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Sustainable Production of Pharmaceutical Compounds Using Plant Cell Culture

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Abstract : Plants have been considered as a source of natural substances for ages. Secondary metabolites from plants are utilized especially in medical applications but are more and more interesting as cosmetical ingredients and in the field of nutraceuticals. However, supply of compounds from natural harvest can be limited by numerous factors i.e. endangered species, low product content, climate impacts and cost intensive extraction. Especially in the pharmaceutical industry the ability to provide sufficient amounts of product and high quality are additional requirements which in some cases are difficult to fulfill by plant harvest. Whereas in many cases the complexity of secondary metabolites precludes chemical synthesis on a reasonable commercial basis, plant cells contain the biosynthetic pathway – a natural chemical factory – for a given compound. A promising approach for the sustainable production of natural products can be plant cell fermentation (PCF®). A thoroughly accomplished development process comprises the identification of a high producing cell line, optimization of growth and production conditions, the development of a robust and reliable production process and its scale-up. In order to address persistent, long lasting production, development of cryopreservation protocols and generation of working cell banks is another important requirement to be considered. So far the most prominent example using a PCF® process is the production of the anticancer compound paclitaxel. To demonstrate the power of plant suspension cultures here we present three case studies: 1) For more than 17 years Phyton produces paclitaxel at industrial scale i.e. up to 75,000 L in scale. With 60 g/kg dw this fully controlled process which is applied according to GMP results in outstanding high yields. 2) Thapsigargin is another anticancer compound which is currently isolated from seeds of Thapsia garganica. Thapsigargin is a powerful cytotoxin – a SERCA inhibitor – and the precursor for the derivative ADT, the key ingredient of the investigational prodrug Mipsagargin (G-202) which is in several clinical trials. Phyton successfully generated plant cell lines capable to express this compound. Here we present data about the screening for high producing cell lines. 3) The third case study covers ingenol-3-mebutate. This compound is found in the milky sap of the intact plants of the Euphorbiacae family at very low concentrations. Ingenol-3-mebutate is used in Picato® which is approved against actinic keratosis. Generation of cell lines expressing significant amounts of ingenol-3-mebutate is another example underlining the strength of plant cell culture. The authors gratefully acknowledge Inspyr Therapeutics for funding.

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