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Plant-derived biopharmaceuticals: Moving plant-derived antibodies and vaccines towards clinical trials

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Abstract

The development of recombinant antibodies and vaccines has allowed us to treat and prevent a large number of life-threatening diseases. However, as things stand in 2013, the capacity and scalability of current production systems is beginning to place limitations on this crucial technology. The large-scale production of antibodies, vaccines and other pharmaceutical recombinant proteins is restricted by the industry's current reliance on fermenter technology, particularly the culture of mammalian cells. This expensive and time-consuming production platform is preventing the distribution of recombinant protein drugs to those most in need. One way in which the above limitations can be addressed is through the use of plants and plant-based expression systems for recombinant pharmaceutical protein production. The economic production of plant-based pharmaceuticals depends on satisfactory yields and product quality. This presentation will discuss the latest development in antibody and vaccine development and their production by molecular farming, focusing particularly on strategies to maximize protein yields during upstream production and optimize protein recovery in the downstream processing steps. Such strategies often involve careful consideration of how the protein is expressed and targeted within the plant cell, a factor which affects yield, stability, quality and ease of isolation. Our long-term objective is to ensure that next generation of plantbased production systems for recombinant proteins will create the opportunity to deliver antibodies, vaccines and other biopharmaceuticals beyond the industrialized nations and into the developing world. Two case studies will be presented: HIV antibodies were chosen to undergo fast-track development, including risk assessment, expression in tobacco and maize, scale-up, downstream processing and regulatory development, with the aim of initiating clinical trials. In addition use of engineered plant cells that produce animal and human vaccines will be discussed. Pharma-Planta is an EU Sixth Framework Integrated Project whose primary goal is to develop an approved production pipeline for plant-derived pharmaceutical proteins (PDPs). Although previous research has provided proof of the PDP concept, Pharma-Planta aims to develop an entire production chain by taking candidate pharmaceutical molecules from the expression platform through all stages of production and processing, ultimately to initiate phase I human trials in Europe. The Pharma-Planta Consortium currently comprises 40 interacting groups representing 33 public institutes and SMEs from 11 European Member States and South Africa. At the beginning of the project, eight target molecules were chosen representing four key indication areas including HIV. From these molecules, two HIV antibodies were chosen to undergo fast-track development, which would include risk assessment, cloning, expression and optimization of production in plants, scale-up, downstream processing and regulatory development, with the aim of submitting at least one of them for clinical trials within the five years of the program. Two HIV neutralizing antibodies have been expressed successfully in the two main production crops being developed within the consortium – maize and tobacco. One of these antibodies, 2G12, has been expressed at levels up greater 100 mg per kg of plant material. The plant-derived antibodies remain stable and functional and retain their neutralizing activity. The consortium has investigated novel upscaling and downstream processing strategies to provide multiple grams clinical grade antibody material for human clinical trials. Preclinical trials in rabbits have been completed successfully and we also conducted successfully a phase I clinical trial in the UK. This work will now be moved forward for a phase IIa clinical trial which is funded by an Advanced ERC grant from the European Commission. We have also developed an interesting multi-stage malaria vaccine and neutralizing candidate and will discuss how both products have matured over the years both in performance and in manufacturing with the aim in mind to bring these two products into translational research within the next 12 – 18 months.