

State of plant-made pharmaceuticals sector 2005: Setting healthy roots

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REPORT

Organized by the Moleculture Society, the 2005 Conference on Plant-Made Pharmaceuticals (PMP) took place from January 30 to February 2, in Montreal, Canada. This conference is the most recent edition of three previous events held in Saskatoon, Saskatchewan; London, Ontario; and Quebec City, Quebec. The first conference, held in 1997, is believed to be the place where the term “molecular farming”, widely used later, was employed for the first time.

The Moleculture Society (formerly known as the International Association of Molecular Farming) is funded by organizations using plant-factories to produce biopharmaceuticals. Moleculture, as defined by this society, is the use of eukaryotic organisms as plants and animals to produce recombinant molecules useful to human or animal health, industrial applications, nutrition, bioremediation, etc. This society is aimed to disseminate information on moleculture, to support the emergence and create links with stakeholders (pharma companies, regulators, foundations, consumers, activists groups and general public) of a manufacturing sector that, as of 2004, comprised more than 200 companies and research institutions worldwide.

The conference had a very dense program, highly appreciated by the participants. The general program of the three days event started in plenary sessions every morning and afternoon with a series of mutually linked presentations, featuring the main present activities of the sector, the points of view of the big pharma companies on PMP, and the predictions of the sector for the years to come. The rest of the daily programs were organized in two split sessions running in parallel. Several invitational activities were also organized in order to maximize networking development, as PMP Club Plant-Factory breakfasts and lunches, both including PowerPoint presentations.

In spite of the rather elitist inscription costs, worthy of the classical ambience of the Fairmont Queen Elizabeth Montreal downtown hotel where all the activities were held, registrants were above 350, including 29 host presenter companies.

Although the number of presentations of interest largely surpasses the scope of this report, we'll assume the difficult task of providing a glimpse of some of them.

As an updated continuation of his presentation in the 2003 PMP conference in Quebec, Ulrich Steiner, Bayer Healthcare, Germany, brought to the audience relevant data on the current situation of the biopharmaceutical sector. Steiner's presentation should be better mentioned in conjunction with another one from a big pharma company, by Hans Kocher, Novartis, Switzerland. Both presentations agreed that

the biopharmaceutical sector is steadily growing, with more than 600 products on clinical trials. They are expecting revenues of more than 65 USD billions by 2008, half of them being monoclonal antibodies (MAbs), and, about half of the MAbs, are targeted to combat cancer. Hermann Katinger, from the Institute of Applied Microbiology, University of Natural Resources and Applied Life Sciences, Austria, introduced a view of the antibody sector, showing recent data with the good news of the existence of solutions to HIV. However, this was combined with the not so good one that, to be effective enough, they would be needed by the ton. Katinger also described other antibodies on the horizon that could match with the nature of plant-factories, including those amenable to dermal or mucosal administration of partially purified compounds. These three presentations, among others, once again showed the forthcoming challenges for the pharmaceutical sector, to which keeping the eyes on the developments achieved by plant expression productive platforms seems to be a must.

Robert Adamson, Wyeth BioPharma, USA, presented an updated review of the progress recently made by mammalian cell culture technologies in order to remain a competitive alternative for large-scale, cost-effective production of biopharmaceuticals. Since comparisons on advantages of the PMP systems over traditional ones are often simplistic and enthusiastic, this presentation draws attention on the need of a pragmatical analysis of the real challenges faced by PMP technologies from its counterparts.

A block of presentations was devoted to discussing the very important issue of recombinant pharmaceutical purification from transgenic plants. Zivko Nikolov, Texas A&M University, USA, stressed the challenges (to perform as well as mammalian cells) and opportunities (plant-specific capacity) of turning plant-expressed proteins into products through appropriate purification technologies. His presentation was mostly based on one of his recent papers [1], concluding that either with seeds or green tissues, plants can do as well or better than cell lines.

Peter G. Brown, Applied Process Technologies Inc., USA, explored the potential impact of terrestrial and aquatic transgenic plant technologies on the key drivers for the biopharmaceutical industry, Time-to-Market, Cost-to-Build and Cost-of-Goods, relative to CHO, *E. coli* and other biopharmaceutical product sources. The pre-chromatographic processes for these product sources relative to the above drivers were compared. He analyzed the downstream process options for transgenic plant technologies and the development of an “ideal” biopharmaceutical process based

1. Menkhaus TJ, Bai Y, Zhang C, Nikolov ZL, Glatz CE. Considerations for the Recovery of Recombinant Proteins from Plants. *Biotechnology Progress*, 2004; 20:1001-14.

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on non-chromatographic technologies for initial purification, continuous liquid chromatography for final purification and a new continuous process support system design, proposing short term objectives for transgenic plant technologies.

A comparative assessment of downstream processing for PMP's from green tissue and the development of a compliance strategy for these processes was presented by Barry Holtz, Holtz BioPharma Consulting, USA. The post-harvest recovery and purification of therapeutic biologics from green leaf tissue was discussed. The downstream processing considerations for several known plant expression systems were reviewed. Holtz presented potential compliance issues and process analytical technologies based on several examples of specific protein categories, as well as the development of a regulatory bio-processing strategy, and the presentation of release criteria to the regulators.

Confirming the growing interest of big pharma on these technologies, Jochen Strube, from Bayer Technology Services, Germany, delivered a presentation on the design of downstream processing of Plant-Made Pharmaceuticals. He discussed the role of costs of the different production steps, particularly those related to downstream processing, which are seen as the bottleneck for PMPs.

Since no economy of scale is possible at the moment for the selective units (e.g. chromatography, membrane and extraction units), the development of highly selective materials by design, which would be able to process large-scale amounts at reasonable costs was proposed as a key factor to boost the competitiveness of PMP technologies.

In a divergent presentation, Uwe Gottschalk, Sartorius AG -Biotechnology, Germany, emphasized the potential of already existing technologies to cope with the challenges of developing cost-affordable purification processes for recombinant proteins from transgenic plants.

Although PMP technologies have been said to be particularly attractive to offer modern drugs (not presently available) to a large sector of the population in the Developing World, the attendance and presentations confirmed that these technologies are being developed almost exclusively by institutions and companies of Developed Countries. This is of concern, since the development of capabilities for this technology in Developing World institutions, to address local problems, must be a priority. An exception in this trend was shown by Cuban institutions, led by the work of the Center for Genetic Engineering and Biotechnology (CIGB). The CIGB platform and achievements on PMP was displayed in an oral presentation by Merardo Pujol [2], accompanied by two posters; one of them reported the expression in plants of a single chain Fv antibody fragment against carcinoembryonic antigen (CEA) for the diagnosis and follow-up of human colorectal tumors (Marta Ayala, *et al.*), and a second poster (Merardo Pujol, *et al.*) appraised the use, regulatory and technical advan-

tages of contained facilities for PMP biomass production. Furthermore, a poster from the Cuban regulatory agency (CECMED), presented by Yanet Hechavarría, *et al.*, documented the process followed to set up a national regulation ensuring the appropriate exploitation of PMP technologies in Cuba.

Recalling on the use of contained facilities for PMP production, Brian Hooker, Battelle Memorial Institute, USA, presented his experience to produce therapeutic proteins using transgenic plants, which is based on the large-scale production of biomass in greenhouses, thereby facilitating the regulatory and public acceptance of the technology.

Which are the most advanced cases of recombinant plant-made molecules thus far? As shown in table 1, some of the pioneer projects for the production of PMP are now in advanced phases of clinical trials.

Among various presentations referring to regulatory issues, Elwyn Griffiths, Health Canada, explained his points of view on the challenges of novel biotechnologies, including PMPs:

- Adequate control needed to safeguard recipients against adverse effects and to ensure they receive full benefits from scientific innovations and knowledge.
- To ensure public safety but not to inhibit development and innovation.
- Novel systems equal new scientific/technical issues.
- Recognize/deal with regulatory issues early in the development of the product: early dialogue between manufactures and regulators.
- To ensure a sound scientific database on which to make regulatory decisions.
- To ensure regulatory positions that are clear and adequately reflect scientific advances and the international dimension.

Several other topics were discussed during the sessions, including financial and commercial issues related to PMPs.

To end with, a very picturesque and generally enjoyed moment was when several senior officers from PMP companies and stakeholders, during the official banquet provided entertainment with songs from the seventies.

Further information on this conference, comprising data on presenters, hosts and PMP companies, could be found at the website www.cmp2005.org. It was also announced by the organizers that the website will be shortly updated to contain the PowerPoint presentations.

2. Pujol M, Ramírez NI, Ayala M, Gavilondo J, Valdés R, Rodríguez M, *et al.* An integral approach towards a practical application for a plant-made monoclonal antibody in vaccine purification. *Vaccine* 2005;23:1833-7.

3. Abstracts Book, Conference on Plant-Made Pharmaceuticals. 2005. February 30-March 2, Montreal, Canada.

Table 1. Plant-Made Pharmaceuticals in clinical trials

Indication	Molecule	Company	Plant	Phase
<i>E. coli</i> /Travelers' disease	Lt-B	Prodigene	Corn	Phase I
Non-Hodgkins lymphoma	Mab (scFv)	Large Scale Biology	Tobacco	Phase II
Cystic fibrosis	Gastric Lipase	Meristem Therapeutics	Corn	Phase II
Tooth decay	Mab (IgA)	Planet Biotechnology	Tobacco	Phase II