HVCfP PROOF OF CONCEPT FUNDED PROJECTS – ROUND ONE

UNCOVERING TRANSCRIPTIONAL REGULATORS OF PACLITAXEL BIOSYNTHESIS

Gary Loake - University of Edinburgh.

Paclitaxel is a blockbuster anticancer drug with an annual world market value of ~$3.5 billion. This pharmaceutical is currently predominantly produced by a semi-synthetic method using a chemical building block from yew trees. Due to the slow growth of yew trees and expanding demand, this strategy is not sustainable. In collaboration with industry we have isolated, characterised and cultured, on an industrial scale, plant cambial meristematic cells (CMCs). These stem cells circumvent many of the problems associated with the growth of plant cells on an industrial scale. Significantly, CMCs from yew produce strikingly more paclitaxel than typical cell cultures compromised of dedifferentiated cells (DDCs). To further increase production of this key pharmaceutical from CMCs insights into the regulation of paclitaxel synthesis is required. This project will identify key proteins that control the level of production of paclitaxel. Manipulating the expression of these proteins in CMCs may lead to enhanced and sustainable production, securing the supply of this important pharmaceutical.

TARGETING THE MOST CLINICALLY BIOACTIVE OAT AVENANTHRAMIDES

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Oats are important cereals and have a reputation for health giving properties which are now being characterised at a molecular level by modern science. One group of chemicals that seem to be a significant cause of the "healthiness" of oats are avenanthramides (AVAs). AVAs have been linked to the reduction of inflammation, beneficial effects on heart disease and the inhibition of cell division in bowel and colon cancer cells. At IBERS, we have an oat breeding project which aims to increase the amount of AVA in oats to further improve the healthiness of the oat product and allowing it to be isolated from the husk – which would be otherwise discarded - and used as a drug or as a drug precursor. However, there are many AVAs and not all of which need be active in conferring healthiness. By simply increasing all AVA, oats' resources that could be used to make the healthy AVAs could be diluted. It would be very useful to find out which AVAs confer healthiness and develop oat varieties which are only increased in these healthy AVAs. This would vastly improve the yield of healthy AVAs and would make extraction more cost-effective. This proof of principle proposal aims to extract large amounts of AVAs from oats and separate these into individual AVAs. These isolated AVAs will be screened for anti-fungal, antioxidant and anti-inflammatory activity and the healthy AVAs will be discovered. These findings will be immediately relayed to the oat breeding project so that they can used this information to select the most appropriate lines to breed from.

LOW COST EXTRACTION OF GALANTHAMINE FROM DAFFODILS

Michael David Hale - Bangor University.

This project aims to develop the basic processes underlying an enzymatic enhanced method of extraction of Galanthamine, a Daffodil derived alkaloid, used for the treatment of moderate Alzheimer's. The drug is one of the few that are approved by NICE to treat this old age disease. The enzymatic process is based on the deconstruction of the Daffodil cell walls and selective digestion of major bio-based polymers present in the plant (polysaccharides and proteins), allowing the reduction in the quantity of solvents used in conventional methods of extracting and purifying alkaloids, and the amount of energy used while increasing yields of bioactive.

NEW DRUGS FROM OLD: A PHYTOCHEMICAL GENETICS AND PHARMACOLOGICAL SCREEN OF SALIX

Michael H. Beale, Jane L. Ward, Steve Hanley & Angela Karp - Rothamsted Research.
Martin Michaelis, Ian Blomfield, Alessia Buscaino, Mark Shepherd & Anastasios Tsaousis - University of Kent.

The use of extracts from willow (*Salix* species) in human medicine date back to ancient Egyptian and Greek times. The herbal use of white willow (*Salix alba*) bark as painkiller, particularly in arthritis and back pain still continues today. The compound partly responsible for the analgesic effect of willow extract, salicin, has been known for over 150 years and has, famously, led to the development of the synthetic derivative, acetylsalicylic acid (aspirin) which has become the best known and most widely used medicine in the modern world. Aspirin also has other pharmacological uses, particularly in the treatment of heart disease and in the prevention of stroke via its anti-thrombotic properties. However, the medicinal effect of willow bark extracts cannot be attributed to the salicin content alone. These extracts contain many other complex analogues of salicin as well as other natural products, whose pharmacological activities have not been explored in the modern era. Furthermore, other bio-activities, associated with various *Salix* species have not been fully investigated but include anti-cancer activity and neurological effects in counteracting the effects of alcohol and improving cognition.

Using *Salix* as an exemplar system, the project aims to develop and apply the latest technologies to drug discovery from natural sources. The approach combines plant genetics with phytochemical profiling and pharmacological screening. We will map directly the phytochemical diversity residing in our large collection (several thousand plants) of *Salix* species, that have either been collected from all over the world or produced as part of an established willow breeding programme at Rothamsted Research. Utilising powerful modern analytical instrumentation we aim to profile, at very high resolution, the chemical components in unpurified aqueous extracts from 200 *Salix* species, chosen to represent the genetic diversity across the whole Rothamsted collection. A subset of the same extracts will also be tested for pharmacological activity against cancer, bacteria, fungal and protozoan parasites at the University of Kent. The data from the 'chemical fingerprints' will be aligned with that from the 'pharmacological footprints' and then mined using multivariate statistics to associate particular bioactivities with individual metabolites across the profiles. In this way we expect to be able to rapidly pinpoint candidate drugs in these complex mixtures, and select these compounds for further study. This 'systems approach' to new drug discovery from plants is potentially much faster than the more traditional approach of one-by-one isolation and testing of compounds, achieved by tedious splitting of crude extracts into many fractions. The approach will also identify synergistic effects - apparent in the case of salicin - whereby more than one natural product may be involved in the observed pharmacology of the total extract. Such data are lost by the traditional bioassay-guided fractionation approach.