA. These building blocks are assembled into MbA by five different UDP-dependent glycosyltransferases (UGTs) and a BAHD-acyltransferase (AT). Here we present new results from metabolic engineering of MbA in the plant system *Nicotiana benthamiana* (Nb), which is used in the biotech industry for production of vaccines, therapeutic and diagnostic proteins. Having shown in principle that bioengineered Nb can produce MbA, we are now focusing on yield improvement. Current engineering strategies include optimization of precursor formation, use and optimization of modular multigene expression systems for MbA assembly, and RNAi silencing of interfering Nb genes. For example, by enhancing the availability of the phenylpropanoid precursor caffeic acid, we achieved MbA levels in engineered Nb that are more than 10 times above the levels in montbretia corms. Our presentation highlights the potential of bioengineering of MbA in Nb to overcome limitation in the development of a novel treatment for T2D.