



Project number: **LSH-2002-1.2.5-2**

Project acronym: **PHARMA-PLANTA**

Project title: **RECOMBINANT PHARMACEUTICALS FROM PLANTS FOR HUMAN HEALTH**

Instrument: Integrated Project

Thematic Priority: Life Sciences 1

PUBLISHABLE EXECUTIVE SUMMARY
FROM THE
FOURTH PERIODIC ACTIVITY REPORT
OF THE PHARMA-PLANTA CONSORTIUM

Covering period from 1st February 2007 to 31st January 2008

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PUBLISHABLE EXECUTIVE SUMMARY



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 research carried out prior to 2004 has primarily focused on proving 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. Now at the end of its fourth year, the Pharma-Planta Consortium comprises more than 40 interacting groups representing 32 public institutes, SMEs and larger industrial collaborators from 11 European Member States and South Africa.

The objectives of the program can be summarized as follows:

- To produce recombinant pharmaceutical molecules in transgenic plants and develop them through all regulatory requirements, GMP standards and pre-clinical toxicity testing, ultimately to initiate Phase I human clinical trials.
- To develop robust risk assessment practices for recombinant pharmaceutical molecules produced in plants, based on health and environmental impact, working with regulatory authorities within the EU as well as public groups to ensure that the production systems are as safe and as acceptable as possible, and that they comply with all biosafety regulations.
- To define and carry out a coordinated program for securing and managing intellectual property that will facilitate the availability of high priority plant-derived recombinant pharmaceuticals to the poor in developing countries while simultaneously allowing the products to be developed commercially in Europe and North America.
- To develop and refine new strategies for the expression of recombinant pharmaceuticals in plants, which can be used on a generic basis for molecules that are normally expressed poorly.

- To develop and generate transgenic plants expressing a second generation of recombinant molecules that will be used in future clinical trials.

At the beginning of the project, eight target molecules were chosen representing four key indication areas – human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), tuberculosis (TB), rabies and diabetes. These molecules comprised two HIV-neutralizing antibodies, two HIV antigens, two rabies antibodies, a TB antigen and a diabetes autoantigen. Early in the first project year, the two HIV antibodies were selected for fast-track production, meaning that these molecules were to be taken through the production pipeline as pioneers. They would be the first to enter key areas such as risk assessment, plant production, scale-up and regulatory development, with the aim of submitting at least one of them for clinical trials within the five years of the program. In the third year, an additional HIV antibody was added to the fast-track program, bringing the total number of target molecules to nine. As well as the fast-track, there is also a ‘development loop’ of enabling technologies to improve product yield and quality. The development loop currently focuses on the second generation products (HIV antigens, and the rabies, TB and diabetes target molecules).

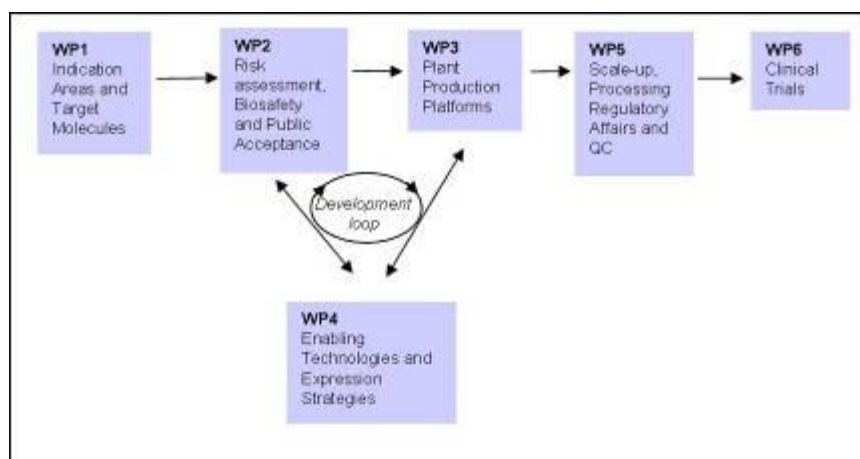


Figure 1.1 - Organization of the Pharma-Planta programme

The project is divided into six interacting work packages, as shown in **Figure 1.1**. WP1 provides the target molecules and the associated genetic constructs and assays for target molecule detection in transgenic plant material. Much of this work is already complete, although work is ongoing in the TB subproject where the objective is to design and engineer optimized constructs for the expression of a TB fusion antigen in plants and validate that antigen in animal models to facilitate vaccine

development. WP2 considers the potential environmental impact of different strategies for PDP production, and leads interactions with appropriate regulatory agencies and other stakeholders. WP2 has again been at the forefront of the project this year, due to further interactions with EFSA and EMEA, and has enjoyed close collaboration with WPs 5 and 6 in the development of appropriate processing strategies and the compilation of dossiers in preparation for the forthcoming preclinical studies and clinical trial. WP3 provides expression platforms for the fast-track molecules and generates the bulk material for their production. This year has been pivotal with the final selection of a single target molecule and production system to take forward into preclinical and clinical development. After much discussion and weighing up the possibilities of each system in terms of how much product could be supplied within the project timeframe, the Pharma-Planta consortium finally settled on HIV antibody 2G12 produced in tobacco as the primary focus of the closing stages of the project. Most of the scale up, processing and regulatory development work carried out in WP5 and WP6 is now concentrating on this line, although work continues with the maize system based in South Africa and on some of the novel technologies arising from work in WP4 (the development loop). Although most of the work envisaged from WP4 has been completed, several new technologies are worthy of further development and the groups involved are continuing to work on them using additional sources of funding. It is the fond hope of the consortium that the outputs from WP4 will now seed further EU projects under the FP7 umbrella, leading to the further improvement, development and eventual exploitation of these technologies in a growing molecular farming industry within the EU. WP5 oversees the scaling, processing, quality assurance and quality control of the fast-track material, and also leads interactions with regulatory agencies concerned with GMP in pharmaceutical production. WP5 remains at the forefront of the project this year, with the development of a pilot-scale recovery and purification process for the isolation of 2G12 from tobacco leaf material. The individual unit operations of the process have been designed and combined to allow linear up-scaling to the final intended scale of the first clinical batch of 2G12 under cGMP conditions. Finally, WP6 is charged with organizing and performing the clinical trial, and work in this WP has started in earnest this year with the hiring of a clinical trials coordinator and a consultant to oversee the regulatory affairs and complete the complex clinical trials application process while cooperating closely with the team of project partners engaged directly with the

regulatory authorities. The challenge is to present a clinical trials application which is acceptable to the regulators despite involving an effectively new class of medicinal product, a plant-derived microbicide for the prevention of HIV transmission.

Pharma-Planta is coordinated by the Fraunhofer Gesellschaft, which provides professional project management, administrative and financial coordination, and runs the project website (<http://www.pharma-planta.org>). Scientific aspects of the project are coordinated by Professor Julian Ma of St George's Hospital Medical School, where the clinical trials will be performed. The management of the program also includes intellectual property management, biosafety risk assessment and a comprehensive training program realized through seven ongoing PhD projects which are funded from a ringfenced component of the budget. Many of these projects will outlast the main part of the project, and hopefully will lead to follow-on projects hosted by individual participant organizations. These studentships complement and extend the work envisaged within the Technical Annex thus giving the project added value.