The plant cell factory:
Biochemical and metabolic engineering

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In the past 25 years plant cell biotechnology has been one of the themes of plant cell, tissue and organ culture research. It aimed at the production of fine chemicals such as medicines by means of plant cells. Originally it was thought that plant cells would be difficult to grow in bioreactors because of shear forces caused by stirring. These shear forces would make the cells to collapse. However, studies on this aspect showed that plant cells are reasonable shear resistant, and large bioreactors are presently used for the production of among others taxol by plant cells. Calculations on the economy of the system showed that at a production of 0.3g/l per 14 days, costs would be 1500 €/kg. This seems high, but compared to prices of compounds like taxol and vincristine, in fact, is quite low.

First all efforts were focused on improving production of cell cultures for the desired compounds by screening for high producing cell lines and by optimizing growth and production media. However, in many cases this did not result in the required improvement. Poor understanding of the regulation of the biosynthesis of the products was a major reason to change the focus to studying biosynthesis in more detail. Identification of intermediates and the enzymes eventually led to the cloning of the genes encoding various steps in the pathways. This opened the way to further studies of the regulation and to metabolic engineering. These new possibilities have been applied both to cell and organ cultures, but can also be applied to the plant. Several interesting results were obtained, but not sufficient improvement of production to increase the number of applications. Still too many steps in the pathways remain unsolved, and it is now recognized that also compartmentation, and thus transport do play an important regulatory role. To further elucidate the pathways novel approaches have to be developed, as in many cases the intermediates are not known, or not available. Functional genomics, using transcriptomics, proteomics and metabolomics are presently the major approaches used for unraveling the production of secondary metabolite sin cell cultures. The cell cultures are a quite useful system for this purpose as they are easy to use for feeding experiments, and the number of cell types is limited whereas in plant tissues many different cell types are present, and consequently the –omes of all cell types are mixed. Plant cell cultures will thus be a major tool in the years to come for studying biosynthesis.

References

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Do negative results exist?

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Metabolomics as the latest of the –omics has got quite some attention in the past years. It is a major tool, for example, in functional genomics, quality control of botanicals, studies on the activity of medicines and medicinal plants, and systems biology type of studies of the plant cell factory (Verpoorte et al. 2007, 2008). Metabolomics has the very ambitious objective to identify and quantify all metabolites in an organism. Numerous reviews have been written in the meantime pointing out the various advantages and limitations of the possible analytical methods.

A major area for the application of metabolomics is systems biology. There are many definitions of systems biology. But basically systems biology is an unbiased measurement of as many different parameters as possible under different conditions (e.g. healthy plant versus infected plant) and uses various statistical/mathematical methods to determine possible correlations between certain compounds present and the effects observed. With other words there is no starting hypothesis, systems biology is fully based on observations, which are subsequently analyzed using various chemometric methods to find possible correlations between the different data, and based on that try to find (novel) explanations for what is observed. I.e. the hypothesis is made after the experiments.

The methods used in systems biology include metabolomics (determining as many as possible metabolites in an organism, or in an extract), proteomics (to determine possible changes in an organism on the level of proteins) and transcriptomics (which should detect up- and down regulated genes), as well as all kind of physiological measurements (e.g. plant growth, leave size). Such a systems biology approach is quite promising as, for example, for phytomedicines it offers new possibilities to relate activity to certain compounds, including the possibility to detect synergy and pro-drugs.

So coming back to the title, when you understand what systems biology means you have the answer. This might also help to understand the problem noticed by Ioannidis (2005) who has shown that most research findings in life sciences are false, due to biased experiments. I very much look forward to further discuss this with you at the meeting!

Ioannidis JPA (2005) Why most published research findings are false. PLoS Med 2:696-701
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Curriculum vitae Robert Verpoorte

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He holds a Pharmacists degree (1972) from Leiden University, and he passed his PhD at the same university on a thesis on pharmacologically active compounds from *Strychnos* species (1976). He was lecturer at Leiden University 1976-1987, and became professor and head of the department of Pharmacognosy in 1987. He was guest professor in London (UK), Uppsala (Sweden), Amiens (France) and Reims (France). From 1992-1998 he was Vice-Chairman and Chairman of the committee of the Phytochemical Society of Europe. Since May 2011 he is professor Emeritus at Leiden University and member of the Natural Products Laboratory.

He is author/co-author of 715+ scientific papers, 4 books and 5 patent applications and is Editor-in-chief of Journal of Ethnopharmacology and Phytochemical Reviews, and Executive Editor of Biotechnology Letters. He serves on the editorial board of number of journals. He supervised 62 PhD-theses, and 150+ MSc theses.

He received an Honorary Doctorate University of Amiens, France (2004) and of the University of Uppsala, Sweden (2012). In 2007 he received the Phytochemical Society of Europe Medal.

Current research interests

- Isolation of new biological active compounds (medicines, biopesticides) from plants or plant cell cultures.
- Centrifugal partitioning chromatography as a preseparation method in screening for new biological active compounds.
- Studies on Cannabis, including biosynthesis and metabolomics of this plant in connection with medicinal applications.
- Metabolomics as a tool to determine the functions of genes, to do quality control of medicinal plants and in dereplication in natural products lead finding.
- Natural ionic liquids and deep eutectic solvents (NADES): biological implications and applications.
- Plant cell biotechnology: in particular production of fine chemicals (including drugs) by means of plant cell cultures.
- Biosynthesis of secondary metabolites in plants, mapping of pathways
- NMR-based metabolomics of plants.
- Genetic engineering of plant secondary metabolism (metabolic engineering).
- Studying plant resistance against pests and diseases using metabolomics in a systems biology approach.