Plant Factory for Biopharmaceuticals

IN SUMMARY

- **PROCESSES AND STATE OF ART -** Plants hold the potential for cost-effective, large-scale production of recombinant proteins for industrial and pharmaceutical uses. Among these, the therapeutic monoclonal antibodies (Mabs) are expected to account for at least 40% of the total production of biopharmaceuticals. With existing methods and infrastructures for growing, processing and storing crops, plants may offer a flexible system for producing potentially unlimited quantities of biopharmaceuticals for human need at a relatively low cost. The process basically consists of inserting the DNA of the target molecule into a proper host plant, which will reproduce the molecule during its own growth, with possible accumulation into specific cellular compartments or organs. The production of antibodies in plants is particularly attractive as the natural lack of antibodies in the plants facilitates significantly the recovery and purification processes. Encouraging results obtained worldwide demonstrate that this production system is robust and commercially attractive. In the United Kingdom, an antibody for use in dental care is currently in a pre-commercial phase. In the United States, in-plants produced enzymes are already commercialized. In Europe, the first functional engineered antibody produced in a transgenic plant was obtained in 1991-1993 by ENEA, which still holds a primary position in plant factory R&D.

- **APPLICATIONS AND COSTS –** Currently, major application areas for biopharmaceuticals include oncology, anti-infective diseases, blood disorders (market leader) and vaccines. The need for manufacturing capacity is rapidly increasing following the approval of new biopharmaceuticals for clinic use, and the future approval of those that are currently undergoing clinical trials, many of which being antibodies. Significant investment and time are needed to improve the production capacity for meeting the growing demand. However, market prospects for biopharmaceuticals are such that manufacturers will certainly take action to meet the demand. In such a context, the plant factory option is at an early stage of development, but it is actively investigated as a valid candidate to compete in the emerging market. It requires low initial investment and offers scalable manufacturing capacity, easy recovery and purification and high safety in the overall production process. These characteristics anticipate substantial economic benefits in terms of production cost. However, a comparison with the current technologies is either premature or impossible because of the early stage of plant factory technology and the unavailability of the costs of the most advanced biopharma, particularly antibodies, which are currently distributed only in hospital structures.

POTENTIAL AND BARRIERS - Biopharmaceuticals have undergone a rapid expansion with growth rates higher than most other pharmaceutical segments. In the Global Biotech Report 2005, the 2005 bio-pharma market value was estimated at $70.8 billion, with a 16.5% growth over 2004, and representing some 17% of all prescriptions, to be compared with 12% in 2004. The "guideline for the quality of biological active substances produced by stable transgene expression in higher plants" as released by EMEA (European Medicines Agency) in July 2006, has given a first answer to the need of regulation and rules, which has heavily affected the development of this sector in Europe. At present, the production of biopharmaceuticals in plants is legally permitted. However, in Europe, a negative public perception towards transgenic plants could vanish the R&D achievements and jeopardise the completion with other countries, notably the US, diverting R&D investment.

PROCESSES AND STATE OF ART - The demand for safe, recombinant pharmaceutical proteins is a rapidly expanding field. The world market for biotech has undergone rapid expansion since its emergence about twenty years ago and it is still thriving. Since 2001, the Human Genome Project has been driving huge profits obtained from growth hormones, insulin and red-blood-cell stimulating agents (well- known molecules, but produced by innovative ways) and accelerating the R&D and the market in targeting a wider range of diseases, from growth deficiency to arthritis, multiple sclerosis and orphan diseases. Currently, some 80 biopharmaceuticals are on sales and more than 500 are being tested at different clinical level. Among them, the recombinant antibodies (rAbs) and their derivative are finding ever more promising clinical uses. Since 1975, when first in vitro monoclonal antibodies by hybridomas were successfully developed, antibodies have been studied and tested as diagnostic or therapeutic agents either in vivo or ex-vivo. However, their introduction in human healthcare has been particularly slow because of initial negative effects (Hama), which made them either toxic or ineffective for use in humans., Since then, technological advances have enabled the development of humanised and fully human antibodies, with improved therapeutic potential. Therapeutic monoclonal antibodies (Mabs) have today immense potential and their production is considered a very attractive area that is expected to account for at least 40% of total production of biopharmaceuticals. Clear clinical applications have been identified in cancer and other key medical areas such as transplants, auto-immunity and cardiovascular disorders.

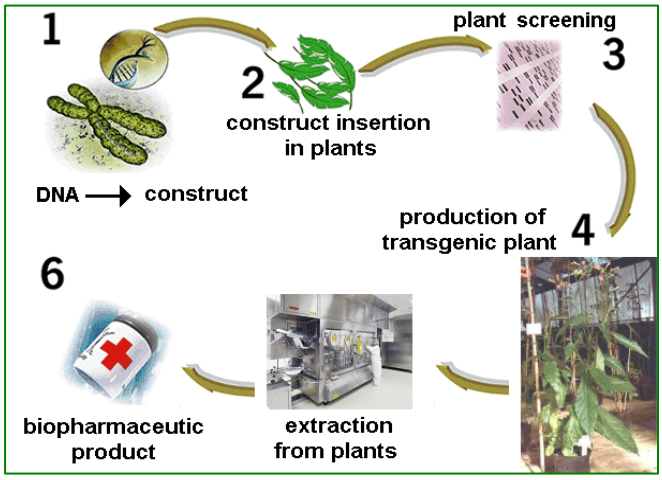

Fig.1 – Schematic diagram of Molecula Farming aimed to biopharmaceutical production in transgenic plants

Development and production costs remain however very high. Mammalian cell-culture is the main method used for producing most commercially available recombinant proteins. It is affected by high costs because of the use of sophisticated infrastructures, qualified personal and expensive safety procedures to avoid possible contaminations by pathogens and toxins.The development of plant biotechnology has enabled the use of plants as a viable alternative to cell-culture systems. Plants (Fig. 1) are able to carry out acetylation, phosphorylation and glycosilation as well as other post-translation protein modifications required for the biological activity of many eukaryotic proteins. The proteins obtained are substantially indistinguishable from natural equivalents or those from other sources. The available skills in agricultural practices are fully applicable and useful in xenogenic protein in-plant production. Large amounts of biopharmaceuticals can be produced at a relatively low cost using existing techniques and infrastructure for crop growing, processing and storage, with moderate capital investment. This is a flexible production system that can be easily adjusted to market demand. Moreover, plants may offer key potential advantages. Notably, they cannot host harmful human pathogens, thus reducing purification and safety production cost, and allowing vaccines to be directly delivered to patients in form of edible vaccine products, thus facilitating large vaccination programs.

■ **Experimental and technological phases -** The technology for in-plants production of exogenic proteins requires a series of steps, each one based on robust R&D to ensure safe handling and applications. Each molecule has its own specific characteristics in connection with the target pathology and requires a specific, "case-by-case" approach. The identification of the target molecule is a medical pathology problem which is beyond the scope of the present paper. We only deal with the technology for in-plant production of exogenic molecules. The process includes varied phases and different manufacturing strategies that are summarized as follows. **FIRST PHASE.** It is necessary to first prepare the system containing the target DNA in a suitable form for protein production. The codifying DNA is then cloned in a appropriate expression system. The selection of this system depends on the subsequent steps and on the production strategy, with the following options: ● **Stable insertion of DNA and production of a transgenic plant** – In this option, crop selection (food, non-food, high protein content, etc.) may be based on varied considerations including, for example, the opportunity of using non-food plants or the need of revitalising declining agriculture sectors (e.g., tobacco). The selection of the compartment or the organ for protein accumulation (plant tissue, root, seed, chloroplast, seed oil-bodies, etc) depends on the expected yields and on the downstream process. It is also important, in this phase, to identify strategies to avoid *transgene silencing* and to optimise transgenic plant production; ● **Stable insertion of DNA and production of a transgenic plant cells** – In this second option, high priority is given to the safety aspects to avoid possible contaminations. Technologically transformed plant cells (instead of animal cells used in current conventional methods) are cultivated in fermentors, with *bio-containment* techniques; ● **DNA Insertion in a disarmed plant virus –** In this case, the virus infects the plant that gains transiently the ability to express the target protein. In this third option, the plants do not become transgenic, that is the transgene is not inheritable. **SECOND PHASE -** Whatever the selected strategy, it is then necessary to sets-up and optimises a recovery and purification process of the target protein (which may depend on previous step) and to characterize the final product. As a biopharmaceutical, this requires high quality standards including biological safety and full identity with natural counterparts (e.g., antibodies, if any) or counterparts produced by conventional systems. During the past twenty years, biopharmaceuticals for important diseases have been developed to demonstrate the feasibility of plant factory, and technologies and systems have been extensively tested. Among these, recombinant antibodies and derived fragments represent an important drug-development platform, given the wide spectrum of possible targets and applications in diagnosis and therapy. To be mentioned are the 38C13scFvNHL[1], a promising vaccine for non-Hodgkin lymphoma, and various edible vaccines produced in edible transgenic plants, as maize, potato and spinach. In 2006, Dow AgriSciences has received the world's first regulatory approval for a plant-made vaccine from the United States Department of Agriculture (USDA). It is produced from plant cells - instead of from whole plants- in a safe bio-contained environment, which eliminates concerns and challenges associated to vaccines produced in whole plants or food crops. The selection of the production strategy not only depends on technical aspects, but also on regulatory framework and public acceptance, which both play a key role. In Europe, permitted strategies have been recently (July 2006) defined, and they exclude both transient and plant cell systems. The social opposition to "transgenics" could lead to use *bio-contained* production systems (e.g., plant cells, hydro/aeroponic cultivations) and non-food plants to avoid any possible contaminations.

APPLICATIONS AND COSTS - The first pharmacological molecule dates back to 1986, when a human growth hormone chimera was expressed in transgenic tobacco. In the US, the first in-plant monoclonal antibody was produced in 1989. In Europe, the first achievement was an in-plants expressed antibody, which enabled tobacco to resist a harmful plant virus (ENEA, 1993). Since then, considerable effort has been devoted to developing reliable transformation systems and expression vectors to permit high levels of gene expression and to direct recombinant proteins to specific plant tissues. A list of relevant patents can be found at the web site **http://www.molecularfarming.com/molecular-farming-patents.html** that also provides an overview of the work done worldwide and the results obtained by this technology, mainly in the US. While the commercialization proceeds slowly and prudently, some enzymes such as avidine, b-glucuronidase (GUS), trypsin and aprotinin from genetically engineered plants, have been launched in the

[1] the transient system was electively selected for its production in order to quickly obtain sufficient amounts of the protein for individualised NHL therapy.

pharmaceutical markets as an alternative to bacterial and animal sources (Sigma-Aldrich Inc., San Diego). Edible human vaccines against hepatitis B and traveller's diarrhoea (TD), produced in raw potatoes, have been tested in human volunteers and have resulted in a successful protective immuno-response. More palatable products like bananas and tomatoes are currently considered. Considerable research efforts on engineered edible plants have been devoted to developing multi-component and sub-unit vaccines for oral delivery of antigens, against cholera, rotavirus and enterotoxigenic E. coli (ETEC), which represent the three major causes of acute infectious enteric diseases, causing dramatic effects, especially in poor countries. Various forms of recombinant antibodies have been produced in plants, such as full size IgG, single chain variable fragment (scFv), diabodies and bispecific scFvs, culminating in more complex multimeric secretory SIgG and SIgA antibodies. Active vaccines have been developed for infecious deseases as herpes virus (HSV), anti-Respiratory Syncytial Virus (RSV), *Clostridium difficile*-associated diarrhea, rabies, hepatitis B and C viruses, cytomegalovirus, and against tumor associated antigens (such as colorectal, brain, and ovary cancers and non-Hodgkin lymphoma) and carcinoembryonic antigen, CEA. In the UK, CaroRx™, an antibody for topycal use in human dental caries, is the most clinically advanced antibody produced in plants. While antibodies and antigens are the main R&D targets, other important molecules have been - or are being- produced in plants, such as the human collagen that was obtained in tobacco in form of fully processed, triple helix. In general terms, the path to the market of completely new molecules (never tested before) implies a very long process and large investment, with considerable risk of flaw in final trial phase. The Figure 2 provides a typical cash flow for the whole process and the typical value of the technology for producing a molecule. A comparison of costs and yields of antibody production using different technologies is provided in Tab. 1. While the source of the Table 1 dates back to 1999 and more recent studies are not available, the figures in Table 1 may still represent - in relative terms - costs and yields of antibody production via different biotechnologies.

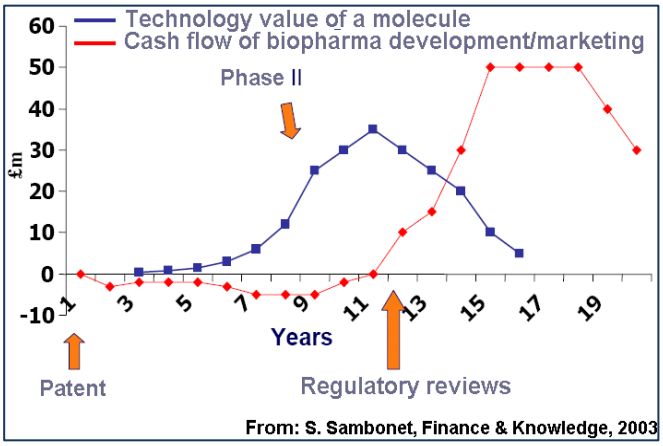

Fig. 2 - Typical cash-flow and potential value in the development and marketing of a biopharmaceutical

Table 1 - Costs and yields of antibodies production in different biotechnological systems (Harris, 1999)

Source	Yields	Costs (£/g)
Mammalian cells	0,5-1 g/l	300
Transgenic milk	10 g/l	60
Bacteria	3 g/l	1
Transgenic plants	2 g/kg	0.3
Transient expression	10 g/kg	0.06

POTENTIAL AND BARRIERS - Biotechnology for drug production holds a virtually unlimited potential. Advances in pathogenesis are constantly achieved from genomics, proteomics and metabolomics and can potentially solve any diseases, with a continuous increase in life expectancy. In principle, all diseases and traumas might be successfully treated with specific biopharma, though this requires a long development time and high investment cost. In this context, the production of biopharmaceuticals in plants may be able to significantly reduce the production costs and to increase safety. A list of molecules under development can be found in **http://www.molecularfarming.com/PMPs-and-PMIPs.html.** according to the World Global Biotech Report, the 2005 biopharma market amounted to some $71 billion. It is expected to represent 17% of all prescriptions by 2010, to be compared with 12% in 2004. At present, major therapeutic areas include biopharmaceuticals for oncology and blood disorders (market leaders) as well as anti-infectives and vaccines. The US currently dominates the global biotech market and will continue to do so in the short to mid-term, while Japanese and EU shares are expected to decline. The European effort for introducing a regulatory framework could change the declining trend in Europe. The "guidelines for the quality of biological active substances produced by stable transgene expression in higher plants", provided by the European Medicines Agency (EMEA) in July 2006, are expected to provide directives and regulations to attract investors and to boost research. Each step of the process is regulated, from biopharma genetic development to manufacturing and controls, but the use of transiently transfected plants and the production in plant cells in not included in the regulations and it not clear whether future guidelines will deal with such aspects. The fact that in a preliminary 2002 version of such regulations the transient expression was not considered eligible, suggests that the stable transformation in transgenic plants is the only permitted approach. It is obvious that such a choice has a technical impact. It may limit the research in critical areas, eventually excluding promising solutions and preventing Europe to compete effectively with the United States. On the other hand, the use of transgenic plants for human health could in principle improve the social acceptability, but relevant data are missing and the European general feeling seems to be still against the use of transgenic plants. The Table 2 provides a non-exhaustive list of achievements including molecules produced in plant, their potential applications and the plants used in the production process. It is clear that the technology may apply to a number of major human pathologies, for some of which clinical trials are currently underway.

Tab. 2 – Some molecules produced in plants and their applications as biopharmaceuticals and vaccines

Biofarmaceuticals produced in plants		
Biopharmaceuticals	**Applications**	**Host plant**
Human growth hormone	Growth hormone	Tobacco, Sunflower
Enkephalin	Antihyperanalgesic by opiate activity	Arabidopsis
Human serum albumin	Liver cirrhosis, burns, surgery	Tobacco, Potato
Human β-interferon	Antiviral treatment	Tobacco
Angiotensin-I-converting enzyme	Hypertension	Tobacco, Tomato
Human epidermal growth factor	Wound repair and control of cell proliferation	Tobacco
α-trichosanthin from TMV-U1subgenomic coat protein	HIV therapies	Benthamiana
Trout growth factor	Growth factor	Tobacco
Human α-interferon	Hepatitis C and B treatment	Rice
Hirudin	Thrombin inhibitor	Canola
Erythropoetin	Anaemia	Tobacco Suspension cells
Glucocerebrosidase, human protein C serum protease	Anticoagulant	Tobacco
Human α and β haemoglobin	Blood substitute	Tobacco
Human muscarinic cholinergic receptors	Cell receptors	Tobacco
Interleukin-2 and Interleukin-4	Immune regulation	Tobacco Suspension cells
Human placental alkaline phosphatase	Reporter gene	Tobacco Rhizosecretion
Human α1-antitrypsin	Cystic fibrosis, liver disease and haemorrhage	Rice Suspension cells
Human growth hormone (somatotrophin)	Growth hormone	Tobacco Seeds
Human growth hormone (somatotrophin)	Growth hormone	Tobacco Chloroplasts
Human homotrimeric collagen	Collagen	Tobacco
Human lactoferrin	Antimicrobial	Potato
scFv	Oxazolone	Potato tuber, ER
igG1	HSV-2	Glycine max Plant, Secretory pathway
scFv	Dihydro-flavonol 4-reductase	P.hybrida Leaf, Cytosol
IgG	Colon cancer surface antigen	Benthamiana
IgG	HSV-2	Soybean
IgG	Human IgG	Alfa Plant, Apoplast
ScFv, IgG1	CEA	Tobacco Leaf, Transient expression
scFv	Tospovisuses	Benthamiana Plant, ER, Apoplast
bi-scFv	TMV	Tobacco Suspension cells, Leaf, Apoplast, ER
scFv	CEA	Rice Suspension cells, Leaf, ER and Apoplast
scFv	38C13 mouse B cell lymphoma	Benthamiana Leaf, Apoplast
scFv	CEA	Bread wheat Plant, ER and Apoplast
scFv	TMV	Tobacco Leaf, Apoplast and Membrane
IgG1	Streptococcal surface antigen (I/II)	Tobacco Plasma membrane
scFv	Chloropropham	Arabidopsis ER, Apoplast
Recombinant Vaccines produced in plants		
Vaccine	**Applications**	**Host plant**
Envelope surface protein	Hepatitis B virus (humans)	Tobacco, Potato, Lupin (Lupinus spp.), Lettuce
Heat-labile toxin B-subunit	Enterotoxigenic E.coli (humans)	Tobacco , Potato, Maize
Glycoprotein	Rabies virus (humans)	Tomato (expressed on virus particles
Malarial B-cell epitope	Malaria (humans)	Tobacco
Capsid protein	Norwalk virus	Tobacco, Potato
Hemagglutinin	Influenza	Tobacco
V.cholerae toxin CtoxA and CtoxB subunits	Vibrio cholerae (humans)	Potato
Mink enteritis virus epitope (VP2)	Resistance to mink enteritis virus (domestic animals)	Blackeyed bean
VP1	Foot-and-mouth disease virus (agric.domestic animals)	Arabidopsis, Alfalfa
Glycoprotein S	Transmissible gastroenteritis coronavirus (pigs)	Arabidopsis, Maize,Tobacco
E.coli Lt-B toxin	Enterotoxigenic E.coli (humans)	Potato
Streptococcus mutans surface protein SpaA	Dental caries (humans)	Tobacco, Potato
VP60	Rabbit emhorragic disease virus (rabbit)	Potato
Glycoprotein B	Human cytomegalovirus (humans)	Tobacco
D2 peptide of fibronectin-binding protein of Staphylococcus aureus	Mucosal vaccine not requiring adjuvants (human)	Cow-pea
Peptides 10 and 18 OMP-FP.auruginosa	Pulmonary infections	Cow-pea
Diabetes associated autoantigen	Diabetes	Tobacco, Carrot ,Potato
Human rhinovirus epitope (HR14)	Rhinovirus	Blackeyed bean(Expressed on virus particles)
HIV epitopes	HIV	Tobacco, Cow-pea, Blackeyed bean

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Main R&D Institutions and Commercial Players - Meristem Therapeutic, Fr; Planet Biotecnology, USA; Dow Agrisciences, USA; Arizona State University-USA, University of Central Florida, USA; Loma Linda University, CA, USA; Guy's Hospital, London-UK; Fraunhofer Institute-IME, D

Table 3 - Information on Relevant ENEA Activities

Processes and Technologies Developed by ENEA
Binary vector technology for antibodies production in plants, an innovative tool patented by ENEA, resulting from internal R&D efforts. Technologies for the production of xenogenic in plants and for their addressing to roots of higher plants for hydroponic/aeroponic cultivation, in order to enhance yields, to simplify recovery/purification steps and to eliminate concerns and challenges associated with using transgenic plants by a fully bio-contained environment.
Experimental and Demonstration Facilities
The research is carried out in the molecular biology laboratories and infrastructure at ENEA Casaccia Labs, including a containment greenhouse. R&D activities are carried out at lab scale. A a small hydroponic bench-scale plant is planned.
Achieved and Expected R&D Objectives
Over twenty years, the technology has been developed and applied to the production of various proteins for different diagnosis/therapeutic targets: ● Cloning, expression and characterization of the scfv-800E6 antibody against HER2 antigen associated to human ovary/breast cancer. A chimera protein has also been prepared and tested by conjugation with a fluorophore for diagnostic applications. The project has been funded by various grants. At present, the optimization of the production in roots is progressing. ● Cloning, expression and characterization of a scfv-antiHMW antibody against a human melanoma antigen. The project was stopped, due to transgene silencing. ● Expression and characterization of a scfv-antiAD antibody to be used for Alzheimer therapy, specifically studied for production in a hydroponic system in potato and tobacco ● Modelling of antibodies and use of modelling as a tool for gaining information about phisyco-chemical, biological and toxicological characteristics of engineered antibodies.
Resources Employed in R&D Activities
Current staff: Patrizia Galeffi, Cristina Cantale, Maria Sperandei, Vittorio Rosato (Senior Scientists); Caterina Arcangeli (Scientist); Eleonora Palmieri (Technician); Margherita Pugnali (PhD student). Infrastructures and instruments available at CR Casaccia Labs and/or purchased by project funds and ENEA investment (transgenic greenhouse): biochemical and molecular biology laboratories, containment greenhouse for transgenic plants, monoclonal antibody laboratory, growth chambers, freezers -80, Quantitative Real-Time PCR, Workstation SGI for modelling by specific software (InsightII) and other computers used for molecular dynamics. The ENEA funds include only funds for professionals and other personnel)
Collaborationsi, R&D Funds and Grants
Collaborations: Immunology Laboratory at Regina Elena Institute, IFO-IRE, Rome; Prof. M. Bucher, Institute of Botany, Koln University, Germany. Current R&D funds and grants: AIRC (Italian Association for Cancer Researches): €15,000; CNR Biotechnology: €15,000; CNR Progetto Finalizzato Biotecnologie: € 50,000; FIDAF fellowship for young people: € 3600; MIUR: FIRB project RBNE03FH5Y AD-ART: € 368,000
Patents, Articles and Publications, Conferences and Congresses
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PATRIZIA GALEFFI is Senior Researcher at the ENEA Biotechnology Department. She is involved in antibody molecular biology research for applications in plant pathogen resistance and in plant molecular factory. Her research results are available in many papers and publications on international scientific journals. She holds five national and European patents in biotechnology. Since 2003, she is responsible for research activities for the genetic improvement of durum wheat for drought tolerance, in collaboration with CIMMYT (International Maize and Wheat Improvement Centre). She is panel editor of the "Food, Agriculture and Environment" journal and Referee for a number of international scientific journals in the field of Plant Molecular Biology and Biotechnology. She has been principal investigator in several Italian and EU programs, member of commissions on biotechnology and biomedicine and advisor of the ENEA patent office. Patrizia Galeffi has been supervisor of many university degree thesis and trainings as well as of national and International Ph.D. works. She holds a University Degree in Biology (1982) and a Ph.D. in Human Molecular and Cellular Biology (1988), both granted by the University of Rome "La Sapienza".