COST

Domain Committee Food and Agriculture

COST Action FA0804

Start Date 27/11/2008
End date 26/05/2013

Molecular Farming: Plants as a Production Platform for High Value Proteins

FINAL REPORT

Reporting Period: *from 27 November 2008 to 31 March 2013*

This Report is presented to the relevant Domain Committee.
It contains three parts:

I. Management Report *prepared by the COST Office/Grant Holder*
II. Scientific Report *prepared by the Chair of the Management Committee of the Action*
III. Previous versions of the Scientific Report*; i.e., part II of past reporting periods*

The report is a "cumulative" report and covers the entire period of the Action.

Confidentiality: the documents will be made available to the public via the COST Action web page except for chapter *II.D. Self evaluation*.

Executive summary:

The objective for the Action was to co-ordinate European efforts in plant Molecular Farming (MF) to ensure rapid generation, development and commercialization of plant MF products that will sustain the industry. The scientific program was pursued through three topics: WG1 Strategic development of MF, WG2 Production systems and process development, WG3 Target molecules – assessment of (clinical) need and production feasibility. The outcome of the Action is a sustainable European plant MF community with clear frameworks for regulatory, bio-safety and IP issues. A European Society of MF will be established in order to influence European policy and to guarantee continuity of the activities in the fast developing field of recombinant proteins. The Road Map of MF demonstrated promising future trends, verified the availability of a rich toolbox and showed a clear orientation towards products and production systems. The work carried out under WP1 was divided into four focus groups: Regulatory framework, Public perception/stakeholder interactions, Developing country aspects and IP licensing. The outcome was taken the form of Position, Information and Vision papers and Strategic Documents. Plant MF can be only successful when it meets industrial requirements with respect to cost of goods as well as product yield, quality and homogeneity. The success of specific plant production platforms is tightly interlinked with the features of specific protein products and the activities of WG2 and WG3 were therefore performed in close cooperation. To facilitate this, Molecular Farming Protein Expression database has been formulated and is now fully operational.

I. Management Report

I.A. COST Action Fact Sheet

Action FA0804 Fact Sheet

Title

Molecular farming: plants as a production platform for high value proteins

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Details

Draft Mou:		Mou:	222/08
Start of Action:	27/11/2008	Entry into force:	30/07/2008
End of Action:	26/05/2013	CSO approval date:	18/06/2008

Objectives

Proof-of-principle for Molecular Farming (MF) has been established over the last 15 years through sustained efforts of a growing number of European research groups. This work has been supported by the strategic decision of the EU to fund several initiatives through FPs 4-6 resulting in an impressive volume of generated knowledge. The aim of the Action was to leverage fruits of earlier EU, national and industrial investments in Molecular Farming to reach the next level, i.e. to move from R&D to applications, to develop product-oriented platforms, to enable new classes of products, to lower the costs and ultimately to commercialize the products. This Action has created new opportunities for European agriculture, horticulture and related technology sectors as the plants dedicated to Molecular Farming constitute new high-value crops. The Action has brought the key players together and has increased European momentum, capacity and infrastructure. It has also expanded activities to countries that had not thus far been able to participate, including developing countries. The concrete outcome is a sustainable European Molecular Farming community with a clear vision, and links and input into scientific, regulatory, biosafety, intellectual property (IP), dissemination and public engagement activities.

Keywords: Plant-made recombinant proteins, Scale-up and downstream processing, Contained growth or in-field production, Path to commercialization, Intellectual Property Rights, regulatory framework and biosafety

Parties							
Country	Date	Country	Date	Country	Date	Country	Date
Austria	05/09/2008	Belgium	30/07/2008	Bulgaria	21/08/2008	Czech Republic	05/09/2008
Denmark	16/01/2009	Estonia	08/10/2008	Finland	22/09/2008	France	01/10/2008
Germany	30/07/2008	Greece	22/09/2008	Iceland	01/04/2009	Israel	30/03/2009
Italy	01/10/2008	Lithuania	30/03/2009	Netherlands	30/07/2008	Norway	22/09/2008
Poland	30/07/2008	Portugal	26/01/2009	Slovenia	05/02/2009	Spain	07/08/2008
Sweden	14/01/2010	Switzerland	21/10/2008	United Kingdom	30/07/2008		

Total: 23

Intentions to accept the MoU							
Country	Date	Country	Date	Country	Date	Country	Date

Total: 0

Participating Institutions from non-COST countries	
India	International Centre for Genetic Engineering and Biotechnology, New Delhi
China	China Jiliang University, Hangzhou
Australia	Monash University, Clayton
Brazil	Brazilian Agricultural Research Corporation, Brazilia

Working Groups
WG1: Strategic development of Molecular Farming in Europe WG2: Production systems and process development WG3: Target molecules assessment of (clinical) need and production feasibility

Website
www.molecularfarming.org

I.B. Management Committee member list

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I.C. Overview activities and expenditure

Type	Domain	Start	End	City	Type	Title	Amount	Total EUR
MEETING	FA	27.11.2008		Brussels (BE)	Kick-off		14982.09	
MEETING	FA	5.3.2009	6.3.2009	Athens	Management Committee Meeting, Working Group Meeting (all WGs)	COST FA0804 meeting, Athens, Greece, 5-6 March 2009	39091.79	
MEETING	FA	27.5.2009	28.5.2009	Lleida	Working Group Meeting (WG1)	COST Action FA0804 (WG1 meeting), Lleida, Spain, 27-28 May 2009	12874.24	
MEETING	FA	5.10.2009	6.10.2009	Prague	Management Committee Meeting, Working Group Meeting (all WGs)	COST Action FA0804 meeting, Prague, Czech Republic, 5-6 October, 2009	33282.93	
MEETING	FA	25.1.2010	26.1.2010	Wageningen	Working Group Meeting (WG2+3)	COST Action FA0804 (WG2/3 meeting), Wageningen, Netherlands, 25-26 January, 2010	27303.28	
MEETING	FA	5.3.2009 and 5.10.2009	6.3.2009 and 6.10.2009	Athens (EL), Prague (CZ)	Local Organiser Support		3143.00	**130677.33**
STSM	FA	6.4.2009	5.5.2009	Norwich	STSM from Bulgaria to United Kingdom	Expression of HBcAg-AIV chimaeras in plants using CPMV-HT technology	2000.00	

STSM	FA	15.4.2009	20.4.2009	Gent	STSM from Austria to Belgium	Subcellular localization and N-glycosylation of seed-produced antibodies	400.00	
STSM	FA	20.4.2009	20.5.2009	Warsaw	STSM from Czech Republic to Poland	Aim of the work is to learn various methods connected to plant molecular farming	2000.00	
STSM	FA	1.6.2009	31.8.2009	Oxford	STSM from France to United Kingdom	Study of wheat prolamins traffic in plant cell model	3500.00	
STSM	FA	15.3.2010	25.3.2010	Norwich (UK)	STSM from Spain to United Kingdom	Chemical modification of viral capsids for high yield antibody production	1200.00	**9100.00**
GASG (General Action Support Grants)	FA	1.1.2009				General	2000.00	**2000.00**
DISSEMINATION	FA	1.4.2010	31.3.2011	(n.a.)	(n.a.)	leaflets	1416.00	
DISSEMINATION	FA	1.4.2010	31.3.2011	(n.a.)	(n.a.)	database	2500.00	**3916.00**
MEETING	FA	17.6.2010	17.6.2010	Brussels	Management Committee Meeting	MC Meeting Brussels	9792.60	
MEETING	FA	5.8.2010	5.8.2010	London	Other COST relevant meeting	WG Leaders	1496.17	
MEETING	FA	6.10.2010	8.10.2010	Vico Equense (Naples)	Management Committee Meeting, Working Group Meeting (all WGs)	Annual Meeting with all WG, MC Meeting	30396.88	

MEETING	FA	23.3.2011	25.3.2011	Plovdiv	Working Group Meeting (WG1)	Meeting WG 1	19078.63	**60764.28**
OTHER	FA	1.4.2010	31.3.2011	(n.a.)	(n.a.)	Action website	60.00	**60.00**
STSM	FA	11.1.2010	11.4.2010	Norwich	STSM from Lithuania to United Kingdom	Transient expression of heterologous proteins by LAB into plants using versatile expression vectors	2500.00	
STSM	FA	11.1.2010	9.4.2010	Espoo	STSM from Bulgaria to Finland	Production of recombinant proteins in plants and plant cell cultures	2500.00	
STSM	FA	15.3.2010	30.4.2010	Nantes	STSM from Germany to France	Spider silk variants from plants	1666.00	
STSM	FA	12.4.2010	3.5.2010	Louvain-la-Neuve	STSM from United Kingdom to Belgium	Mass Spectrometric analysis of recombinant protein proteolytic degradation in transgenic plants	1240.00	
STSM	FA	15.7.2010	8.10.2010	Ghent	STSM from Czech Republic to Belgium	Molecular Characterization of Antibodies Expressed in Plants	2500.00	
STSM	FA	1.11.2010	21.1.2011	Aachen	STSM from Italy to Germany	Purification of GAD65mut from transgenic tobacco leaf tissue	2100.00	**12506.00**
DISSEMINATION	FA	1.4.2011	31.3.2012	(n.a.)	(n.a.)	Action veb maintenance	500.00	**500.00**

MEETING	FA	14.9.2011	16.9.2011	Gent	Management Committee Meeting, Working Group Meeting (all WGs)	Annual COST meeting Gent	31983.92	
MEETING	FA	3.11.2011	4.11.2011	Munich	Other COST relevant meeting	Trans-Action meeting	4510.44	
MEETING	FA	16.2.2012	17.2.2012	Vienna	Working Group Meeting (WG2 + 3)	Meeting Vienna	24489.00	**60983.36**
STSM	FA	9.11.2011	16.11.2011	London	STSM from Switzerland to United Kingdom	Identifying main features of socially responsible licensing schemes	2000.00	
STSM	FA	29.8.2011	23.9.2011	Rostock	STSM from Belgium to Germany	Evaluation of a Phaseolin Promoter Driven Expression Cassette in Pea Seeds	2060.00	
STSM	FA	1.3.2012	31.3.2012	Vienna	STSM from Germany to Austria	Characterisation of pea seed derived CTB::VP60	2500.00	**6560.00**
TRAINING SCHOOL	FA	17.10.2011	28.10.2011	Helsinki	(n.a.)	Training school in Helsinki	1590.00	**1590.00**
DISSEMINATION	FA	1.4.2012	31.3.2013	(n.a.)	(n.a.)	Action veb maintenance	500.00	**500.00**
MEETING	FA	5.9.2012	7.9.2012	Warsaw	Management Committee Meeting, Working Group Meeting (all WGs)	MC & WG meeting	25019.13	

MEETING	FA	26.11.2012	28.11.2012	Cheltenham	Working Group Meeting	Small WG1-meeting	4146.71	
MEETING	FA	6.2.2013	8.2.2013	Rostock	Working Group Meeting	WG1 meeting and WG2+WG3 workshop	16403.30	**45569.14**
STSM	FA	16.4.2012	15.6.2012	Odense	STSM from Germany to Denmark	Purification and characterization of the plant-produced human Surfactant Protein D (hSP-D)	1500.00	
STSM	FA	11.5.2012	4.6.2012	Brussels	STSM from Germany to Belgium	Generation of plant-derived nanobodies inhibiting plasmodium development	2000.00	
STSM	FA	1.10.2012	14.10.2012	Wienna	STSM from Spain to Austria	Glycosylation profiling of IgA	1100.00	
STSM	FA	1.10.2012	22.12.2012	Aachen	STSM from Portugal to Germany	Characterization of a putative substrate for the tobacco matrix-metalloproteinase NtMMP1	2500.00	
STSM	FA	1.10.2012	16.11.2012	Aachen	STSM from Finland to Germany	Production of recombinant proteases in tobacco BY-2 cell line and a crash course on flow cytometry	2500.00	**9600.00**
GASG (General Action Support Grants)	FA					General	35151.37	**35151.37**
						TOTAL	**379477.48**	**379477.48**

II. Scientific report during the period 27.11.2008 – 31.3.2013

II. A. Innovative networking

In the kick-off meeting of this Action, held in Brussels on November 27th, 2008 the Management Committee (MC) elected Dr. Kirsi-Marja Oksman-Caldentey (Finland) the Chair of the Action. Prof. Julian Ma (UK) was elected the Vice-Chair. The Action has the following Working Groups (WG):

- WG1: Paul Christou (Spain), Bart Van Droogenbroeck (Belgium)
- WG2: Stefan Schillberg (Germany), Einar Mäntylä (Iceland)
- WG3: Dirk Bosch (The Netherlands); Arjen Schots (The Netherlands)

Dr. Tomas Vanek (Czech Republic) was elected the co-ordinator of STSM committee. In accordance with the existing COST rules the MC has set up an Executive Committee (EC) consisting of the Chair, Vice-Chair, the three WG leaders and the STSM Coordinator. In addition, the coordinator of the Public Engagement Committee (PEC) of the Action, Dr. George Sakellaris (Greece), is also a member of EC.

The main objective for the Action is to co-ordinate European efforts in Plant Molecular Farming (PMF) and to ensure the rapid development and commercialization of PMF products as well as the efficient establishment of a pipeline of second and third generation products that will sustain the industry for the next two decades.

The outcome of the Action is a sustainable European plant Molecular Farming (MF) community with clear frameworks for regulatory, bio-safety and IP issues. The Action is currently in a process of planning the establishment of a **European Society of Molecular Farming**. The Vice-Chair has taken a lead of the process. This Society will be established in order to influence policy in Europe for MF in a more positive direction, which would guarantee the continuity of the activities, after this COST Action, in the fast developing field of complex recombinant proteins, including biopharmaceuticals.

The scientific program of the Action has been pursued through three main topics. These have shown significant overlap and interaction, and the overall success of the Action has relied on strong interactions between the different topics.

Strategic development of Molecular Farming (WG1)

This WG aimed to provide a broad and global overview of the state of MF in the world today. Its primary purpose was to survey the global MF sector, identifying the main contributors, the technologies that are being used, the products that are being developed, the financial implications of these strategies, the contributions from academia and government research organizations, the involvement of SMEs and large companies, the IP framework and the juxtaposition with developing regulatory guidelines. This broad overview involved reciprocal interactions with the other WGs.

The implementation of WG1 activities has been performed through the formation of specialized focus groups (FGs), comprising academic and industrial members.

For each of these FGs two short term objectives and two measurable outputs were defined at the Lleida

meeting (May, 2009). These were presented to all Action members and further elaborated on the four annual Action meetings. Action members have collaborated to achieve the defined short term objectives and measurable outputs. A special workshops on WG1 were organized in Plovdiv (March, 2011) and in Rostock (February 2013).

FG1 (Regulatory Framework)

The current EU situation has been compared to the situation in the US. Action members being part of EFSA GMO panel further brought MF under the attention of EU regulators. The EFSA working group on plants as production platforms chaired by Joachim Schiemann provided the scientific input for EFSAs Scientific Opinion on Guidance for the risk assessment of genetically engineered plants used for non-food or non-feed purposes (EFSA Journal 2009; 1164: 1-42). In addition, Action members participated at the 4th Meeting of the European Advisory Committees on Bio-safety (October 2009, Brussels), again with the aim to discuss specific regulatory MF issues.

Since the regulatory requirements for contained use and open field production differ substantially, it was decided at the meeting Vico to divide FG1 (Regulatory Framework) into 2 subgroups: FG1-1 Regulatory Framework for contained use production of PMP and approval process for medicinal products; FG1-2 Regulatory Framework for open field production of PMP and approval process for medicinal products.

The Action agreed on two key messages to be delivered at events where members of FG1 were present:

- To be able to fully explore the advances of GM technology a paradigm shift in the risk assessment of GM plants is needed. At present the risk assessment in Europe (as for all GM crops) is based on the process, not on the new trait (product). The experience gained from more than 25 years of experimental field releases and more than 15 years of commercial use of GM plants and derived products has demonstrated that the technology is not inherently more risky than other classical technologies. The risk assessment should be based on the new trait, rather than on the technology used to introduce it.
- The placing on the market of a GM plant, containing a substance to be purified from it and to be used as a medicinal product needs a separate authorization from the European Commission under Part C of Directive 2001/18/EC. During the field trial stage (Part B of Directive 2001/18/EC) Member States shall ensure that no material derived from GMOs is placed on the market, unless in accordance with Part C of the Directive. The majority of GM plants used as a production platform for PMP and PMI will not be placed on the market and commercialized as varieties but will be grown on limited acreage by contract farmers. Therefore, the costly authorization under Part C is not appropriate. On the other hand, the commercialization of medicinal or industrial products produced under part B conditions is not allowed in Europe. Therefore, amendments of Directive 2001/18/EC are necessary to allow the commercialization of products from GM plants which are grown under conditions to be defined (e.g. limited acreage, contract cropping, and confinement) without the need of an authorization under Part C. With the aim to discuss the specific regulatory MF issues and issues related to the safety assessment and regulation of all plant breeding technologies FG1 members provided talks at several scientific meetings, including ISBGMO11 (Buenos Aires, November 2010), Session 3 “Biosafety considerations for crops for non-food/feed uses, biofuels and energy crops”; Botanikertagung 2011 (Berlin, September 2011); Workshop on Value Communication of Novel Agro-technologies (Vienna, November 2011); Annual Meeting Plant Biotech Denmark (Copenhagen, January 2013) and provided input for position papers and reports, e.g. Position Paper of the European Technology Platform ‘Plants for the Future’ “On New Breeding Techniques - Ensuring an Innovative and Diversified European

Agriculture" (September 2012); EASAC Report Planting the Future: Opportunities and Challenges for Sustainable Crop Production" (June 2013). Several of these activities have been coordinated with the European Plant Science Organization (EPSO) where members of the Action are actively involved in Working Groups, e.g. Molecular Farming; Agricultural Technologies.

FG1 members have recently published a paper in Current Pharmaceutical Design: "Risk assessment and regulation of molecular farming – a comparison between Europe and US", resulting in a web chat organized on the website "Sense about science". Action participants from different countries answered questions in relation to the topic of 'Using GM plants to grow medicine'. A link to a summary of the Q&A was posted on our Action website (http://www.senseaboutscience.org/pages/-using-gm-plants-to-grow-medicine-482.html). A paper on MF risk assessment and regulation focusing on contained use and an opinion paper "Better products through better regulations" will be finalized in the second quarter of 2013. In addition, FG1 will provide a chapter on risk assessment and regulation as part of the Compendium planned by the Action.

FG2 (Public perception/stakeholder interactions)

The main success undoubtedly has been the increased visibility of our Action through refreshing the Action website (http://www.molecularfarming.org) and publishing the leaflet - Molecular Farming: a field of opportunity. English version was made available *via* Action website and distributed to all Action members at Vico meeting (October, 2010). The Action Members themselves further spread it at any relevant occasion towards decision makers and other relevant stakeholders. In addition the leaflet is translated into at least 7 languages (German, Greek, Spanish, Italian, Dutch, French and Finnish) and these versions are downloadable as Word file and pdf format from our Action website. During the past period a detailed list of Action members was finally made available via the website. In the news section relevant press releases, recent publications and other news have been included to keep the website up to date. Also the webpage 'Meetings' has been frequently updated with minutes, presentations and pictures of the past meetings. For upcoming meetings, participants can now also find all relevant info and documents to register via this webpage.

Interaction with the scientific community has been guaranteed by the participation of numerous Action members to a diverse set of scientific meetings. One excellent example was the PBVA meeting held in June 2011, at Tiara Park Atlantico Hotel, Porto, Portugal. The COST Action on MF was especially visible thanks to our logo that was included on meeting advertisements and the official program booklet. This meeting was chaired by the Vice-chair of this Action, Prof. Julian Ma. Many other members took part in the Scientific Advisory Panel, gave an oral presentation or presented a poster. This will again be the case for the PBVA meeting in Verona, June 2013. Our logo is again included in the meeting leaflet and multiple Action participants will contribute to this meeting, which is the most prominent Molecular Farming meeting in Europe.

Based on the outcome of the Plovdiv workshop (March, 2011) cases were selected for targeted interaction with different stakeholders to overcome specific difficulties. These have now been initiated.

The first group is organisations grouping (scientific) teachers. In Belgium, e.g. contact was established with the VeLeWe (Society of Science Teachers) and VIB, the organizer of 'Scientist@work' (http://www.scientistsatwork.be/), a scientist-school interaction program. During the last year, multiple participants also gave lectures specific about MF to graduate and undergraduate students (e.g. at the Ghent University), for a group of horticulture specialists (http://www.sietinet.be) and several other audiences.

A valuable addition is the development of a school information package. In the Netherlands the COST members (Dirk Bosch and Arjen Schots) presented the feasibility of producing pharmaceutical proteins for a group of 50 secondary school biology teachers in January 2010. The presentation included not only the science and technology behind plant-made –pharmaceuticals but also economical, ethical and regulatory elements that are relevant. The teachers expressed a great interest. The teachers indicated that they are willing together with COST members to contribute to the development of a school package that can fill a few lessons on this topic wherein they can combine medical practice with plant biology in a societal context. An informative slideshow useful for students and teachers will be prepared and launched at our Action website by the time of the final meeting in Valencia (May 2013).

Specific interaction with **regulatory authorities and policy makers** has also been developed during the Action. One example from November 2012 is the fact that the UK Parliamentary Office of Science and Technology has published a briefing paper and interested parties on molecular farming (http://www.parliament.uk/business/publications/research/briefing-papers/POST-PN-424). UK representatives of the Action provided guidance to the person who wrote this 'POSTnote'. The document can be downloaded from our Action website.

A laboratory course was organised by University of Helsinki and VTT in Helsinki, Finland in October 2011 on the production of heterologous proteins in plants. This course was directly orientated towards young scientists interested in MF.

A positive statement towards MF, is under development and will be presented at the final meeting in Valencia. The idea is to build this deliverable based on a SWOT analysis of MF in Europe. Stakeholders contributing to the strengths and opportunities of EU MF (strong plant biotech and greenhouse sector, niche markets e.g. orphan drugs, etc) will be asked to support our positive message. This message, including the list of stakeholders supporting it will then be sent to the stakeholders that could help us to tackle the EU MF weaknesses and threats (funding bodies, regulatory authorities, policy-makers, amongst others).
In order to inform the general public and direct interested readers to our Action's webpages, a short description of Action was added to the Wikipedia pages on MF.

An inventory of all dissemination activities and stakeholder interactions will be set up and made available by the end of the Action.

FG3 (developing country aspects), the activities have focused on the following aspects: support research targeted at developing country diseases; contribute to capacity building in developing country science; work towards technology transfer or better, co-development; focus on freedom to operate as a commitment to developing country access; and finally try to develop a global access strategy. Additionally four non-COST country partners, China, India, Australia and Brizil have been joining this Action. A document focusing on the relationship between MF and Developing Countries is being drafted. The COST Action has engaged with experts in India, Argentina, South Africa, China, Cuba and Brazil to develop a global perspective, and we will work with our Eastern European colleagues in the Action to finalise and publish this paper.

Bart Van Droogenbroeck contributed to a GMO workshop held in Kampala, Uganda from 24 to 28 of October 2011, held in the framework of the Bill & Melinda Gates Foundation funded SASHA project: "Sweet potato Action for Security and Health in Africa - Weevil resistant sweet potato through biotechnology". He took benefit from this opportunity to give lectures on GM legislation, field trials with

GM plants and also MF. The African scientists involved in the project were especially interested in the MF applications and the specific EU and VS regulatory guidelines for this application of plant biotechnology.

At the Warsaw Meeting (2012) it was decided that outputs from FG3 and FG4 be merged into single Position and Information papers since both FGs have synergy and focus on developing country technology transfer and IP aspects.

FG4 (IP licensing strategy), an inventory of IP on MF within EU is one of the objectives worked upon. In addition to this, on-going activities will focus on the following aspects of IP and licensing: use of IP for commercial leverage of MF; advocate principles and best practices for socially responsible licensing of MF technologies to address access and affordability for economically disadvantaged populations without unduly compromising commercial incentives for IP owners. Certain aspects of this form a synergy with the activities of FG3.

All these activities will contribute to produce the outputs of WG1. These have taken the form of Position and Information papers, Strategic Documents, Vision Paper(s) and Activities and actions to inform other WGs.

Production systems and process development (WG2)

A major objective of WG2 was to produce a critical evaluation of all current systems for the cost-effective production of valuable recombinant proteins like pharmaceuticals in plants and plant cells. The aim was to create new and attractive options for moving from the R&D phase to the clinic and to create market opportunities for SMEs and other corporate entities interested in the field of MF. Specifically, WG2 - together with WG3 - carried out an inventory and literature study to summarize the state-of-the-art in MF and identify major bottlenecks hindering commercial exploitation. This was supported by a database summarizing MF activities. This is in a publishable form and constitutes one of the major early deliverables of this Action.

The first activities of WG2 concentrated on the presentation of the different plant production systems including the description of their intrinsic benefits and challenges to establish a competitive and sustainable MF platform. Different MF systems producing pharmaceutical and technical proteins have been presented by representatives from academia and industry in the kick-off meeting in Athens (March, 2009). During the discussions two major conclusions were made:

- The pharmaceutical industry, which currently uses conventional systems such as animal cell and microbes, will define the needs for an efficient production platform. Plant-based production systems can be only successful when they meet industrial requirements with respect to cost of goods as well as product yield, quality and homogeneity as well as compliance with regulatory guidelines. Therefore, the implementation of industrial partners including representatives from non-plant production platforms was considered in the following meetings to evaluate the achievements of the MF community and to define process steps that have to be improved.
- The success of specific plant production platforms is tightly interlinked with the features of specific protein products. Therefore, future activities have carefully considered those interactions requiring a close cooperation of WG2 and WG3. This was successfully implemented during the meeting in Prague (October, 2009) by organizing a joint WG2/WG3 workshop (see chapter ‘Target molecules’ for more details) as well as a joined workshops in Wageningen (January, 2010), Vico Equense

(October, 2010), Ghent (September, 2011) Vienna (February, 2012) and Rostock (February, 2013).

At the Prague meeting (2009) the structure of a database summarizing the various efforts in producing recombinant proteins in was discussed. The database is interactive allowing the extraction of specific information and more than initially described in the proposal. A next versions of the interactive database were presented and discussed during the joint WG2/WG3 meeting in Wageningen (January, 2010) and in the second annual meeting in Vico (October, 2010). The database holds relevant records regarding therapeutic proteins that have been expressed in plants. It should be possible to query this database. For example: 1) provide all proteins (records) that have been expressed to more than 5% TSP in leaves, 2) in which plants/tissues have interleukins been expressed. URL: http://dev3.ab.wur.nl/~hvdg/bosch/src/ Index.py (see below WG3 report).

The focus of the WG2/WG3 workshop (Wageningen, 2010) was especially in the production systems and process development including down-stream processing of plant material for therapeutic proteins. The plant-based systems e.g. the production of antibodies in moss using various bioreactors was compared to developments on the expression of antibodies in CHO cells. The advances made in greenhouse technology and the possibilities this could offer to PMP production was included to the program and state of the art greenhouses of Wageningen UR were visited. In addition, the ESRs presented their works.

A questionnaire was compiled and distributed among the participants during the meeting in Vico (October, 2010). Twenty-five colleagues filled in the questionnaire and the evaluation of the document revealed that they favour the transient expression platform (14) as the expression method with the greatest potential followed by stable nuclear (10) and chloroplast transformation (1). For the following questions also multiple answers were allowed. Tobacco (11) and *Nicotiana benthamiana* (6) are seen as the most promising plant species whereas other plant species including *Arabidopsis*, barley, *Medicago*, pea and cereals play only a minor role. However, seeds (12) and leaves (12) were indicated as the most suitable tissue for protein accumulation followed by cell suspension cultures (7), whole plants (5), roots (4), tissue suspension cultures (1), tubers (1) and fruits (1). Interestingly, infectious diseases (13) where mentioned as application and disease area where production in plants could provide a benefit. Other mentioning includes cancer (7), immunological disorders (6), metabolic disorders (5), gastro/intestinal disorders (3), personalized medicine (3), cardiovascular disorders (2), dermatological disorders (1), endocrinological disorders (1), cosmetics (1) and veterinary medicines (1). Regulation (19) was identified as the most limiting factor and knowledge gap for market introduction, respectively. Other limiting factors comprise technical issues like expression levels (10), DSP (7), protein quality (2), transformation method (2) and the speed from gene to product (1). Finally, safety (14) and costs (11) were listed as the most important advantage of producing proteins in plants. Of minor importance protein quality (5), speed (3), scale up (2) and CO_2 neutral (1) were mentioned.

Although the questionnaire comprised only a small sample its outcome reflected mainly the conclusion of the discussions during several COST Action meetings.

The annual meeting in Ghent (September, 2011) and WG2/WG3 workshops in Vienna (February, 2012) and Rostock (February, 2013) highlighted specific aspects of the different production platforms, e.g. the automatization of the production process, the non-invasive monitoring during the cultivation of intact plants and plant suspension cells/tissue as well as measures to increase stability of the target proteins and evaluation of the economic sustainability of the plant production platform. Moreover, the GMP-compliance of the plant process was presented and discussed.

In conclusion, the WG2 has intensively discussed and evaluated different plant production platforms and has defined bottlenecks hampering commercial exploitation, like the lack of suitable target proteins, poor expression levels and stability of specific target proteins, lack of cost-effective downstream procedures and difficulties in the transition of plant-produced proteins to clinical trials. However, we do not have identified an elite plant expression platform that should be used for the production of all the different target proteins but rather recommend to exploit different systems depending on the specific production needs, such as the fast production of vaccines in transient systems or the secretion of target proteins to the culture supernatant of suspended tissue or cells to facilitate purification. Our conclusions and evaluation of the different plant production systems has been implemented in various review articles, e.g. in the Journal Current Pharmaceutical Design.

Target molecules – assessment of (clinical) need and production feasibility (WG3)

The production of complex valuable recombinant proteins such as biopharmaceuticals, including vaccines, in plants can potentially address many of the challenges posed by existing methods of production. WG3 focused on the following issues of plant produced systems when choosing the best production system: **i)** Scalability, **ii)** Costs, **iii)** Adaptability, and **iv)** Speed. However, it has always been cases that as new technologies are developed, potential applications also develop to capitalize on the innovative aspects of the new technologies. This will undoubtedly also be the case for plant biotechnology and MF, and it will be extremely important to monitor potential targets for MF, with the latest plant biotechnological developments in mind.

In the first year WG3 tried to answer the question of how to identify target molecules which have the highest potential for production via plants. In the first meeting in Athens (March, 2009) expert opinions were presented by industry and academia followed by plenary discussions (Annex 1). Since specifics of the plant production platform (WG2) are tightly interlinked with the properties of specific products (WG3), a subsequent joint WG2/WG3 workshop session was organized in Prague (October, 2009) (see Annex 1). The specific aim of this workshop was to leverage MF activities carried out by the various organizations in Europe. The presentations were divided over the following topics: Viral expression systems, Plastid transformation, Seed systems, Suspension cultures, Glycoproteins, Technical proteins and Metabolites (see program in Annex 1). They were very useful with respect to providing the status quo and new activities within the area of MF from various European laboratories. Speakers were asked to specifically address the following issues: *why did you choose for a specific platform or for a specific protein and provide your opinion of which plant platform and what protein (combinations) are most suitable for production via plants*. This has provided input for the discussions related to the aim of WG2 and WG3, respectively.

The added value of a plant based platform should not be based on lower Cost of Goods (COGs) since COGs have only relative limited impact on prize and success of a drug. The plant expression platform should bring advantages to the product itself, *e.g.* in terms of product quality (efficacy), product safety or time to patient. It is recognized that different types, or groups of drugs, might be specifically suitable for production in plants. Plant systems could offer advantages for difficult to express proteins (complex or toxic to other hosts), specific glycosylation characteristics, emergency drugs (transient plant systems), drugs for developing countries, ultra high volume drugs, veterinary drugs and drugs were IP issues would be favourable for plant expression. At this stage, it turns out to be difficult to more specifically identify the most suitable candidate drugs for expression in plants.

It was therefore decided, together with WG2, to aim for an interactive, intelligent database. This kind of database was a starting point for the inventory to be made of molecules that potentially can be produced in a MF platform. It also provided information of what the status quo is of various molecules that have been produced in plants using a MF platform. Taken together this information was the starting point for the identification of target molecules and production feasibility. Combined with information on clinical need, to be obtained through bodies like the WHO, European and national health agencies and patients' organisations, an inventory can be made of the relevant molecules to be expressed in a MF platform. In addition the database will also hold information on the 'developmental status' of each molecule listed such as entry in clinical phases and can provide both users (industry) and academic guidelines and support in developing their activities.

During the October 2010 meeting in Vico the ready-to-use database was presented. The database was named MPED: Molecular farming Protein Expression Database and can be found under: http://dev3.ab.wur.nl/~hvdg/dev/bosch/src/Index.py. In 2011 it turned out that the database format still needed improvement before it could be filled with actual data. In particular, certain query fields were lacking in which data were to be inserted. In addition, the output of searches needed improvement to include also graphical representations of the results to facilitate interpretation. Thus, more time was spent on the format of the database. This was discussed in detail in the Vienna workshop (February 2012).

During the annual COST Action meeting in Ghent (September 2011), a session was dedicated to WG3. The session focused on glycosylation and on antibodies as these two topics appear to be particularly relevant in the context of plant made pharmaceuticals. During summer/autumn 2012 many delegates contributed to the filling of the MPED database. Thereto, the 600 papers were divided among the participating groups who used the details in the papers to describe all PMP's produced to date. This was illustrated during the September 2012 meeting in Warsaw. At the Warsaw meeting joined sessions were organised with WG2 where some invited speakers, including those from companies, gave state of the art lectures on Target molecules and their production systems. In addition young researchers were given the opportunity to communicate their scientific achievements. The target molecules presented were of diverse origin, including vaccines, antibodies, hormones and cytokines. During the Rostock meeting in February 2013, next to WG1 issues, some more WG3 issues were discussed.

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The Action has been closely linked to the following on-going EU-projects:

EU-Framework 6:

- Pharma-Planta (coordinators: Rainer Fischer and Julian Ma)
- SAGE (coordinator: Stefan Schillberg)

EU-Framework 7:

- CoMoFarm (coordinator: Stefan Schillberg)
- SmartCell (coodinator: Kirsi-Marja Oksman)
- PLAPROVA (coordinator: George Lomonossoff)
- Access to Pharmaceuticals (ATP coordinator: Harry Thangaraj)

There are many on-going national programmes or planned activities in the partner countries related to MF. As an example a new interdisciplinary project with potential focus on MF *"Communicating about novel*

technologies: the use of two-sided messages. Plant biotechnology as a case study" between ILVO – VIB-University of Ghent, Belgium, could be mentioned.

II.B. Inter-disciplinary networking

The exchange of PhD students and young post-doctoral fellows has been active during our Action. These activities have taken place mainly in the form of short term scientific missions (STSMs). The detailed information of the nineteen accomplished STSMs is given in Annex 2. Moreover, there has been some interaction between plant scientists and communication scientists. Trans-Action Value Communication of Novel Agro-technologies workshop was held in Munich, Germany (November 2011) together with FA0806 and FP0905 (see Annex 1). More activities in the frame of Trans-Action workshops took place in Neustadt (Germany) as a workshop on Science Commercialization was held in collaboration with FA0806, FA0907 and FA1006 in August 2012.

The Action is in the interaction with the European Technology Platform "Plants for the future" (Launch of the Strategic Research Agenda, SRA, was at 25th June, 2007 in European Parliament – the SRA includes the topic plant MF), and with the European Plant Science Organization (EPSO). Two members of the Action are board members and several participating institutes are institutional EPSO members. The COST Action further discusses with EPSO about the possibilities to influence the future topics of Horizon 2020 work programmes.

It is difficult to determine whether inter-disciplinarity is sufficient to potentially provide scientific impacts because the scientific work will anyway be done then in joined projects which COST is not funding. However, socio-economic impacts may be possible to be achieved later if the interaction is considered beneficial.

II.C. New networking

The Action involves 23 member countries including 68 research institutes, universities or industrial partners. We have 66 management or substitute management committee members. We have four non-COST country members (China, India, Australia, Brazil). Their involvement has been rather minimal but in the annual meeting in Ghent, Belgium (2011) the partner from India had a very active role. The other three non-COST members have not taken part in any meetings.

The total number of individual participants is approximately 125 from which 35% are female and 15% ESRs. Several ESRs have taken part in the STSMs and in spring 2011 Rolinde Demeyer (ILVO, Belgium) obtained an Early Stage Research Grant to participate to PBVA 2011 in Porto, and this in competition with 16 other candidates. Moreover, she also visited RWTH Aachen (Germany) for a one day training course in "Fluorometric quantification of seed-specific DsRed accumulation". Furthermore 5 more applications to obtain the ESR grant were sent in 2011 but unfortunately none of them was granted.

Dissemination of results

The promotion through the publications and other outreach activities has continued to be active during the

whole period of the Action. The Action has organized altogether eleven scientific meetings (annual meetings and workshops) and two small group meetings in which the latest developments and results in the field of MF have been presented and actively discussed by the Action partners and invited experts. Moreover, several members of the Action participated in the Trans-Action communication workshop in Munich (November 2011). The scientific programs and reports can be found in Annex 1. In the Netherlands the COST members presented the feasibility of producing pharmaceutical proteins for a group of 50 secondary school teachers. This was favourably taken by the teachers who will contribute to the development of a school package to be presented in lessons (see in detail IIA in WG1 description). Also the Action has been very active in science politics and in discussions on regulatory aspects (see WG1)

The Action has established the web site and is found in the following address: http://www.molecularfarming.org/. The web site is in full function since it was refreshed several times and has now better visibility to broader audience. It has been updated regularly with new content, news and links. During 2011 all the Action annual plans and reports as well as meeting reports and MC minutes have been added. The web site is also linked to the COST Office web. The establishment and maintaining are performed by Dr Tomas Vanek (Czech Republic), the vice-chair Prof. Julian Ma (UK) and WG1 vice-leader Dr Bart van Droogenbroeck (Belgium).

We have also published a leaflet – Molecular Farming: a field of opportunity - in autumn 2010, and it available in English and seven other languages. It is downloadable in the webpage of our Action. The number of the joined publications has been increasing (see Annex 3). To support the various communication and dissemination activities of the three working groups a series of perspective articles were published in Current Pharmaceutical Design in 2013. **This issue forms the final publication of our Action**.

The dissemination article called “Plant – our first line of defence?” was published in Research Media Innovation International in February 2012. The link of the article is available from our web site.

Our COST Action logo was included in the Advertisement leaflet of the only dedicated Molecular Farming congress in Europe, i.e. Plant-Based Vaccines and Antibody congress in Porto, Portugal (June 2011) and in Verona, Italy (June 2013).

ANNEX 1

Programs and scientific reports of the organized meetings

COST FA0804 meeting, Athens, Greece, 5-6 March 2009

Thursday 5.3.2009

09:30 – 10:15 *Welcome and introduction to the ACTION* / Kirsi-Marja Oksman, VTT, Finland

10:15 – 10:45 *Molecular Farming: Potentials based on economical, regulatory, educational and social issues* / George Sakellaris, National Hellenic research Foundation, Greece

WG1 Session: **(Chair: Paul Christou)**

10:45 – 11:15 *Introduction and summary of commitments, tasks and deliverables in the context of the COST Action* / Paul Christou, University of Lleida, Spain

11:45 – 12:10 *Vision and strategies for the development of molecular farming in Europe I – A personal perspective* / Julian Ma, St. George's, University of London**,** UK

12:10 – 12:35 *Vision and strategies for the development of molecular farming in Europe II -A personal perspective* / Dirk Bosch, Plant Research International, The Netherlands

13:30 – 14:00 *Status quo of the regulatory framework on plant-made pharmaceuticals in Europe* / Joachim Schiemann, Julius Kuehn Institute, Germany

14:00 – 15:30 Panel discussion with all the speakers and Action plan for WG1 (lead by Paul Christou)

16:00 – 18:00 Management Committee meeting (separate agenda)

Friday 6.3.2009

WG3 session: (Chair: Dirk Bosch)

8:30 – 8:45 *Introduction: aim of WG3 and of this discussion session* / Dirk Bosch, Plant Research International**,** The Netherlands

8:45 – 9:15 *Target molecules – assessment of clinical need and production feasibility; where are we today?* / Arjen Schots, Plant Research International**,** The Netherlands

9:15 – 9:45 Which target molecules are suited for plants and can we produce them? / John Butler, Bayer Innovation GmbH, Germany

10:20 – 10:50 *Potential target proteins for molecular farming in plants* / Stefan Schillberg, Fraunhofer IME, Germany

10:50 – 12:00 Open discussion between all the participants and Action plan for WG3 / (lead by Dirk Bosch and Arjen Schots)

WG2 session: (Chair: Stefan Schillberg)

13:00 – 13:30 *Overview on plant systems and expression strategies for molecular farming* / Stefan Schillberg, Fraunhofer IME, Germany

13:30 – 14:00 *Elastin-like-peptide fusions: a general tool to improve expression and purification of recombinant antibody fragments and vaccines* / Udo Conrad, Leibniz Institute of Crop Plant Research Gatersleben, Germany

14:00 – 14:30 *Harvesting the benefits of plant-made pharmaceuticals* / Einar Mäntylä, ORF Genetics, Iceland

15:00 – 16:00 Open discussion between all the participants (lead by Stefan Schillberg)
Discussion topics: *"A top-down view on molecular farming from industry: requirements and expectations" & "What does academia expect from molecular farming?"*

Scientific report (Athens, 5-6 March, 2009)

The meeting took place at the Conference Centre of the Agricultural Bank of Greece. In the meeting there were present 52 participants from 19 countries.

The first session was devoted to general presentations according to the attached program and then three sessions on the WG1, WG2 and WG3, respectively, took place. The Leader of each Working Group made an introductory presentation to the respective WG followed by a number of presentations related to the respective WG. (See program)

After the presentations discussions dedicated to each working group took place where the appointment of each WG leader and sub-leader, as well as the priorities, tasks, steps and milestones were decided. Also, a time schedule in the execution of each Working Group was agreed. All participants have committed in more than one task in various WGs.

STSM and PEC Coordinators have also been confirmed.

In parallel with the scientific program Management Committee and Executive Committee meetings took place (Minutes of MC meeting has been sent separately).

COST Action FA0804 (WG1 workshop), Lleida, Spain, 27-28 May 2009

May 27 **arrival Zenit Hotel**

20:30 Informal dinner with discussions

May 28 **Zenit hotel**

08:30 Introduction and agenda (P Christou)

08:45 Constitution of Focus Groups and nomination/election of FG leaders

09:15 Focus Group 1 Regulatory framework

10:15 Focus Group 2 Public perception/stakeholder interactions

11:15 Coffee break

11:45 Focus Group 3 Developing country aspects

12:45 Focus Group 4 IP licensing strategy

13:45 Sum up and action points

14:15 End of meeting and lunch

Scientific report (Lleida, 27-28 May, 2009)

The first WG1 meeting was held in Lleida, Spain on the 27th and the 28th of May, 2009. Thirty members, including six local hosts (UdL) attended the meeting. The Agenda and list of participants are attached to this report. The aim of WG1 is to develop a medium and long term strategy for molecular farming in Europe with a global perspective. Paul Christou as WG1 leader and local host initiated the discussion by setting the stage for the meeting. Participants agreed formally that the implementation of WG1 activities will be through the formation of focus groups (comprising academic and industrial members) with expertise AND INTEREST in specific aspects of the Action. He then presented the Agenda which had been circulated earlier. It was formally agreed that the major task for the day was the constitution of the four focus groups agreed at the last meeting in Athens (March, 2009) and the establishment of a mechanism for gathering and compiling information which can then be utilized to inform the outputs of the WG, in putting together: position and information papers, strategic documents, vision paper(s) and activities and actions to inform other WGs.

The initial major output from WG1 will be a position report summarizing the global state of Molecular Farming and the position of European research within that global picture. This will lead to the development of a strategic vision document whose purpose will be to identify areas where European R&D effort can have the most significant and global impact, and set out a long term strategy detailing how such aims will be achieved. Ultimately, the strategic vision document will act as a guide for relevant EU bodies and scientists to find science-based information that will help to focus European efforts, reduce redundancy in research and development, identify impact areas to enhance European competitiveness and identify a dissemination strategy to maximize stakeholder awareness, public acceptance and support, and regulatory support for Molecular Farming in Europe and beyond.

It was agreed that the short term objectives of the focus groups will be:

- Nominate and subsequently confirm focus group leaders
- Constitute definitive membership list
- Select 2 short term objectives per focus group
- Define 2 measurable outputs
- Implement activities and apportion tasks among focus group members
- Identify and exploit synergies with WGs 2 & 3

Focus Group 1. Regulatory framework

Joachim Schiemann and Frans van Dalen were nominated as leader and vice-leader, respectively. The short term objectives proposed (subject to further discussions lead by FG leader and vice-leader) were:

1. Make scientific (and if possible socio-political) case to lower the regulatory burden for molecular farming, primarily in Europe but also in the US through linking up with similar ongoing initiatives in the US.
2. Draft position paper and agree dissemination options

As Joachim Schiemann was not present at the meeting, Paul Christou agreed to let him know about his nomination as FG leader. Frans van Dalen was present and he accepted the nomination. A lively discussion ensued which is briefly summarized below: Possible targets for position paper should be regulators and politicians and we should aim to critique existing regulations using arguments which have not been used extensively in the past, i.e. economic benefits to the EU. Additional elements should be safety, distinction between risk identification and risk management, and other documents generated by organizations such as EFSA, etc.

Focus on a comparative analysis of regulation. This should raise the question of lower regulatory barriers in emerging economies, how this will unavoidably lead to lower also EU barriers when strategic technology positions are taken by emerging economies. This will have a negative impact on job creation in the EU (Diego Orzaez).

Stefan Schillberg indicated that it might be useful to generate a table listing the different steps of the regulatory framework. In the second row actions can be indicated to lower the regulatory burden, where appropriate. If required, we may also indicate actions that are required to provide additional knowledge to fill the gaps. However, the regulatory framework will be highly dependent on the production systems used to produce the pharmaceutical proteins. Therefore, we may focus only on specific production systems.

Tomas Vanek suggested putting together a list of MEPs who could be engaged in discussions on the severe constraints of the current EU regulatory framework and how this results in an unfair disadvantage for EU SMEs as only the big multinationals are able to go through the EU regulatory system.

Focus Group 2. Public perception/stakeholder interactions

Georg Sakelaris & Bart Van Droogenbroeck were nominated as leader and vice-leader, respectively (both present and accepted the nomination). George then made a presentation on methodology and existing guidance documents in Europe and elsewhere. The major issue to emerge from George's presentation and the subsequent discussion was that a crucial task for FG2 is to identify the most appropriate stakeholder(s). A number of views were expressed on this but the prevailing view was to target stakeholders who are not biased or have entrenched positions. It was generally agreed that to do otherwise will simply be counterproductive as such approaches have failed repeatedly in the past. Further issues discussed are listed below:

- Objective: Increase awareness and information
- Use online communication tools such as:
  http://www.agbiotechnet.com/index.asp
- Make the public aware about use of transgenic plants for molecular farming; biosimilars as examples of drugs that are accepted. Both insulin and glucocerebrosidase are examples of biosimilars. These

will reach the market following an unconventional regulatory PMP path in Canada and Israel respectively (Bart Van Droogenbroeck).

- Identify the stakeholder groups at the national level (Agnieszka Sirko and Margaret Korbin) involved in the relevant research –production-processing-exploitation chain (e.g. patients organizations, farmers, animal breeders). Development of interaction with patient groups that can be linked to existing MF products or proof-of-concept studies is very important.
- Deliverable – a positive declaration or endorsement of molecular farming from stakeholders
- Another argument that can be used in communication is that MF products are safer, and produced in a natural way, sometimes replacing chemically synthesized molecules (Bart Van Droogenbroeck) .
- Reduction of expenses of social security could also be used (Declan Nolan)
- Molecular Farming questions will be included in the next Euro barometer survey and we should have a say in formulating the questions if possible (George Sakelaris to lead)
- Diego Orzaez suggested a potential tangible deliverable. Documentary video for educational/promotion purposes, bringing the view of scientist? Distribution: YouTube/ University courses. Might this be covered by the COST action? Also joint educational programs at seecondary and tertiary educational establishments.
- Jon Veramendi indicated that the format of questions/answers is quite attractive and facilitates the global comprehension of the reader. For example, documents from the German Academy of Sciences and the Spanish Biotechnology Society have used this structure successfully.

Focus Group 3. Developing country aspects

Julian Ma & Paul Christou were nominated as leader and vice-leader, respectively. Paul Christou accepted the nomination agreed to let Julian Ma know about his nomination as FG leader.

A possible short term objective was proposed: strategies to facilitate technology transfer and capacity building. This will be discussed further.

Fernando Ponz stated the following: different stages of development exist in different developing countries. In Latin America, for instance, it would not be sensible to develop the same strategy for Argentina, Chile, Brazil, or Mexico, countries with research institutes and universities ready to adapt and/or develop MF almost immediately, compared to less-developed countries in Central America, for example. With the first group of countries, MF European policies can be developed that seek collaboration for implementation of technologies with specific goals. It is important to note that all these countries have quite tolerant attitudes towards genetic engineering, some being leaders in production globally. It is less clear what type of strategy could be developed in the other cases. Here, most likely training specialists from pre-existing R+D centers would be an almost mandatory first step. In all cases, project funding will be an issue, but that is an aspect to be dealt with later in the development of the strategies.

Other points discussed:

- Consider developing countries as production sites
- Which regions will be considered as developing countries? Proposal not to include China and India which are booming economies, but rather focus on Latin-America and Sub-Saharan Africa

- Define benefits to the Action by having a FG on developing countries. Overlap with WG3; some examples of the organizations dealing with developing countries which we might approach: (i) Bill Gates Foundation; (ii) European Action on Global Life Sciences http://www.efb-central.org/eagles/

Focus Group 4. IP licensing strategy

Kirsi Marja Oksman agreed to contact an appropriate individual from VIB, Gent with expertise in IP licensing to serve as focus group leader. Antonio Molina was nominated as vice leader. Paul Christou agreed to contact Antonio (subsequently accepted nomination).

- Stefan Schillberg stated that it will be impossible to establish plant production systems without infringing IP generated by third parties. Therefore, an overview of patents and patent applications might be helpful to discuss potential licensing strategies. Similar to FG1 we focus only on specific production systems because this exercise will be pretty time-consuming.

Key points from discussion:

- Protecting inventions from an academic point of view
- Looking for collaborations, licensing opportunities etc from an industrial point of view. What is the value of an invention?
- Chris De Jonghe (VIB HQ, Belgium) will be invited to participate in future discussion to give input.

General comments

1. WG1 needs a strong link with WG2 and 3 because regulatory frameworks, public perception, developing country aspects and IP licensing strategies heavily depend on the system that will be used for the production of pharmaceutical proteins (Stefan Schillberg and others).
2. We still need a good example demonstrating the advantage of plant-based production. So far, nobody has actually demonstrated that production of a specific protein is advantageous to production in for example conventional systems. Also arguments that we will face a lot of new product candidates are rather weak since many candidates fail within the first phases of development (Stefan Schillberg, Declan Nolan and others).
3. Andreas Voloudakis indicated that he will contact Kirsi and Tomas to propose a link between our Action and the one he chairs on transient expression systems.

Action points: To be developed through consultation with FG leaders and other members of the Action.

COST Action FA0804 meeting, Prague, Czech Republic, 5-6 October, 2009

Monday 5th October 2009

9.00 Introduction to the Action (*Kirsi-Marja Oksman*)

WG2 and WG3 Session (Chair: Stefan Schillberg and Dirk Bosch)

9.30 Introduction to WG2 and WG3
Dirk Bosch and Stefan Schillberg

Viral expression systems

10.00 Potato virus A infected plants as a production platform for heterologous proteins
Mäkinen K, Kelloniemi J, Hafren A, Valkonen J – University of Helsinki, Finland

10.25 Transient expression of the human papillomavirus type 16 epitopes derived from E7 and L2 proteins using the *Potato virus X*-based vector
Cerovska N, Plchova H, Moravec T, Hoffmeisterova H – Institute of Experimental Botany, Prague, Czech Republic

10.50 *Coffee break*

11.15 pEAQ: versatile vectors for easy and quick transient expression of heterologous proteins in plants
Lomonossoff G – John Innes Centre, Norwich, UK

Plastid transformation

11.40 Plastid transformation as a means to produce subunit recombinant antigens in plants
Cardi T, Scotti N, Rigano MM – CNR-IGV, Portici, Italy

12:05 General discussion

12.35 *Lunch*

Seed based systems and down-stream processing

13.35 Recombinant production of a full length and of a 45-kDa fragment of collagen type Iβ1 in barley seeds
Ritala A, Eskelin K, Suntio T, Blumer S, Holkeri H, Wahlström EH, Baez J, Mäkinen K, Nuutila AM – VTT, Espoo, Finland

14.00 Fusion protein technologies for efficient production and purification in plants
Joensuu JJ – VTT, Espoo, Finland

Suspension cultures

14.25 The Bryotechnology: contained, secretion based production of glyco-engineered biologicals
Jost W – Greenovation Biotech GmbH, Freiburg, Germany

Glyco-proteins

14.50 Customized protein glycosylation in plants: an advantaged over established expression platform
Castilho A – BOKU, Vienna, Austria

15.20 *Coffee break*

Technical proteins

15.45 Genetic engineering of spider silk protein derivates, plant-based expression and characterization
Hauptmann V, Junghans F, Schalllau K, Menzel M, Gunkel P, Spohn U, Conrad U – IPK Gatersleben, Germany

16.10 Expression of storage proteins designed for elastomeric properties
Saumonneau A, Allami M, Marché L, Lourdin D, Conrad U, Jones H, Shewry P, Popineau Y, Guéguen J – INRA, Nantes, France

Metabolites

16.35 Production of recombinant proteins involved in secondary metabolite biosynthesis
Cusido RM – University of Barcelona, Spain

17.00 General discussion

Tuesday, 6th October 2009

WG1 Session (Chair: Bart Van Droogenbroeck)

8.30 **Introduction to WG1**
Bart Van Droogenbroeck - ILVO, Flemish Government, Belgium

Focus group 1 – Regulatory Framework

8.35 Improving the Regulatory Framework for Molecular Farming
Introduction by Joachim Schiemann - Julius Kühn Institute (JKI), Germany

8.45 **Plenary lecture**:
Reducing the regulatory Burden for Molecular Farming in the US
Elizabeth E. Hood - Arkansas State University, USA

9.30 EFSA-Guidance for the assessment of genetically modified plants for non-food/feed purposes
Schiemann J - Julius Kühn Institute (JKI), Federal Research Centre for Cultivated Plants, Germany

9.50 Discussion and further planning

10.20 *Coffee break*

Focus group 2 – Public perception and stakeholder interaction

10.35 Introduction by *George Sakellaris – EIE, Athens, Greece*

10.45 Molecular Farming in Flanders: the opinion of the Flemish greenhouse grower
Demeyer R – ILVO, Flemish Government, Belgium

10.55 Discussion and further planning

Focus group 3 – Developing country aspects

11.25 Introduction by *Julian Ma* – St. George's, University of London, UK

11.35 Short presentation by *Fernando Ponz – INIA, Madrid, Spain*

11.45 Discussion and further planning

12.15 *Lunch*

Focus group 4 – IP Licensing strategies

13.15 Introduction by *Antonio Molina - Agrenvec, Madrid, Spain*

13.25 Discussion and further planning

13.55 **Links of WG1 with WG2 & WG3**
WG Leaders – *Bart Van Droogenbroeck, Stefan Schillberg, Dirk Bosch*

14.15 Management committee meeting (only for MC members)

Scientific report (Prague, 5-6 October, 2009)

The meeting took place at the Vila Lanna, conference facility of the Czech Academy of Sciences in Prague. In the meeting there were present 56 participants from 19 countries.

The first day was devoted to general introduction by the chair according to the attached program and then a joined session on the WG2 and WG 3 took place. The Leader of each Working Group made an introductory presentation to the respective WG followed by a number of presentations related to the respective WG's (see program). The second day WG1 related presentations took place. At the end of the meeting links of WG1 with WG2 and WG3 working groups were shortly discussed.

Main outputs

WG1

During the WG1 session, presentations were given related to the four different focus groups that were established during earlier WG1 meetings, held in Athens (March 09) and Lleida (May 09). The topics of the four focus groups are the following: 1) Regulatory Framework, 2) Public perception and stakeholder interaction, 3) Developing country aspects and 4) IP Licensing strategies.

For the **first focus group** on Regulatory Framework, Elizabeth Hood was invited as a guest speaker to comment on regulatory framework for GM crops and Molecular Farming crops more specifically. An overview was provided of the US regulatory framework: EPA, FDA, and USDA were involved. Some of these actors (not all, not always …) work in concert. Main conclusions were that there are indeed many regulations to take into account – these are driven by technology, not by product. The process is complex and expensive. As a consequence there is only a limited opportunity for value capture, almost excluding R&D investments and investments in regulatory programs for 'small' crops. To illustrate the current EU situation, Joachim Schiemann then gave a presentation on the EFSA-Guidance for the assessment of genetically modified plants for non-food/feed. As one of the conclusions it can be stated that the risk assessment of GM crops by EFSA works fine, but the risk management by the MS and EU works only for import and processing, but not for cultivation of GM crops.

In the **second focus group** two presentations were given, encouraging the discussion on i) how to interact in a positive way with the possible stakeholders, and ii) have an impact on the public perception of Molecular Farming. Specific actions were proposed and these will be discussed and worked out in further WG1 meetings.

In **third focus group** on developing country aspects Julian Ma and Fernando Ponz gave important indications on how to proceed with Molecular Farming and get developing countries involved. It is clear that also among the developing countries different opinions toward plant biotech applications exist. Together with the developing countries, where major disease like HIV/AIDS, tuberculosis and others are most prevalent, platforms and target proteins should be selected & developed to tackle these diseases. Training and involvement of local researchers, even when the projects are running in EU labs, is another important commitment.

Finally, the **fourth focus group** dealt with IP licensing strategies. In his presentation, Antonio Molina pointed out that we could be more creative in generating value out of our Molecular Farming research. Not only claims linked to the target protein are important, but we should also pay attention to claims related with new expression technologies, purification processes and so on. Another important point is the selection of the protein to be produced by Molecular Farming: this should be based upon market opportunities (e.g. proteins/technologies that come of patent) and specific consumer demands and not solely upon technological feasibility.

Conclusions/Action points

- Describe regulatory pathway to be followed for most important examples of Molecular Farming applications, being, at least: stable nuclear expression (open field/contained) and transient expression (contained)- link with WG2&3.
- EFSA does not deal with contained use of GM crops, this is a regional or national matter. However, given the public opinion towards GM cultivation in open field, these contained platforms will most likely be the ones used in the EU to deliver a commercial product. Therefore it would be of interest to make an inventory of current regulations in EU on contained use and eventually propose measures to harmonize these regulations.
- Target a young public (schools etc.) with a promotional video, educational document on plant biotechnology and Molecular Farming – include questions on Molecular Farming in next EuroBarometer.

WG2 + WG3

During the combined WG2 and WG3 session, research of participants was presented. The presentations were divided over the following topics: Viral expression systems, Plastid transformation, Seed systems, Suspension cultures, Glycoproteins, Technical proteins and Metabolites.

The presentations were very diverse, covering issues such as characteristics of expression platforms, different proteins and their optimization to purification and downstream processing. They were very useful with respect to providing the status quo and new activities within the area of Molecular Farming from various European laboratories. In addition, the speakers were asked to specifically address the following issues: "why did you choose for a specific platform or for a specific protein and provide your opinion of which plant platform and what protein (combinations) are most suitable for production via plants". This has provided input for the discussions related to the aim of WG2 and WG3, respectively.

Finally, also links of WG2 and WG3 with WG1 have been formulated such as Public information/perception of Molecular Farming (by case example), Identification of proteins specifically relevant with respect to clinical need for developing countries (as opposed to economical need ($$) and IP situation (which proteins/technologies come of patent.

Conclusions/Action points

- A database will be constructed that contains information on available data of proteins that have been expressed in plants. The format of this database and the way it will be made available will be communicated.
- A follow-up joint WG2 and WG3 meeting will be held in January 25th and 26th in Wageningen, the Netherlands.

MC meeting

After the scientific program Management Committee meeting took place (Minutes of MC meeting have been sent separately).

COST Action FA0804 (WG2/3 workshop), Wageningen, Netherlands, 25-26 January, 2010

Monday January 25

08.00-08.30 Registration

08.30-08.45 Introduction: Kirsi Marja Oksman
08.45-09.30 Patrick van Berkel (Genmab, Utrecht, NL): Production platform assessment for biopharmaceutical proteins
09.30-10.15 Juergen Drossard (Fraunhofer IME, Aachen, D): Technical and regulatory developments in PMP production – lessons learned from Pharma-Planta

10.15-10.45 Coffee Break

10.45-11.45 Silke Hemming (Wageningen UR, Wageningen, NL): Efficient crop production in controlled greenhouses
11.45-12.30 Erik Pekkeriet (Wageningen UR, Wageningen, NL): Automation in plant handling and monitoring

12.30-13.45 Lunch

13.45-14.15 Ronald Bassuner (Greenovation Biotech GmbH, Freiburg, D) tba
14.15-14.45 Udo Conrad (IPK, Gatersleben, D): Purification of ELPylated proteins from plants by Inverse Transition Cycling: antigens, antibodies and spider silk proteins
15.00-15.30 Bus to Wageningen UR facilities
15.30-17.30 Tour Greenhouse facilities Wageningen UR

18.00-23.00 Dinner (by bus)

Tuesday January 26

PhD session (20 minutes presentations by PhDs and PostDocs)

08.10-08.30 Albino Maggio, Brussels: COST office
08.30-08.50 Luisa Bortesi, Verona: Interleukin-10: targeting\transient\stable
08.50-09.10 Petya Stoykova, Sofia: Expression of human acidic fibroblast growth factor in tomato *Solanum lycopersicum*
09.10-09.30 Stefanie Goedeke, Gatersleben: Production of Recombinant Protein in Transgenic Barley Grains
09.30-09.50 Eva Thuenemann, Norwich: Transient Expression of Complex Heteromeric Bluetongue Virus-like Particles

09.50-10.40 Coffee break

10.40-11.00 Lotte Westerhof, Wageningen: Aggregation as a Bottleneck for IL-10 Production in *Nicotiana benthamiana*
11.00-11.20 Inge Broer, Rostock: Biopolymers in Transgenic Plants: Optimization of Cyanophycin Production in Different Species
11.20-12.00 Dirk Bosch & Arjen Schots,Wageningen – Stefan Schillberg, Aachen Interactive database: presentation and discussion

12.15-13.30 Lunch

13.30-13.50 Kirsten de Wilde, Gent: Inter-transformant transgene expression variability in *Arabidopsis* leaves and seeds.
13.50-14.10 Michele Belluci, Perugia: Enzyme Replacement Therapy: Production of Human α-Mannosidase in Transgenic Tobacco Plants
14.10-15.00 Evaluation and wrap up
15.00 Closure

Scientific report (Wageningen, 25-26 January, 2010)

The combined WG2/3 workshop took place in the Hotel de Wageningse Berg Wageningen, the Netherlands. The focus of the meeting was especially the production systems and process development including down-stream processing of plant material for therapeutic proteins. The workshop gathered 44 reimbursed participants and many of them were early stage researchers i.e young PhD student and post-doctoral fellows.

The first day of the workshop focused on the possibilities to produce pharmaceutical proteins. Some state of the art examples were presented, one focusing on the (historic) developments on the expression of antibodies in CHO cells (van Berkel). Another focus was on the production of antibodies in moss cell using various

bioreactors (Bassuner). Two researchers from Wageningen UR (Pekkeriet, Hemming) presented the advances made in greenhouse technology and the possibilities this could offer to PMP production. In the afternoon of the first day state of the art greenhouses of Wageningen UR were visited.
On the second day the opportunity was given to ESRs to present their work. In addition a format for an interactive database was presented (see attached Powerpoint file). The database should hold relevant records regarding therapeutic proteins that have been expressed in plants. It should be possible to query this database. For example: 1>provide all proteins (records) that have been expressed to more than 5% TSP in leaves. 2> in which plants/tissues have interleukins been expressed. URL: http://dev3.ab.wur.nl/~hvdg/bosch/src/Index.py

Abstract book containing short presentation abstracts of ESRs and the program of the workshop was published.

COST Action FA0804 meeting, Vico Equence, Italy, 6-8 October, 2010

Wednesday 6.10.2010

18:00 Registration and hanging up the posters

20:00 Welcome dinner

Thursday 7.10.2010

09:00 Kirsi-Marja Oksman: Current status of the Action

09:15 **Working groups 2 and 3**
Stefan Schillberg and Dirk Bosch: Introduction and presentation of the goals of the WG2 and 3

09:45 Yoseph Shaaltiel (Protalix, Israel): Molecular farming approach for production of recombinant glucocerebrosidase in carrot cells

10:15 Maurice Moloney (Rothamsted Research, UK) Oilseed-based biopharmaceutical production: from clone to clinic

10:45 Discussion: What are the best platforms and product candidates for molecular farming?

11:30 Coffee break

12:00 **Working group 1**
Paul Christou: Introduction and presentation of the goals of the WG1

12:15 **WG1 focus groups**
Paul Christou and Bart van Droogenbroeck: goals, action plan, broadening participation and discussion

12:30 FG1 Regulatory framework (leader Joachim Schiemann)

- Joachim Schiemann: The regulatory frame for molecular farming (10 min.)
- Inge Broer (University of Kiel, Germany): Approaches to reduce the regulatory burden for experimental field conditions and placing on the market (20 +10 min.)

13:15 Lunch

14:15 FG1 Regulatory framework (continue)
- Maurice Moloney (Rothamsted Research, UK): How to meet GMP requirements for PMP production under open field conditions (20 + 10 min.)
- General discussion (including an open letter drafted by Joachim Schiemann)

15:00 FG2 Public perception/stakeholder interactions (leader Bart van Droogenbroeck)
15:45 General discussion, action points, deliverables and outputs, assignments of FG1 and FG2
16:30 FG3 Developing country aspects (leaders: Julian Ma and Paul Christou)
17:00 Sylvia Burssens (IPBO, Belgium): Industrial Biotechnology Applications for Developing Countries
17:20 General discussion, action points, deliverables and outputs, assignments of FG3 and the whole WG1
17:50 – Poster presentation with aperitif

20:00 – Pizza dinner in a local Pizzeria (optional)

Friday 8.10.2010

09:00 WG2 and WG3 (continue)
Franco M. Buonaguro (Cancer Institute, Naples, Italy): Development of a vaccine for HIV
09:30 Einar Mäntylä (OrfGenetics, Iceland): Molecular farming approach for cosmetic products
10:00 Discussion on production platforms, products, down-stream processing, future activities (action points, deliverables)

11.00 Coffee break

11:30 Dirk Bosch: Status of molecular farming database, demonstration
12:00 Karin Metzlaff (Executive Director, EPSO, Brussels): How can we further increase impact and visibility of plant science in Europe? (30 min talk + 30 min discussion)

13:00 Lunch

14:30 - 18:00 Management committee meeting (for only MC members)

Scientific report (Vico Equense, 6-8 October, 2010)

The 2nd Annual meeting of the Action FA0804 was held in Vico Equense (Naples), Italy from 6 to 8 October, 2010. Sixty-two participants from 19 countries were present. Most of them were located at the same Hotel where the meeting was hosted (Aequa Hotel) and the remaining in nearby Hotels at walking distance. This allowed fruitful continuous and close interactions between all participants not only during the meeting, but also during breaks and meals. The meeting program (attached) started on Wednesday 6 with registration of participants and hanging up of posters. Presentations were given during the all Thursday 7 and the morning of Friday 8, and were organized according to the three Working Groups of the Action.

The topics and goals of WG1 ("Strategic development of Molecular Farming") were introduced by the WG1 leader Dr. P. Christou. Subsequently, three out of the four Focus Groups were discussed by the respective leaders. Dr. J. Schiemann, leader of FG1 ("Regulatory framework") gave a introductory talk focusing on the regulatory frame for Molecular Farming (MF), including issues related to the use of GMOs in open field. It was proposed to divide the FG1 into two subgroups:

- FG1-1 Regulatory framework for contained use production of PMP and approval process for medicinal products (co-chaired by Heribert Warzecha). Julian Ma will contact John Edward Butler, Bayer Innovation, to suggest him as another co-chair.
- FG1-2 Regulatory framework for open field production of PMP and approval process for medicinal products (co-chairs Inge Broer and Maurice Moloney).

Contributions of Dr. I. Broer ("Approaches to reduce the regulatory burden for experimental field conditions and placing on the market") and Dr. M. Moloney ("How to meet GMP requirements for PMP production under open field conditions") were mainly devoted to the actions to be taken in order to lower the regulatory burden and meet the GMP requirements related to the production of Plant Made Pharmaceuticals (PMPs) in open field. The experience of BioOK, an interdisciplinary network bridging academia and private companies, on developing risk assessment procedures for transgenic plants was reported by Dr. Broer. Dr. Moloney, instead, focused on its own experience at SemBioSys of producing insulin in open-field grown safflower plants.

Since the commercialization of medicinal or industrial products produced in the frame of experimental field releases is not allowed in Europe and placing on the market of the respective GM plants is very costly and not appropriate for most of the PMP/PMI applications, amendments of Directive 2001/18/EC are necessary to allow the commercialization of products from GM plants which are grown under conditions to be defined without the need of an authorization under Part C (placing on the market). Dr. Schiemann will provide a first draft to be illustrated by two examples: insulin production in safflower seeds and production of antimicrobial substances with a short description, provided by Dr. Moloney and Dr. Ma, respectively, of the advantages for Europe to produce these products under open field conditions. Some suggestions for Action points to be taken in 2011, aiming to lower the regulatory burden for MF, were discussed. Among others, they include: a letter to the Commission on amending Directive 2001/18/EC, a review/discussion paper on regulatory issues to be published in Transgenic Research, a kick-off discussion with "strategic partners" to make the case for *trait*- rather than *event*- based regulations.

Dr. B. van Droogenbroeck, leader of FG2 ("Public perception/stakeholder interactions") reported on the actions to be taken in order to improve interactions between the different stakeholders of MF. Dr. U. Conrad volunteered to act as future co-chair of this FG2. As a tool to improve the degree of public perception towards MF, a leaflet, describing general aspects on the use of plants for MF purposes, different production platforms and most advanced products, has been printed. To better spread MF concepts, it was also discussed the opportunity to translate the leaflet content in the different languages of the Countries participating to the Action, and distribute the resulting flyers to journalists, teachers, etc., and suggested several Action points (*i.e.* prepare information package on MF to be used in secondary schools, develop informative slideshow presentation that can be downloaded from our Action website for broad public, realize MF promotional video that could be placed on YouTube etc.).

The topics of FG3 ("Developing country aspects") were introduced by leaders Drs J. Ma and P. Christou. Dr. Sylvia Burssens of the Institute of Plant Biotechnology for Developing Countries (IPBO, Belgium) was invited to give a lecture on the "Industrial Biotechnology Applications for Developing Countries". The organization and goals of the International Industrial Biotechnology Network, aiming to promote the use of biotechnologies and the development of sustainable bio-economies in developing and emerging countries were described. More specifically, the opportunities to cooperate in the field of pharmaceutical production in

plants were discussed and some joint initiatives (manuscripts, events etc.) with people in developing countries involved in MF were suggested.

The aims and on-going activities of FG4 ("IP licensing strategy") were only summarized by Dr. P. Christou since the leader in charge was not present at the meeting.

Presentations related to WG2 ("Production systems and process development") and 3 ("Target molecules") were arranged in the same sessions, considering the strong interactions of the two WGs. After the introduction and general comments on the scopes of the two WGs by the respective leaders, Drs S. Schillberg and D. Bosch, three invited speakers (Dr. E. Mäntylä, although included in the program, was not able to participate at the very last moment) reported on different aspects of pharmaceutical development and production. In their lectures, Dr. Y. Shaaltiel from Protalix and Dr. M. Moloney, formerly at SemBioSys, reported on the production of glucocerebrosidase and insulin in carrot cells and safflower seeds, respectively. Since the latter products are among those closest to the market, that was a nice opportunity to understand, from a private company perspective, potentialities and practical problems of plant MF. Dr. F.M. Buonaguro, a virologist at the Cancer Institute in Naples, gave an overview of the different issues related to the development of a vaccine for HIV, commenting also on the specific usefulness of plants, in comparison to other systems, for antigen production.

Subsequently, Dr. A. Schots presented the beta version of a revised database containing information on available data of plant-expressed proteins. The fields included in the database to categorize results and the tools to retrieve/analyze results were described and discussed. Several suggestions were taken in order to improve the Database. A general discussion was done on the possibility and utility to define a consensus production system for plant MF, highlighting the difficulties in finding such a system.

A questionnaire was prepared and distributed during the meeting to obtain insights from the COST Action members about MF.

Besides the oral presentations, 22 posters were presented at the meeting. They mostly included reports about the production of various kinds of proteins (antigens, antibodies, microbicides, HSPs, spider silk proteins, enzymes) in a range of species and plant parts. Other posters reported results of research activities on the manipulation of protein glycosilation in plant cells, the improvement of purification procedures, and biosynthesis of anthocyanins in plants.

The meeting was closed by the lecture of Dr. K. Metzlaff, Executive Director of the European Plant Science Organization (EPSO), who highlighted the different opportunities for funding MF research within EU. In order to promote such funding opportunities, the necessity of the involvement in lobbying activities of "Health people" together with plant experts was underscored.

Finally, the MC meeting took place on Friday 8 from 2 to 5 pm. Twenty-four representatives were present. All aspects listed in the Agenda were thoroughly discussed. The minutes of the MC meeting have been prepared separately.

COST Action FA0804 (WG1 workshop), Plovdiv, Bulgaria, 23-25 March, 2011

Wednesday 23rd March 2011

Arrival during the afternoon - informal get together on Wednesday evening

Thursday 24th March 2011

9.00 Introduction to WG1
Paul Christou

Focus group 2 – Public perception and stakeholder interaction

9.15 Introduction by *Bart Van Droogenbroeck - ILVO, Flemish Government, Belgium*
9.30 Invited speaker 1: *Thorsteinn Tomasson* – Director, Ministry of Fisheries and Agriculture, Reykjavík, Iceland
"Aspects of Public perception on the use of GMO barley for molecular farming in Iceland"
10.00 Questions and discussion
10.15 Invited speaker 2: *Filip Cnudde* – Senior Manager Green Biotech, EuropaBio
"Plant Molecular Farming: On which side of the red/green division in public attitudes to biotechnology?"
10.45 Questions and discussion

11.00 *Coffee break*

11.15 On-going initiatives: website, leaflet
Bart Van Droogenbroeck- ILVO, Flemish Government, Belgium
Discussion and future plans/actions
11.30 Future initiatives: School information package
Udo Conrad/Dirk Bosch/ Arjen Schots/Bart Van Droogenbroeck
Discussion & Future plans/actions
12.00 Other initiatives: PPT, MF statement, video ...
Discussion & Future plans/actions
12:30 General discussion – What are relevant and achievable target deliverables?

13.00 *Lunch*

14.00 Brainstorm – workshop session towards FG deliverables

15.00 *Coffee break*

15.15 Brainstorm – workshop session towards FG deliverables
15.50 FG2 Wrap up - conclusions

Update on Focus group 3 – Developing country aspects
16.00 Introduction by *Julian Ma* – St. George's, University of London, UK
16.30 Discussion and further planning FG3

Update on Focus group 1 – Regulatory Framework
16.45 Introduction by *Joachim Schiemann - Julius Kühn Institute (JKI), Germany*

17:15 Discussion and further planning FG1
17:25 *Julian Ma* – St. George's, University of London, UK: Update on Lobbying activities
17.40 Discussion and further steps

Friday 25th March 2011

Focus group 4 – Leveraging intellectual property for commercial and social goals in Molecular Farming

09.00 Introduction by *Harry Thangaraj- St George's University London, United Kingdom*
09.15 Invited Speaker: *Beatrice Stirner- Université de Neuchâtel, Neuchâtel, Switzerland:* Neglected diseases: Using IP, public-private partnerships and other incentive options to promote R&D for diseases disproportionately affecting developing countries
09.50 Questions and discussions
10.00 *Harry Thangaraj - St George's University London, United Kingdom:* Effective leverage of IP in Molecular Pharming: towards building a comprehensive strategy
10.40 Questions and discussions

10.50 *Coffee break*
10.51
11.15 Invited speaker: *John Butler- Bayer Innovation GmbH:* Solutions in Search of a Problem?" Revisited, Industrial Applications of Plant-based Protein Expression
11.45 Questions and discussion
12.00 General discussion

12.30 *Lunch*

14.00 Overall publication strategy for WG1
Invited Speaker: *Stefan Schillberg- Fraunhofer IME, Germany*
14.35 Questions and discussion
14.45 General Brainstorm – workshop session towards FG deliverables

15.45 *Coffee break*

16.00 General Brainstorm – workshop session towards FG deliverables
16.30 Wrap up – conclusions
16.45 Future Action Meetings
17.00 End

Scientific report (Plovdiv, 23-25 March, 2011)

Paul Christou opened the session by summarizing the key objectives of the WG and the expected outcomes of the meeting. The meeting focused primarily on activities relating to FG2 (Public perception and stakeholder interaction) and FG4 (IP and Licensing strategies). Short status reports from Joachim Schiemann and Julian Ma on activities in FGs 1 and 3, respectively, were also given. Bart van Droogenbroeck chaired the session on FG2 activities. A summary of the session is given below.

The audience was introduced to FG2 by stating the general goals: stimulate awareness and support for Molecular Farming, influence public perception in a positive way and to reach all these goals *via* interaction with relevant stakeholders. In addition the Action Points that were defined after the last meeting in Vico (October, 2010) for FG2 were listed:

1. Information package school teachers – initiated

2. Informative Slideshow broad public – no action so far
3. Stakeholder interviews – no action so far
4. EuroBarometer Questions – missed 2010
5. Positive MF statement – open letter /white paper – no action so far
6. Promotional video YouTube – no action so far

Two speakers were invited; however Thorstein Tomasson (Director, Ministry of Fisheries and Agriculture, Reykjavík, Iceland) had to cancel his participation, so a bit more time was given to the other invited speaker.

After the introduction Dr. Filip Cnudde (Senior Manager Green Biotech, Europabio) introduced the audience to the "*European association of biotechnology industries"*. EuropaBio represents 66 corporate members, 7 associate members, 4 Bioregions and 22 national biotech associations. In total, over 1800 SMEs are represented by EuropaBio. As a consequence, EuropaBio is an important strategic partner in reaching many relevant stakeholders. Another aspect that was discussed was the heavy EU regulatory burden for GMO approval. The enormous amount of data needed (huge cost – 10-20 million Euros) and the long period a dossier needs to go through the approval process makes it extremely difficult for any remaining Plant Biotech companies active in the EU to sustain their operations. The general view is that Europe is a training centre but then high caliber employees' move to North- and South-America, Asia etc, where GMO crops are adopted widely (brain-drain). For the moment only two crops are authorized for cultivation. More than 70 dossiers are awaiting approval.

In his second presentation Dr. Cnudde talked about public perception of GMOs and stakeholder interactions. He concluded that there is little awareness in Europe, there are few industry players in the EU and there is not a lot of active attention by stakeholders. Though not relevant at first sight, food industry has been identified as an important, powerful stakeholder: if they want to block products, they are able to do so. Also patient groups could have a strong role as important player that could positively influence other relevant stakeholders (regulators, industry), they have a big moral weight in discussions. Other tips are to look for 'red biotech' flag where possible for a product produced (regulatory burden on red biotech is lower). Containment is the way to go for production of biopharmaceuticals and might provide entry in to this red biotech evaluation process that is more efficient than that of Green Biotech product.

The rest of the program for FG2 was organized in the form of two workshops. During the first workshop the idea was to list stakeholders (SHs), and identify the organizations that represent the different stakeholders. In a next step the aim was to think how these SHs could be contacted (communication tool used?) and what the goal of interaction with these stakeholders could be.

In relation to biopharmaceuticals patient organizations were selected as one of the most relevant stakeholders to interact with. In connection with these health care professionals and also health insurance companies are considered as relevant. A second group of stakeholders that was considered as important is the group of students (undergraduate & university students), their teachers and academic personnel, also from other disciplines (communication sciences, social sciences etc…).

After the identification of these stakeholder group, it was discussed how we could approach them and what the goals of our interaction should be. Concerning health care professionals and insurance companies it is most important to create awareness of Molecular Farming. In approaching patient organizations it was clear from the discussion that we should be cautious in the way we approach these patient groups and organizations. We have to provide them correct information in order to avoid the creation of false hope. A

clear statement about the hurdles to PMP commercialization (regulatory and competition with other platforms), together with a realistic timeline is of utmost importance. Bottleneck in this exercise remains the lack of any successful PMP product on the market at this moment. Nevertheless it seems worthwhile to contact them, provide them info and try to get support from them. This stakeholder group could be very influential towards other stakeholder groups (e.g., politicians, regulators ….). The idea to interact with students and their teachers, professors etc. is to try to attract the interest of the next generation of scientists. Through the students also the parents, friends and family of these students could be reached.

Concrete action steps were defined to interact with these two stakeholder groups in the next year. The presentations of the authors who agreed to share their ppt will be available from the website.

Short report on Website and Leaflet

In order to make the website content more up to date and attractive, it would be good if a dedicated person could take care of this. However, as this is not possible, it was proposed to provide more info directly to the webmaster Petr Soudek. New publications for example and news items could be sent directly to Petr with the chair and vice-chair of our Action in cc. The collected participant info will be put online as soon as possible; labs not providing info will just be listed with their names.

Regarding the leaflet an update was provided –five countries have provided translations (Finnish, Dutch, French, Spanish, Italian). The next step is that an A4 layout document will be prepared by the FG leader and sent around for approval. This A4 layout could then be used by the countries to paste their translations into the document and further spread it.

A next initiative that would be useful is a basic power point presentation that would be available for the Action. This could then be adapted for specific uses.

Trans-COST Activity

COST FA0804 was contacted by COST action FA0806 in order to participate in a communication workshop organized by Valcom Biotechnology on "Value Communication in the Field of RNA-based Vaccines and Molecular Farming". Due to the budget limitations it was discussed that participation of COST Action FA0804 would be limited to maximum 5 persons. The workshop will focus on value-laden risk and benefit communication. The organizers will support the participants' in their endeavors to develop a communication strategy. The outcome will be a brief report that will summarize the main ideas and outcome. The preliminary program will be provided together with this document.

Annual Meeting in Ghent

The Belgian participants presented Ghent as candidate city and proposed to stick with the date of 14-16 September. If budget is limited, the meeting will be reduced to two days, i.e; three half day sessions (related to each WG) and a MC meeting. After having cleared budget availability a tentative program will be sent around for discussion.

Julian Ma gave a brief update of FG3 activities and interactions with developing country colleagues active in molecular farming and he discussed in more detail a draft white paper which is one of the key planned outputs of FG3. Julian also lead a short discussion on lobbying activities to sustain molecular farming as a topic in EU FPs. Joachim and Kirsi will coordinate these activities at least in the first instance with EPSO.

Joachim Schiemann then discussed FG1 activities which can be summarized as follows:

GMO Regulation in the EU: recent developments

Recent developments in GMO regulations:

- *Communication from the Commission to the European Parliament, the Council, the Economics and Social Committee and the Committee of the Regions on the freedom for Member States to decide on the cultivation of genetically modified crops*, including a *Proposal for a Regulation of the European Parliament and of the Council amending Directive 2001/18/EC as regards the possibility for the Member States to restrict or prohibit the cultivation of GMOs in their territory* and *Commission Recommendation of 13 July 2010 on guidelines for the development of national co-existence measures to avoid the unintended presence of GMOs in conventional and organic crops*
- DG SANCO working paper (February, 2011) suggesting reasoning for future national safeguard clauses (ban of cultivation)
- 0.1% threshold for admixture of unapproved events in imported feedstuff (February, 2011)

Recent EU publication on GMO research:

A decade of EU-funded GMO research [2001 - 2010]

Chapter 1 Environmental Impacts of GMO; Chapter 2 GMO and Food Safety; Chapter 3 GMOs for biomaterials and biofuels – Emerging technologies; Chapter 4 Risk assessment and management – Policy support and communication

- 130 research projects in 25 years, EU funding 300 million €, 500 independent research groups
- Commission conclusions: GM technology – no higher risk than other breeding methods
- Commissioner for research: GM plants can provide solutions – improving agricultural production, global food security

Management issues

FG1 Regulatory Framework (chair Joachim Schiemann) has been divided into 2 subgroups:

- FG1-1 Regulatory Framework for contained use production of PMP and approval process for medicinal products (co-chairs Heribert Warzecha, NN - John Butler agreed to suggest a co-chair)
- FG1-2 Regulatory Framework for open field production of PMP and approval process for medicinal products (co-chairs Inge Broer, Maurice Moloney)

Action points discussed in Vico

1. Bringing the necessity for reducing the regulatory burden for GM plants to the attention of an international auditory and to provide suggestions (November, 2010)
2. Letter to the Commission on amending Directive 2001/18/EC (April, 2011)
3. Review / discussion papers for Transgenic Research on regulatory issues, 1 draft April 2011
4. Kick-off for a debate on *event vs trait*, including arrangements with "strategic partners", Autumn 2011

Action point 1

JS has been organizing and chairing a session at ISBGMO11 (Buenos Aires, November 15-20, 2010):

SESSION 3

Biosafety considerations for crops for non-food/feed uses, biofuels and energy crops

3.1 Status and regulation of non-food/feed crops in Europe

Inge Broer & Kerstin Schmidt

3.2 Status and regulation of non-food/feed crops in the USA
Elizabeth E. Hood
3.3 Recent advances in biological confinement technologies
Joachim Schiemann & Alexandra Hüsken
3.4 The Benefits and Risks of Next Generation Microalgal Biofuel Production Systems
Richard T. Sayre
3.5 Comparison of a weedy relative of sugarcane in two environments highlights traits leading to increased invasiveness
Bonnett GD, Olivares-Villegas JJ, Letondor C & Saltonstall K
3.6 Ecological assessment of transgenic grasses: baseline studies of native and improved switchgrass for biofuel
Allison Snow, Amy Campbell, Emily Heaton & Maria Miriti

Action point 2
The following draft provided by JS has been discussed:
The placing on the market of a GM plant, containing a substance to be purified from it and to be used as a medicinal product, needs a separate authorization from the European Commission under Part C of Directive 2001/18/EC. During the field trial stage (Part B of Directive 2001/18/EC) Member States shall ensure that no material derived from GMOs is placed on the market, unless in accordance with Part C of the Directive. The majority of GM plants used as a production platform for PMP and PMI will not be placed on the market and commercialized as varieties but will be grown on limited acreage by contract farmers. Therefore, the costly authorization under Part C is not appropriate. On the other hand, the commercialization of medicinal or industrial products produced under part B conditions is not allowed in Europe. Therefore, amendments of Directive 2001/18/EC are necessary to allow the commercialization of products from GM plants which are grown under conditions to be defined (e.g. limited acreage, contract cropping, confinement) without the need of an authorization under Part C. These amendments would be in line with the Innovation Strategy developed by the Commission.

It has been decided that a modified text (more detailed describing the block for innovation resulting from the existing regulatory frame and illustrated by two examples: insulin production in safflower seeds and production of antimicrobial substances [Maurice Moloney and Julian Ma, respectively, to provide a short description of the advantages for Europe to produce these products under open field conditions]) will be circulated by JS. The final text will be sent to EPSO (Karin Metzlaff) to use the existing channels to bring it to the attention of key policy makers at EU level.

Action point 3
The following proposal has been discussed and agreed:

- Review on regulatory issues for PMP in North America and Europe (open field) including suggestions to reduce the regulatory burden

Co-authors:
Yann Devos, EFSA, Italy
Elizabeth Hood (+ Deborah), Arkansas State University, USA
Inge Broer (+ Heike), University of Rostock, Germany
Joachim Schiemann, JKI, Germany

- Review on regulatory issues for PMP in Europe (contained use - greenhouse) including suggestions to reduce the regulatory burden

Lead: Heribert Warzecha

Action point 4

To be able to fully explore the advances of GM technology we need a paradigm shift in the risk assessment of GM plants. Nowadays the risk assessment is based on the process, not on the new trait. The experience gained from more than 20 years of experimental field releases and more than 10 years of commercial use of GM plants and derived products has demonstrated that the GM technology is not inherently more risky than other classical or new breeding technologies. The risk assessment should be based on the new trait, rather than on the technology used to introduce it. There was an agreement that the COST action should send this message out in the medium term. It is suggested to look for "strategic partners" to strengthen our voice.

The second day of the meeting was devoted to activities, current and potential, of Focus Group 4 (Leveraging IP for commercial and social gains) led by Harry Thangaraj. The main focus of the session was on using IP as a leveraging tool to enhance commercial activity on the PMP sector, and improving access to technologies and products of the future, particularly for impoverished populations in urgent need of solutions. Perspectives of the guest speakers - Beatrice Stirner from the University of Neuchatel, and John Butler from Bayer can be summarized as follows: There are potentially a wide range of incentives that can be used to stimulate innovation through legal and scientific means to address gaps in R&D, production and manufacture, and access to new and essential medicines. On the legal and international levels, a focused approach to addressing trade and incentive bottlenecks to stimulate R&D for unmet needs in global disease was addressed, and the essence of this was increased cooperation between the public and private sectors in the form of partnerships. This theme was further enhanced by the developments in transient expression by plant viral expression vectors by Bayer, potentially offering rapid and scalable production systems to produce vaccine and therapeutic molecules. The role of public sector funding, and partnerships formed a strong underlying theme. Cost of goods in upstream processing appears to be a significant factor for new technology platforms.

FG4 will be led by SGUL with strong cooperation from within this COST Action consortium and external stakeholders. A variety of themes to address IP management and bottlenecks will be addressed. Specific activities include: Information to the technology transfer community, and policymakers/governments on specific concerns will be communicated through an advisory document. Joachim Schiemann offered to be an important communicator to policymakers of "socially responsible" means of enhancing access to essential health technologies through better management of IP. Specific actions include a working document to be finalized as a white paper to inform participants and stakeholders on emerging licensing paradigms in global health, currently spearheaded by the Association for University Technology Managers, specific private and public sector entities, public private partnerships, and non-profit health patent pooling initiatives. Problems in protecting IP and effective commercialization were offered by members of the consortium. Immediately identifiable bottlenecks are: a fundamental disconnect between the scientific and technology transfer communities; conflicts between journal and patent publication and an inefficient system to manage both; problems related to maintenance of patent applications and premature abandonment; and lastly too much disclosure into the public domain that makes it difficult for registration of IP. A number of activities are envisaged to address problems and inform policymakers and stakeholders: A session at the Ghent meeting on FG4. A separate stakeholder consultation meeting for issues related to FG4. A white/position paper should be written on leveraging IP for commercial and social goals in PMP to address policymakers. At least two publications that include both assessments of current thinking, and forward looking means of stimulating commercialization of PMP technologies through better IP management are planned.

Stefan Schillberg then lead a discussion on publication strategy, decisions, plan of action, follow-up and next steps. To support the various communication and dissemination activities of the three working groups a series of prospective articles will be published in the journal Transgenic Research. One to two articles will be published per issue. A list of potential articles (9 articles including Introductory and Summary Editorial) has been presented and discussed during the meeting. In addition lead authors and potential co-authors have been suggested. The article list and some guidelines to be considered when preparing these articles will be presented on the homepage and Stefan Schillberg will prepare a letter to inform and to ask the COST Action members for final input. Subsequently, Stefan Schillberg and Paul Christou will invite the lead authors to provide a prospective article and inform them about deadlines and an appropriate format for the manuscripts.

During the meeting it was also discussed that the white papers for WG1 and WG2/3 may extract information from these prospective articles. Therefore, the preparation of the white papers may start now as a working document but will be finished at the end of the COST Action when all information of the articles is available.

COST Action FA0804 meeting, Ghent, Belgium, 14-16 September, 2011

Wednesday, 14 September 2011 (FSVM building, VIB)

14.00 – 15.00	Registration – coffee
Chairman:	Ann Depicker
15.00 – 15.30	Ann Depicker (VIB, UGhent): Welcome
15.30 – 16.00	Alain Goossens (VIB, UGhent, Belgium) : Production of novel bioactive molecules by combinatorial biosynthesis in plant cells
16.00 – 16.30	Wout Boerjan (VIB, UhGent, Belgium) : Bio-energy from poplar
16.30 – 17.30	Guided tour in the Schell/Fiers/VanMontagu VIB building Coffee
17.30 – 18.00	Marc De Loose (ILVO, Belgium) : Coexistence field trial
18.00 – 18.30	Bart Van Droogenbroeck (ILVO, Belgium): Field trial with transgenic potatoes
18.30 – 19.30	Walk to “Kasteel van Zwijnaarde”
19.30 – 22.30	Reception and Welcome Dinner in “Kasteel van Zwijnaarde”

Thursday, 15 September 2011 (Hotel Poortackere Monasterium)

08.30 – 09.00	Registration
Chairman: Dirk Bosch	
09.00 – 09.15	Introduction: Ann Depicker and Kirsi-Marja Oksman
09.15 – 10.00	Nico Callewaert (VIB, UGent, Belgium): Which glycans in which expression system for which therapeutic application?
10.00 – 10.15	Herta Steinkellner (Vienna, Austria): Plant glycol-engineering: an advantage over mammalian cell based systems?
10.15 – 10.30	Bieke Nagels (UGhent, Belgium): Production of human erythropoietin with multi-

	antennary N-glycan structures in *Nicotiana benthamiana* plants
10.30 – 10.45	Alexandra Castilho (Vienna, Austria): In planta sialylation of recombinant proteins
10.45 – 11.15	Coffee break and poster viewing
11.15 – 12.00	Peter Casteels (Ablynx, Belgium): Manufacture of Nanobodies: from Pipeline into the Clinic
12.00 – 12.15	Sylvie De Buck (VIB, UGhent, Belgium): Production of VHH and VHH-Fc antibodies in *Arabidopsis thaliana* seeds
12.15 – 12.30	Vikram Virdi (VIB, UGhent, Belgium): Passive immunization of piglets against post weaning diarrhoea via anti-ETEC antibodies produced in seeds
12.30 – 13.45	Lunch in Monasterium hotel
13.45 – 14.45	Guided STSM poster tour
Chairman:	Stefan Schillberg
14.45 – 15.30	Anni Van Broeckhoven (Crea Bio Support, Ghent, Belgium): GMP Processing and purification of recombinant proteins
15.30 – 15.45	Geert Angenon (VUB, Belgium): Production in plant seeds of an oral veterinary vaccine against avian influenza
15.45 – 16.05	Siva Reddy (New Delhi, India): Tobacco chloroplast transformation for over production of antibodies and cellulolytic enzymes
16.05 – 16.30	Coffee break and poster viewing
16.30 – 16.45	Kristiina Mäkinen (Helsinki, Finland): Methods to enhance protein expression from Potato virus A gene vector in plants
16.45 – 17.00	George Lomonosoff (Norwich, UK): Production of virus-like particles for therapeutic applications
17.00 – 17.15	Anders Kvarnheden (Uppsala, Sweden): Begomovirus-associated DNA-satellites and their potential as expression vectors in plants
17.15 – 17.30	Catherine Navarre (UCLouvain, Belgium): Expression of different antibody isotypes in suspension cell cultures
17.30- 17.45	Henrik Brinch-Pedersen (Slagelse, Denmark): A cereal platform for the production of phytases
17.45- 18.00	Udo Conrad (Gatersleben): Production of very large spider silk proteins by posttranslational fusions *in vivo*.
18.30 – 20.00	Guided tour in Ghent
20.15	Dinner in “De Foyer”

Friday, 16 September 2011 (Hotel Monasterium)

Chairman:	Paul Christou
09.00 – 09.45	Jan Desomer (Bayer BioScience N.V., Belgium): From "green juice" to "galactosylated plantibodies": IP landscape of molecular farming
09.45 – 10.00	Harry Thangaraj (United Kingdom): Intellectual Property and molecular farming
10.00 – 10.15	Stefan Schillberg (Aachen, Germany): Recent progress of the EU FP7 CoMoFarm project
10.15 – 10.30	Dirk Bosch (Wageningen, the Netherlands): Molecular farming database feedback and update on target products (WP3)
10.30 – 11.00	Coffee break and poster viewing
11.00 – 11.45	Marc Zabeau (Tech Transfer, UGhent): Tech transfer from academics
11.45 – 12.00	Stefan Schillberg and Einar Mäntylä: update on WP2 -plant production platforms and downstream processing
12.00 – 12.15	Paul Christou and Bart van Droogenbroeck: Update on WP1 -the social economic

	position of molecular farming
12.15 – 12.45	Discussion – chaired by the WP leaders
12.45 – 13.00	Concluding remarks: Kirsi-Marja Oksman
13.00 -	Lunch in Monasterium hotel
14.00 – 17.00	Management committee meeting chaired by Kirsi-Marja Oksman

Scientific report COST FA804 meeting in Ghent, Belgium, 14-16 September, 2011

The 3rd Annual meeting of the Action FA0804 was held in Ghent, Belgium from 15th till 16th September 2011. Half of the participants were located at the same Hotel where the meeting was hosted (Poortacker Hotel) and the remaining participants were in nearby Hotels at walking distance. This allowed fruitful continuous and close interactions between all participants not only during the meeting, but also during breaks and meals. At the start of everyday‘s program, participants could register.

The meeting program (see above) was divided in two parts, a first one with a selection of speakers from the Ghent area being organised in the VIB department and a second part with presentations related to know-how of molecular farming.

The meeting program started on Wednesday 14th of September 2011 in the department of the host Prof. Ann Depicker. The aim was to introduce the plant biotechnology department via two talks of the group leaders Prof. Wout Boerjan and Prof. Alain Goossens. Both groups work on the genetic modification of plants for the sustainable production of bioenergy and new pharmaceutical metabolites, respectively. As many of the attending groups also have some activities in metabolite engineering, both presentations of the mentioned experts were very much appreciated.

During the break, a guided walking tour was organized through the labs, the robotics infrastructure, the transformation platform and the greenhouses with *Arabidopsis*, poplar, tobacco, corn, and medicinal plants.

In the second part of the afternoon, two presentations were given by Prof. Marc De Loose and by Dr. Bart Van Droogenbroeck on their experiences with co-existence measures of GMO and non-GMO plants and in the field trial with transgenic potato containing *Phytophtora* resistance genes. Especially the movie made for the Flemish government with recommendations for co-existence was applauded. This movie is available on the COST website for dissemination.

In the evening a welcome dinner took place in a very beautiful surrounding Kasteel van Zwijnaarde.

On Thursday 15th and the morning of Friday 16th, presentations were given in hotel Poortacker in the seminar room on the second floor. The host together with the chair decided to focus the molecular farming program on topics for which local expertise was available, and the sessions were organized according to the three Working Groups of the Action. Presentations related to WG2 ("Production systems and process development") and 3 ("Target molecules") were arranged in the same sessions, considering the strong interactions of the two WGs.

After the welcome, introduction and general comments of the chair Kirsi-Marja Oksman, Prof. Nico Callewaert summarized in a very comprehensive way the relevance of recombinant protein glycosylation for particular applications. Subsequently, 3 members of the COST Action reported on their progress with the in planta production of glycosylated recombinant proteins.

The second morning session started with a talk from industry, presented by Dr Casteels of Ablynx, showing the different steps in the pipeline from discovery till the clinic. Many participants thereby realized that delivering a proof-of-concept is only the beginning of bringing a product to the market. This talk was followed by two research progress presentations from the group of the host, focusing on the in planta production of lama derived antibodies for various applications.

The lunch could be taken in the garden as it was a beautiful autumn day, and at the same time more than 15 posters were discussed.

The afternoon session started with a talk of Dr Anni Van Broeckhoven highlighting the importance of GMP procedures, once a commercial product is made. The non-COST partner, Dr Siva Reddy from New Dehli, India, summarized the projects they have running in their research centre, and he was hoping to start many new collaborations. The program of the day was concluded with 6 short talks presented by the participants.
In the evening, the guided tour in the centre of Ghent and also the walking dinner were highly appreciated. This was followed by a dinner at De Foyer.

To start the program of Friday the 16th, Dr Desomer gave a historical overview of the IP landscape relevant to molecular farming, and he indicated which aspects could limit a freedom to operate. Then, an update of the 3 work packages was presented by the respective leaders, Prof. Paul Christou, Prof. Stefan Schillberg and Dr Dirk Bosch.

Dr. Harry Thangaraj presented an update of FG4 (under WG1) on socially responsible licensing of IP. An early draft of a working paper was underway to be sent to members of the Action for comment and feedback

The meeting was closed by the lecture of Dr. Marc Zabeau, Director of the Ghent University Tech Transfer program. In his typical enthusiastic manner, he promoted collaboration of scientists with administrators to valorise new academic findings and insights by protecting them *via* patenting.

Besides the oral presentations, many posters were presented at the meeting. The abstracts are all available in the abstract book, and in pdf format on the COST website.

Finally, the MC meeting took place on Friday 16th from 2 to 5 pm. All aspects listed in the Agenda were thoroughly discussed. The minutes of the MC meeting have been prepared separately.

COST Trans-Action Workshop on Value Communication of Novel Agro-technologies, Munich, Germany, 3-4 November, 2011

2.11.2011

Dinner in the Ratskeller Munich

3.11.2011

08:15 – 09:00	**Registration**
09:00 – 09:30	**Welcome and introduction** (Krczal/Busch)
09:30 – 10:30	**Introduction of the COST Actions involved:**
09:30 – 09:45	Action FA0806 "Plant virus control employing RNA-based vaccines: A novel non-transgenic strategy (Voloudakis)
09:45 – 10:00	Action FA0804 "Molecular farming: plants as a production platform for high value proteins" (Oksman-Caldentey)
10:00 – 10:15	Action FP0905 "Biosafety of forest transgenic trees: improving the scientific basis for safe tree development and implementation of EU policy directives" (Vettori)
10:15 – 10:30	Action FA1006: "Plant metabolic engineering for high value products" (Warzecha)
10:30 – 10:45	Coffee break

Thematic Section I: Risk technologies and public perception

10:45 – 11:30	**M. Hampel:** *Different Understandings of Risk and the Discourse on Biotechnology*
11:30 – 11:45	Discussion
11:45 – 12:00	**J. Schiemann**: *How to prevent burning of new breeding technologies*
12:00 – 12:15	Discussion
12:15 – 12:45	Workshop: Applying the talk notes to the COST Action Topics (moderation: Busch)
12:45 – 14:15	Lunch Break

Thematic Session II: **Communicating values and trust**

14:15 **–** 14:45	**M. Siegrist**: *Acceptance of gene technology: The influence of trust and confidence*
14:45 – 15:00	Discussion
15:00 – 15:30	**F. Meijboom**: *Communicating on technology: a matter of trustworthiness*
15:30 – 15:45	Discussion
15:45 – 16:45	Workshop: Applying the talk notes to the COST Actions´ topics (moderation: Busch)
16:45 – 17:00	Coffee Break

Thematic session III: Outline of a communication strategy

17:00 – 18:00	Discussion and integrating results (Moderation: Busch)
20:00	Dinner (centre of Munich)

4.11.2011

Thematic session IV: Communication strategies and channels

09:00 – 09:45	**P. Aerni**: *Consumer behavior towards GMOs and what it reveals about the importance of morality and fear in Swiss politic*
09:45 – 10:15	Discussion
10:15 – 10:45	Coffee Break
10:45 – 11:30	**G. Nicolosi**: *The lost food in the "orthorexic society": communication strategies in Southern Europe*
11:30 – 11:45	Discussion
11:45 – 12:15I	ntegration the inputs into the outlined communication strategy (moderation: Busch)
12:15 – 13:15	Lunch break

Session V: "Tying up loose ends" (moderation: Busch)

13:15 – 14:30	Development of an overall communication strategy
14:30 – 15:00	Decisions on corner posts of the future communication strategy
15:00	End of workshop, departure

Scientific report (Munich, 3-4 November, 2011)

COST Actions involved:
Action FA0806 "Plant virus control employing RNA-based vaccines: A novel non-transgenic strategy
Action FA0804 "Molecular farming: plants as a production platform for high value proteins"
Action FP0905 "Biosafety of forest transgenic trees: improving the scientific basis for safe tree development and implementation of EU policy directives"
Action FA1006: "Plant metabolic engineering for high value Products"

Learning from the GM debate, it is plausible to argue that other novel biotechnological strategies are likely to be regarded as problematic risk technologies as well. If scientists only offer facts, but do not address the value laden structures of citizens´ perception as well, communication will fail. Therefore the aim of the workshop was to develop strategies for successful communication in the food sector. In order to reach this goal, specialists on the value-laden risk and benefit communication were invited and space was provided for the participants from the different Cost Actions to utilize the information for the development of communication strategies.

The Workshop addressed the following topics in special thematic sessions:

- **Risk technologies and public perception**
- **Communicating values and trust**
- **Communication strategies and channels**

Between the thematic session the workshop participants tried to integrate the communicated information into an overall strategy. The last afternoon was devoted to identify "loose ends" and to an attempt to structure communication of biotech research:

As a general outcome it can be recorded:
Mere explanations of research (-results) won't be sufficient. Consumers don't have the (mental) capacities to assess these results. But consumers are interested and perhaps even curious to know. In this respect, it is essential to make consumers' approach easier. This implies a modification of wording and framing.
In general applicable: **narrations** (= systematic descriptions of reality by stories using metaphors; social reality is a constructed one and it won't become subject of discourse if it wouldn't be communicated in terms of pictures, allegories etc.). Narrations give **meaning / sense** to systems. This is far more than description and / or explanation.

In this respect, scientists should check if they could develop a narrative story about their project containing

- credible images of selected (involved) researchers, i.e. his/her motives and motivation
- challenge(s) to be managed by the project's results
- "history" of the project
- hurdles to overcome
- description of benefits to society and / or nature
- ethical assessment (reference to and compatibility with cultural values)
- involvement of society (open-mindedness of involved parties + transparency!)

Despite the fact that a lot of respective research had already been done during the last decade, **some important (societal) perceptions** need to be taken up again – and worked on with more emphasis.
In this respect, "internal" tasks – i.e. enhancement of sensitization of scientist – and "external" tasks – i.e. generating / intensifying influence on consumers – have to be distinguished:

a) "Internal" tasks:
Scientists have to analyze societal risk perceptions – which differ even within Europe. A lot of research has been done already. It only should be used!

Science needs products which might serve as "blockade-breakers". They don't need to be commercial blockbusters, but rather plausible products which attract consumers' approval. And scientists need support for the commercialization of research results. Here, access to venture capital would be fruitful.

b) "External" tasks:
Consumers want to trust! This would make their life easier. Therefore, building *trustworthiness* is of utmost importance. Trustworthiness is easier granted individuals, not science as such. Education of scientists presenting and communicating projects and results to an interested public should be fostered:
This might be supported by scientific *success-stories* (proof of concept) and the outlining of *clear aims* of research – the latter with the intention to bridge the time gaps between the start of research and first applicable results.

Telling the truth is a precondition to appear trustworthy. In this respect, using worst-case-scenarios seems to be a fair manner to involve an interested public. This might also become a new kind of consumer approach

and have a significant impact on consumer perceptions of associated risks. In general, applicable tools for education (schools) would be helpful.
There are some **open issues** which might worry scientist – and cause frustration. Here, scientists are the addressees of communication:

- Scientists know that there is a regulatory framework, regulatory bodies and free choice in Europe. But how important –or even necessary – is a European consensus on agro-biotechnology?
- How far reaches politicians responsibility in this respect?
- Which role do NGOs play by blocking labeling of products in many cases?
- Is cooperation with consumer-organizations necessary or feasible?
- Which impact has a respective political system and culture on societal dynamics, rules and restrictions (on agro-biotechnology)?

A lot of information has been collected over the last decades. But scientists need more tailored information which goes beyond Eurobarometer surveys. They need support to cope with societal interpretations and the appropriate framing of information to present research interests in an attractive way. Obviously, scientists lack of easy access to respective information and support.

COST Action FA0804 (WG2/WG3 workshop), Vienna. Austria, 15-17 February 2012

Wednesday 15th February, 2012

17:00 Registration at the IBIS Hotel Vienna
18:30 Departure for dinner

Thursday, 16 February, 2012

8:00 Registration (until 9:00) and poster session set-up
9:00 Welcome and opening of the meeting (Kirsi-Marja Oksman and Herta Steinkellner)

Expression of highly complex proteins (Session 1)

Chair: Kirsi-Marja Oksman
9:15 Glycosylation of therapeutically used plasma proteins (Alfred Weber)
9:45 Recombinant IgMs expressed in mammalian cells (Renate Kunert)
10:05 Recombinant IgMs from plants (Andreas Loos, Clemens Gruber, Frank Hensel, Friedrich Altmann and Herta Steinkellner)
10:25 Coffee break and poster session

Topics of general interest (Session 2)

Chair: Herta Steinkellner

10:55 PhD – programme BioToP – Biomolecular Technology of Proteins (Christian Obinger)
11:15 Foundation of start-up biotech-companies (Gottfried Himmler)
11:35 Strategies for the stabilization of Fc fragments (Gordana Wozniak-Knopp, Johannes Stadlmann, and Florian Rüker)
11:55 Proteomics: identification of glycoproteins (Friedrich Altmann)
12:15 O-glycosylation engineering in plants (Richard Strasser)
12:35 Lunch

Automatization / non-invasive imaging (Session 3)

Chair: Stefan Schillberg

14:00 Monitoring protein concentration via automated, non-invasive image acquisition: an application for Molecular Farming (Martina Becher, Silvia Braun, Fabio Fiorani, Nicole Raven, Stefan Schillberg and Ulrich Schurr)
14:25 Development of online monitoring and fluorescence imaging systems for plant cell suspensions (Wolf Klöckner, Clemens Lattermann, Tibor Anderlei, Nicole Raven, Stefan Schillberg and Jochen Büchs)

Down-stream processing, GMP production (Session 4)

Chair: Stefan Schillberg

14:50 DSP strategies for plant produced antibodies (Stephan Hellwig, Jürgen Drossard)
15:10 Production, purification and characterization of spider silk proteins (Nicola Weichert, Dominic Knoch, Valeska Hauptmann, Norman Paege, Matthias Menzel, Uwe Spohn, Mario Gils and Udo Conrad)
15:30 BryoTechnology™: Recent developments in moss-based production of pharmaceutical proteins (Andreas Schaaf)

15:50 – 16:20 Coffee break and poster session

16:20 – 17:45 **Protein accumulation and subcellular deposition (Session 5)**

Chair: Udo Conrad

16:20 Expression and purification of recombinant proteins in tobacco BY-2 suspension cells with hydrophobin fusion technology (Anneli Ritala, Suvi Häkkinen, Marina Petrova and Jussi Joensuu)
16:40 Molecular farming of selected viral antigenes for vaccination in *Arabidopsis* seeds (Annelies De Paepe, Robin Piron, Els Van Lerberge, Jonah Nolf, and Ann Depicker)
17:00 Immunoglobulin A production in edible plant organs: bridging the gap between Molecular Farming and Plant Synthetic Biology (Paloma Juárez, Alejandro Sarrión-Perdigones, Silvia Presa, Asun Fernández-del-Carmen, Antonio Granell and Diego Orzaez)
17:20 The deposition of recombinant proteins in storage bodies (Elsa Arcalís, Verena Ibl, Thomas Rademacher, Francesca Morandini, Linda Avesani, Mario Pezzotti and Eva Stöger)

18.30 Departure for dinner

Friday, 17 February, 2012

Product degradation/quality (Session 6)

Chair: Dirk Bosch

9:00 Degradation of recombinant proteins by plant cysteine proteinases (Melanie Niemer, Ulrich Mehofer, Maria Verdianz, Andreas Schaller, Renier van der Hoorn and Lukas Mach)
9:25 Novel strategies to reduce recombinant protein degradation in plant uspension lines (Stefan Schillberg, Manoj K. Mandal, Janina Kirchhoff, Nicole Raven and Andreas Schiermeyer)

9:45 Characterisation of the proteolytic degradation of a human IgG1 in plant (Raffaele Lombardi, Verena Hehle, Maria Elena Villani, Mariasole Di Carli, Matthew Paul, Julian K-C. Ma, Eugenio Benvenuto and Marcello Donini)
10:05 Antibody production in culture cells (Bertrand Magy, Jérémie Tollet, Catherine Navarre and Marc Boutry)
10:25 Therapeutic proteins from mushrooms (Elsa Berends, Karin Scholtmeijer, Han Wösten, Luis Lugones, and Dirk Bosch)

10:45 Coffee break and poster session

Topics of general interest (Session7)

Chair: Ann Depicker

11:15 Use of SPR for quantification, characterization and quality control of recombinant antibodies and vaccine antigens produced in plant based expression systems (Holger Spiegel and Markus Sack)
11:45 An universal expression vectors in plants: a seed delivery system (Ofer Gover, Rita Mozes-Koch, Ilan Sela, Edna Tanne, and Haim D. Rabinowitch)
12:05 Presentation of the Molecular Farming Database (Dirk Bosch)

12:25 General discussion and closing remarks (Chair: Kirsi-Marja Oksman)

13:00 Lunch

Scientific report (Vienna, 15-17 February, 2012)

The WG2/WG3 workshop of the COST Action FA0804 was held in Vienna, Austria from 15th to 17th February 2012. Sixty-nine participants from 17 countries were present. All external participants were located at the same Hotel where the meeting was hosted (IBIS-Mariahilf). This allowed fruitful continuous and close interactions between all participants not only during the meeting, but also during breaks and meals. The meeting program (attached) started on Thursday 16th Feb, at 8.00 with registration of participants and hanging up of posters. Presentations were given during the all Thursday and the morning of Friday 17th, and were broken down to seven major topics (see program). Topics with generally interesting issues were scheduled at the beginning and the end. This was given by scientists outside of the MF program and covered recent developments mainly in the area of mammalian expression systems and industry. A focus was given on difficult to express proteins, like highly complex immunoglobulin Ms. A comparison between animal and plant expressed IgMs were given, and it seems that plants are well suitable for the generation of this new potentially therapeutically interesting molecules. New developments in the area of glycosylation and glycol-engineering were presented by external speakers.

Another topic focused on “protein accumulation and subcellular deposition” where recent developments in the enhancement and stabilization of recombinant proteins in plant were shown. In this respect cell and seed based expression and the induction of artificial protein storage compartments were discussed.

In the sessions “Automatization and “Down-stream processing” external speakers updated the audience about recent developments. Very impressive high through-put facilities were shown by Martina Becher (fz-Jülich, Germany) and large scale downstream processing of recombinant monoclonal antibodies were reported by Wolf Klöckner (RWTH-Aachen, Germany). Current estimations about costs of plant produced

mAbs compared to animal cell based production were rather disappointing. To be competitive it seems that in many cases the expression levels need to be increased and plant handling costs need to be decreased.

Friday morning started with "product degradation/quality and internal as well as invited speakers presented new strategies to prevent protein degradation, however so far with limited success. Ilan Sela (Israel) introduced a new universal expression vector for plants and emphasized the possible impact of this viral based vector in the near future. Unfortunately he could not present important details since the vectors are according to his statements under a patenting process. In addition, Dirk Bosch (Wageningen, The Netherlands) introduced all participants to the recently generated online-database. Participants are asked to fill the database with their own publications.

Finally Agnieszka Sirko, who will organize the next MF meeting was introduced. This meeting will be in Warsaw during 6th to 7th September, 2012.

COST Action FA0804 meeting, Warsaw, Poland, 5-6-7 September, 2012

Wednesday, 5 September 2012 (Hotel Gromada)

13:50-14:50 Registration

WG2/WG3 – Part 1A; Session Chair: Agnieszka Sirko

14:50-15:00 Welcome (Kirsi-Marja Oksman-Caldentey – *Chair of the Action*)

15:00-15:20 Tomasz Pniewski (Poland); Pros and cons of a plant-derived oral vaccine against Hepatitis B Virus

15:20-15.35 Tomasz Sarnowski (Poland); The use of modelling techniques, *Arabidopsis thaliana* mutant plants and mice with type II diabetes for identification of new regulators of processes aberrant in metabolic diseases

15:35-15:50 Wojciech Bal (Poland); Novel - non enzymatic method of protein purification

15:50-16:20 Coffee break

WG2/WG3 – Part 1B; Session Chair: Stefan Schillberg

16:20-16:50 Victor Klimyuk (Germany); Plant-Made Biopharmaceuticals and Vaccines: Current Progress in Transient Expression Systems

16:50-17:10 Fernando Ponz, (Spain); A nanoplatform based on Turnip mosaic potyvirus with multiple applications

17:10-17:30 Diego Orzaez (Spain); GoldenBraid 2.0: A comprehensive toolkit for modular DNA assembly in Molecular Farming

17:30-17:45 Lauri Reuter (Finland); Hydrophobin fusion technology assisted production of recombinant proteins in tobacco BY2 cells

17:45-18:00 Andreas Schaaf (Germany); BryoTechnology™ en route to the clinic

18:00-18:20 Andreas Loessl (Austria); Expression of a vaccine candidate against dengue fever in tobacco chloroplasts

19:00 Dinner at Gromada Hotel

Thursday, 6 September 2012 (Hotel Gromada)

8:30-9:00 Registration/ posters viewing

WG2/WG3 – Part 2; Session Chair: Arjen Schots

9:00-9:30 Lynn Dickey (Netherlands); The LEX system: A superior plant expression system for antibodies

9:30-9:45 Anna Urbanowicz (Poland); Identification and preliminary characteristics of candidate antigens for a vaccine against *Borrelia burgdorferi*

9: 45-10:00 Jozef Kapusta (Poland) Expression in transgenic tobacco of recombined mouse monoclonal antibody specific to Anthrax protective antigen is regulated developmentally regardless of applied nominally constitutive Rubisco gene promoter

10:00-10:15 Anneli Ritala (Finland) Secretion of human M12 antibody in tobacco hairy root cultures

10:15-10:30 Bertrand Magy, (Belgium) *Arabidopsis thaliana* as an alternative to *Nicotiana tabacum* for IgG expression in suspension cells

10:30-11:00 Coffee break and posters viewing

WG2/WG3 – Part 3; Session Chair: Dirk Bosch

11:00-11:20 Verena Hehle (UK) Proteases and their role in hindering antibody expression in plants

11:20-11:35 Anna Gora-Sochacka (Poland) Plant-produced protein inhibitors protect fusion partners against digestion with proteases

11:35-11:50 Lotte Westerhof (Netherlands) Resolving 3D-domain swapping of human IL-10 prevents extensive multimerisation and increases yield

11:50-12:05 Inge Broer (Germany) E.coli or Tobacco? Expression of IL6 and C5a in different systems

12:05-13:00 Discussion on WG2 and WG3; Moderators: Stefan Schillberg, Dirk Bosch, Arjen Schots

13:00-14:00 Lunch at at Gromada Hotel

14:00-15:00 Posters viewing / Discussions / Coffee break (14:15-14:45)

15:00-22:00 Walking tour in warsaw and dinner at the Warsaw University

Friday, 7September 2012 (Hotel Gromada)

WG1 – Part 1; Session Chair: Paul Christou

8:30-10:00 FG1 and FG2: Status and deliverables-planning and execution;

Joachim Schiemann (Germany); New biotechnologies in agriculture: safety assessment and prospects for regulation

10:00-10:15 Coffee break

WG 2 – Part 2; Session Chair: Paul Christou

10:15-11:45 FG3 and FG4: Status and deliverables-planning and execution

11:45-12:15 Final discussion (Kirsi-Marja Oksman-Caldentey) and closing of the meeting

12:15-13:00 Lunch at at Gromada Hotel

13:00-16:00 Management Committee meeting chaired by Kirsi-Marja Oksman-Caldentey

Scientific Report (Warsaw, 5-7 September, 2012)

The fifth Annual meeting of COST Action FA0804 was held in Warsaw, Poland from 5th till 7th September 2012. The participants were located in the same hotel (Gromada Hotel) where the meeting took place. This allowed broad interactions between participants not only during the meeting but also during breaks and the meals. The meeting started in the early afternoon of September 5th, 2012. The participants could register at the start of the meeting or at the beginning of the second day.

The meeting program (see above) was divided into the six sessions. Four of them (sessions on Wednesday and Thursday) were related to the topics of WG2 (Production systems and process development) and WG3 (target molecules), while the other two sessions (on Friday) contained talks and discussions related to the topics of WG1 (Strategic development of molecular farming).

After the short welcome by the host, Agnieszka Sirko, the meeting was started by the welcome, introduction and comments of the chair of the Action, Kirsi-Marja Oksman-Caldentey, who briefly reminded the objectives of the Action (as stated in MoU), summarized the current Action achievements and events (meetings, STSM, workshops, conferences, publications). Finally, she shortly discussed the strengths and the weaknesses of the action pointed out by the Action Rapporteaur, Henrique Guedes-Pinto obtained after the APC meeting held in Glasgow at the end of June.

The first session included three talks, all by the group leaders from the polish laboratories. The aim was to present some biotechnology oriented projects conducted in the Polish laboratories. The first talk by Tomasz Pniewski (Institute of Plant Genetics, Polish Academy of Sciences, Poznan) was summarizing the results of the immunization against hepatities B using the injection priming and oral-boost strategy using the tablets developed from powdered lyophilized plant material containing HBV antigens.

In the next talk, Wojciech Bal (Institute of Biochemistry and Biophysics PAS) explained the novel non-enzymatic method of protein purification invented and developed in his laboratory. The method is based on Ni-depended hydrolysis reaction and could be applied in biotechnology, for example for afficity tag removal in protein purification.

Tomasz Sarnowski (Insttitute of Biochemistry and Biophysics PAS) was talking about chromatin remodelling complexes (CRCs) in plants. The important finding of the group was that evolutionary conservation of CRCs enables using the plant mutants in some of the components of these complexes for screening for chemicals useful as drugs for the treatment of metabolome-related diseases in humans. Reversion of the root phenotype of the *atswi3c* Arabidopsis mutant by Metformin, a drug used for treatment of type II diabetes.

The second session of the first day started after the lunch and included 6 presentations: The first talk was delivered by Victor Klimyuk from Icon Genetics, Germany. The industrial company representative explained the strategy and the achievements of the company related to application of the plant virus-based transient expression system, MagnICON for industrial scale-up production of biopharmaceuticals, such as therapeutic antibodies or small batches of individualized pharmaceutical proteins or vaccines.

Fernando Ponz (Centre for Plant Biotechnology and Genomics, Madrid, Spain) was talking about the novel platform based on turnip mosaic virus and its nanobiotechnological exploitation for several purposes.

Diego Orzaez (Institute for Plant Molecular and Cell Biology, Spanish National Research Council, Valencia, Spain) explained the details of functioning of the GoldenBraid 2.0, a novel tool, developed in his laboratory, designed for construction of the complex multigene structures. This very useful tool could have wide applications.

Lauri Reuter (VTT – Technical research center of Finland) presented the results of his and his colleagues work on developing of the plant-based production system, project HydroBY2, which aimsat incorporating the hydrophobin fusion technology in the BY2 production platform.

Andreas Schaaf, the representative of a Greenovation Biotech GmbH, Germany talked about the development of *Physcomitrella*-based technology, which includes both, the transient production system and the stable cell line development and summarized the strategy aims of the company.

The last speaker of this session was Andreas Lössl (University of Natural Resources and Applied Life Sciences, Vienna, Austria) who talked about the collaborative work aiming towards efficient expression of vaccine candidates against Dengue fever in tobacco chloroplasts. The work is done in collaboration with Jihong Liu Clark from Bioforsk, Ås, Norway.

In the evening the dinner took place at the Zlota restaurant at Gromada Hotel and participants had a lot of discussions in small groups.

The sessions on Thursday, September 6th were also related to WG2 and WG3. They included the talks mainly by the academic researchers reporting various stages of plant-based production of either vaccine candidates or antibodies, achievements in identification of plant proteases responsible for hindering antibody expression and some modification of the recombinant proteins resulting in higher yield and/or stability in plant-based systems. The first talk was delivered by Lynn Dickey, the representative of Synthon Biopharmaceuticals BV, Netherland who explained the benefits of the LEX System, the *Lemna*-based platform and its used for the production of several hard-to-make proteins and monoclonal antibodies.

After the series of the lectures related to the topics of WG2 and WG3 the leaders of the working groups (Dirk Bosch, Arjen Schots and Stefan Schillberg) presented the current status and deliverables related to WG2 and WG3. This included development of the database of the plant-produced pharmaceuticals and valuable proteins and the draft of the prospective publications of the Consortium. The delegates broadly discussed and asked multiple questions related to both presented matters.

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After the lunch in the Zlota restaurant at the Gromada Hotel, the formal and individual discussions took place in the conference room during the poster viewing session. 14 posters were displayed in the conference room.

In the afternoon and the evening of Thursday, September 6th, the group participated in the guided tour of Warsaw and after that the dinner at the restaurant in the Palac Kazimierzowski (area of Warsaw University) took place.

The program on Friday, September 7th, consisted of the presentations and discussions related to WG1. This part was chaired by the WG1 leader, Paul Christou. In the part related to FG1 the speakers were Joachim Schiemann and Penelope Sparrow, who talked about current status of regulatory frameworks connected to

molecular farming. The subjects related to FG2 (public perception and scientific visibility of MF) were covered by Bart Van Droogenbroeck, who talked about interaction with greenhouse growers (presentation of the practical course for them related to Molecular farming) and the students. He also highlighted the several activities carried out in the educational level in Mozambique and Uganda. After the short coffee break the WG1-related subjects were continued and concentrated on FG3 (Developing Country aspects) and FG4 (Intellectual Property Licensing strategies) presented by Julian Ma and Harry Thangaraj, respectively. Julian Ma reported establishing links with a number of key developing country groups active in molecular farming (China, India, Brazil, South Africa and Argentina). Harry Thangaraj emphasized the need for the socially to have a responsible licensing and the patent pooling strategy. This might help making plant-made-pharmaceuticals commercial and accessible for developing countries.

One of the final points discussed on Friday was the possibility of formation of the Society, which could be open and which could be interesting for the participants of the meeting. Julian Ma proposed several possible names for such prospective society, described its possible role and asked for the opinion of the delegates. It could be a forum to continue the discussions on molecular farming after the COST Action ends. This point of the program was discussed by the audience very lively.

After the lunch the MC meeting took place on Friday, September 7th from 1 till 4 PM. The aspects listed in the Agenda of MC meeting were thoroughly discussed. The minutes of the MC meeting have been prepared separately.

COST Action FA0804 working group meeting, Cheltenham, UK, 26-28 November, 2012

Scientific Report

The working group meeting was held specifically to identify and plan the COST Action outputs to be completed by the end of the Action. The participants – Kirsi Marja-Oksman, Julian Ma, Paul Christou, Penny Sparrow, Joachim Schiemann, Bart van Droogenbroeck, Inge Broer and Heribert Warzecha convened at the start of the afternoon of the 26th, and worked until midday on the 28th. The meeting was held in The Farmhouse, Cheltenham. A number of small groups were organized with the following outcomes:

DISSEMINATION ACTIVITIES / OUTPUT

• Website update

Update of the current website www.molecularfarming.org was discussed and will be carried out in the coming weeks. Missing meeting reports, and MC minutes will be added. Content of the different pages was revised and will be reorganized, updated (especially the following pages Meetings, Links, News will be revised). New page ‘Downloads’ with subsections ‘Dissemination’ and ‘Publications’ will be included.

• Novel leaflets

A novel leaflet can be produced, also announcing the new “Society on Molecular Farming”. To produce the novel leaflet, collaboration with the company that produced the first leaflet will be used. The translated versions of the original leaflet will be put on the website in pdf format without any further editing or formatting, to save money for the new leaflet and the final publication.

• **Promo video**

The idea to create our own promotional video was abandoned and will be replaced by the effort to make a good inventory of interesting promo material already available at different institutes. Links to this material will be collected and put on the COST action website.

• **Informative slideshow for students/teachers**

An informative slideshow for students and teachers of about 20 slides, with easy to understand info on MF, with plenty of pictures and schemes will be put together, sent around and finalized. This slideshow will be downloadable form our COST Action webpage.

• **Open letter, spreading positive statement on advantages and potential of MF**

A discussion was held on which groups could be contacted to endorse such a statement. It might be hard to convince e.g patient groups suffering from orphan disease. An interesting group to contact might be HIV patient groups. Julian has contacts with them in the UK and from there on we can try to get in touch with other EU HIV patient groups. Anyhow all COST Action participants can sign this statement, but obviously this document is only really valuable if signed by at least one interesting group.

• **Final publication Compendium**

An agreement was reached that an important output from the Action would be a "COST Guide to Molecular Farming". The format of the final publication was discussed. The idea is to give an update on the status of Molecular Farming, tackling different topics. For each topic a short summary will be written, based on the recent insights and referring to relevant scientific papers and other outputs produced during the Action. A small booklet, A5 format, of about 50 pages maximum is envisaged.

1. Molecular Farming products
    a. what are likely products?
    b. routes to commercialization
2. Production platforms
    a. bioreactors
    b. plants (transient and stable)
    c. seeds, fruits, tubers
3. Risk assessment and regulation
    a. is GM regulation science based? Deficiencies in current regulation
    b. production (contained use vs open field)
    c. product (GMP)
4. Global relevance
    a. access
    b. regulatory harmonization
5. Engagement
6. Recommendations

PUBLICATIONS

1. Review on contained use

Authors: Penny Sparrow, Heribert Warzecha and others

Aim: In the context of the reviews in CPD there is no explicit review on contained use. This will close the gap and serve as completion of the picture

Content:
- Decision pathways on where to grow (field/contained)/ the production platforms (GH or bioreactors) etc will be largely led by choice of product
- What is „contained use“, containment? Contained vs. controlled environment (temperature, light, nutrients, pests?)
- What are the benefits of using contained production of PMPs?

Economical more viable option, since no regulatory burden like open field.

Bottom line is that we have a clearly defined regulatory structure for handling GMOs in containment (Cartagena protocol, most countries have guidelines on biosafety) but the GMP compliance for PMP needs to be better defined (?). There are GMP guidelines for stable but not for transient expression of PMP in plants

Other issues to be considered:
Special forms with advantages
Vertical farming/efficient use of area
Combined farming (fish)
Efficient use of energy

- Introduction
  - Current acrage of plants in open field vs. greenhouse (acrage under glas?)
- Advantages of production under controlled environment
  - Uniform growth, development; controlled supply of nutrients, possible alternative substrates. Light and temperature gives uniform growth (and content?)
- Advantages of Contained Production for PMP production
- Decision tree for open field versus CP
- Innovative ways of greenhouse farming

2. GM regulation present and future: what is wrong and how it can be improved
Authors: Joachim Schiemann and others

GMOs are separately regulated or undergoing separate regulation (risk assessment) in more than 170 countries. Experience over the past 30 years is arguing for reducing or eliminating the regulatory burden of GMOs and related technologies. Instead several countries/regions of the world this burden is becoming heavier is based to large extend on misinformation and regulatory barriers are blocking the technology and products from reaching its/their full potential. The purpose of this paper is to provide evidence in favour of science based regulation.

30 years of risk assessment did not provide any evidence for technology-based risk.
Several different types of potential risk have been assessed by hundreds of experts worldwide and the results as summarized by Government reports, EU commission, National Academies of sciences and other professional bodies provide clear evidence for this. (Cite: The report by the EU Commission on 20 years of biosafety research and the report by the German Government, report funded by the Swiss Government. Reports by the National Academies of Science of Hungary, Check republic the royal society in the UK, the NAS, USA and other upcoming report of the African Academies of Sciences).

Regulatory burden is increasing in the absence of any scientific evidence

1. Indian Supreme court decision (cite M Qaim)
2. African examples
3. Switzerland
4. Peru 10 years Moratorium of GMOS

Importance of Molecular Biology in Crop Improvement

1. Role of crop improvement in addressing Global Challenges (any technology capable of contributing to this should be considered; no golden bullet rather multiple/alternative/combinations must be considered-Aim is to address a challenge and solve the problem rather to promote or ban any technology)
2. Sustainable solutions for the grant challenges (event versus trait regulation; problematic to define what novel trait is;
3. The Fallacy of technology-based regulation (omics vs genotype, harvest, climate, environment, seed quality variability Vs GM; genome disruption; mutation breeding (transposon tagging, irradiation chemical mutagenesis-unnatural evolution; foreign genes more dangerous to species-specific genes-cisgenesis e.g pea and bean; soy and ground nut).

Finding a pragmatic way to live with current regulations

Brazil, Argentina, Cuba, S Africa (Moises Buraschik-Argentina to cover all countries)
Unbalanced global regulations (Kentucky bluegrass example)

A new approach to regulation

Canadian example including problems in defining new traits (our suggestions) Jochen to contact Phil McDonald, Canada)

Recommendations

Mid-term: Event versus trait

Longer term: Sustainable approach (including Ag system); focus on new trait (not technology);
labelling (cannot say that any kind of changes in plant genome is a novel trait), risk dependent product based e.g. biopolymer), explicit labelling based on novel trait and science based, post market monitoring (eliminate), co-existence (eliminate but define rules how to prevent admixture on product basis) and harmonisation of global regulations.

3. What does it take to commercialise a new biotechnology product?

Authors: Harry Thangaraj, Mathew Paul, Julian Ma

Plant-based technology platforms promise lower cost manufacturing processes for biopharmaceuticals, including biosimilars and in some cases biobetters. In the early days these hopes applied to potential production of large volumes of vaccines and monoclonal antibodies and such hopes differentiated the need for plant based platforms over conventional cell fermentation based technologies. Recent developments have proved in principle that such economies are feasible, particularly for upstream processing of biomass that obviates the need for expensive production facilities.

However, commercialisation of PMPs has not been as rapid as originally hoped. Many companies have entered the field but not achieved commercial success. But others have made steady progress, and the first

commercial PMP has now been licensed in the USA. What are the bottlenecks? And are the bottlenecks based on the technology per se, product selection or other commercial considerations?

With the licensing of the first commercial product earlier in 2012, and a number of products in clinical trial both in Europe and USA, why does large pharma continue to keep its distance? Is Molecular Pharming still regarded as too risky despite evidence to prove merits?

By examining a series of commercial case studies, this paper will compare decision making processes, from product selection, development strategies and commercialisation routes. We aim to offer insights into the major determinants for commercial success and failure as well as identify plant biotechnology bottlenecks and discuss the commercial future for molecular farming.

Potential case studies:

1) **ICON Genetics**: Transient expression tech. Huge promise, first example of serious commercial interest from a drug major (Bayer). Comprehensive IP portfolio. NHL vaccine taken into clinical trials phase 1. (patient specific vaccine – an example of personalised medicine – aim: complete remission). Rapid production of high yields – an advantage over CHO. Proof of concept of rapidly produced personalised medicine with wider application possible. Impressed by the technology, was taken over by Bayer Innovation, a subsidiary of Bayer. Big hopes but now abandoned by Bayer, resulting in a "reverse" takeover by NOMAD, created by the original founders of ICON. Why? Technology too complex for a big pharma company to understand? Does not fit within established commercial strategy (company mainly focused on small drug molecules rather than biotech)? New CEO – changed perceptions? Other?
2) **Bayer:** The Bayer perspective of the ICON collaboration.
3) **Biolex:** Duckweed lemna platform for production of biopharmaceuticals (Lex platform). Pioneering company having exclusive rights for MAbs expressed in plants – IP portfolio of Scripps (licensed or bought?). However pursued a route for: Product (alpha interferon, Locteron) passed several milestones in clinical trials (phase II?). Results suggest that this is a biobetter – superior to existing products. Biolex was heavily supported by VC funding but eventually collapsed. Why? Maybe the timing between milestones development and VC funding was not quite right? By that time there were a lot of competing products that had equal or better promise? Did Synthon chew off the best bits and left Biolex with little worth funding?
3) **Protalix:** Unique platform (carrot cell culture) that was standalone in IP terms. Lead product to treat Gauchers gained expedited FDA approval due to orphan drug status. Genzyme unable to fulfil market, hence additional advantage for Protalix. Protalix product registered with FDA but what is the marketing staus in the US and elsewhere? Also approval was expedited because of the choice of orphan drug route In the meantime, Shire Pharma has a competing product that has gained orphan drug status in the EU. Registration in the EU apparently blocked due to orphan drug status granted to Shire. Is this legal? Protalix product is a biosimilar, not a "generic". It would be interesting to examine the legal aspects here. For example does the EU law on orphan drugs contradict/conflict with laws on registration of biosimilars?
4) **Sembiosys:** Whole transgenic plant platform (safflower), insulin – generic biologic, meeting global needs/shortages, reached Phase II trials, novel purification strategy. But Sembiosys now in receivership. Lessons learnt?
5) **MAPP:** A different concept in commercial development. Social responsibility, side-stepping IP and licenses. Unusual selections in target products. Now established a commercial partnership with

ICON genetics and Kentucky Bioprocessing.

6) **EpiCyte:** One of the first PMP companies. The two original inventors of plant antibodies.

4. Realising the value of plant molecular farming to benefit the poor in developing countries and emerging economies; Technology transfer and intellectual property management

Authors: Julian K-C. Ma (UK), Paul Christou (Spain), Sathishkumar Ramalingham (India), Edward Rybicki (South Africa), Andres Wigdorowitz (Argentina), Elibio Rech (Brazil), Merardo Pujol (Cuba), Rachel Chikwamba (South Africa), Dai-Chang Yang (China) and Harry Thangaraj (UK).

Manuscript outline:

• The potential importance of PMPs for DCs
• Current status of PMPs in DCs
• Lessons from developed nations – case studies
• A case study from South Africa
• IP management to maximise access – Socially responsible licensing
– Patent pooling
• DC priorities for PMP development

In any discussion of the merits of Molecular Farming (the use of plant biotechnology to manufacture pharmaceuticals), the potential benefits for the poor in developing countries is always a prominent feature. There are many good reasons. Right from the initial introduction of this technology, it was recognized that a major impact could be achieved on global access to health. Despite much change in thinking with regard to the practicalities of the best biotechnological approach, this still holds true.

A major reason for this optimism relates to cost. It was widely enthused that plant production would enable a significant reduction in manufacturing costs, and whilst this is probably so, the savings are unlikely to be as significant as those associated with reduced infrastructure investment costs at early stages of product development.

Production scalability is another important benefit. Most of the pharmaceutical targets that are relevant for developing countries are those that are needed in very large quantities, such as vaccines, microbicides and other drugs such as insulin. The demand for such products far outstretch present production capacity, which is one of the main reasons for lack of availability for medicines in underdeveloped countries.

An important attraction of Molecular Farming is that a major stage of the manufacturing process – plant cultivation – does not require a high level of technological input, and basic agricultural skills are broadly available across the globe. Thus this should be a relatively straightforward technology to transfer. If that is achieved, there will be the additional benefit of stimulating new local industry.

For these reasons, it is quite possible that the major beneficiaries of successful Molecular Farming projects will be those in underdeveloped countries. This has not, of course, escaped the attention of underdeveloped countries themselves, and there are many Molecular Farming efforts in countries such as South Africa, Cuba, as well as in South America and South East Asia. Attitudes towards Molecular Farming are often very different in underdeveloped countries, compared to those in developed nations, particularly in Europe. The risk/benefit analysis is very different, given that many underdeveloped countries have a disproportionately

high burden of infectious disease. In many cases, an approach based on population vaccination is the only affordable and effective intervention and would have a really important impact on public health. At the same time, many countries such as South Africa, Brazil and Argentina, have developed extensive experience and expertise in the risk assessment and risk management of genetically modified crops. They are probably in a much stronger position to determine GM-associated risks compared to those in developed countries where GM cultivation is much more limited.

CONTINUATION OF THE ACTIVITIES AFTER THE END OF THE COST ACTION FA0804?

As the COST Action ends 26th of May 2013, future plans were discussed as well. The idea launched earlier was to start a new 'Society of Molecular Farming'.

Society for Molecular Farming

A club or society is defined by the Charities Commission as a means by which people share a common interest and create a formal structure through which they can pursue it. The basic structure of clubs and charities is the same. There will be a president, secretary and treasurer.

Nominations:

President – Julian Ma

Secretary – Joachim Schiemann

Treasurer – Penelope Sparrow

Keep the current COST logo

Provide a constitution that includes the following:

1. the name of the society
2. the aims and objectives of the society
3. regulations relating to membership eligibility
4. provision for the election of a Committee or Officers by a vote of the membership the responsibility of such Officers
5. provision for meetings of all society members
6. provision for the presentation of any accounts

Financial arrangements

The treasurer is responsible for the organisation's finances, including finding a bank account. The club or society should appoint an auditor or independent examiner to check the accounts. The society needs a bank account to deal with the flow of finances. Once it starts to grow, donations will come in and payments may need to be made. The club should choose a bank account by passing a resolution at a committee meeting. It is useful for the treasurer to set up the financial situation so that more than one person can sign cheques. Money should be banked immediately, receipts and books maintained in an orderly fashion. The person who opens all the mail and records monies received should be different from the treasurer.

Community Directplus – Co-operative Bank

Propose annual membership £50

100 members would support secretarial support for the Society.

Next steps:

- Identify objectives of the society
- Identify benefits of membership
- Draft constitution

- Formal proposal at Rostock meeting
- Form Society and determine minimum no. of target members
- Identify steering committee members (including people not at Rostock)
- Invite membership at Valencia membership, Heribert's Porto meeting and at PBVA.

COST FA0804 Workshop meeting Rostock, 6-8 February, 2013

Venue: Radisson Blue hotel

Program of the meeting

Wednesday, February 6th

14.00	Bus ride from Hotel to Leibniz Institute for Farm Animal Biology in Dummerstorf
14.30 – 17.30	Visit Leibniz Institute
17.30 – 18.15	Bus ride to Warnemünde
18.15 – 19.00	Little walk through Warnemünde to the restaurant
19.00 – 22.00	Dinner at Kurhaus Restaurant & Cafe Paulo Scutarro
22.00 – 22.30 h	Bus ride back to hotel

Thursday February 7th

08.30 – 09.00	Registration
09.00 – 09.15	Welcome Inge Broer (Vice Dean of the Faculty of Agricultural and Environmental Sciences, University of Rostock)
09.15 – 09.30	Introduction Kirsi-Marja Oksman-Caldentey (VTT Technical Research Centre of Finland)
09.30 – 10.00	Günther Keil (Friedrich-Loeffler-Institute, Germany): Molecular farming for livestock farming: Plant produced vaccines in sight?
10.00 – 10.30	Manfred Schwerin (Leibniz Institute for Farm Animal Biology, Germany): Study of metabolic dietary effects by expression profiling in pigs
10.30 – 11.00	Coffee break and posters viewing
11.00 – 11.30	Julian Ma (St George's University of London, Research Center for Infection & Immunity, Clinical Science, UK): Hydroponic Cultivation of *Nicotiana tabacum* for Production of Recombinant Pharmaceutical Proteins by Rhizosecretion
11.30 – 12.00	Einar Mäntylä (ORF Genetics, Iceland): From seeds to stem cells and skin care
12.00 – 12.30	Yuri Gleba (Nomad Bioscience GmbH, Germany): Plant biotechnologies based on transient expression
12.30 – 12.45	Ann Depicker (VIB Department of Plant Systems Biology, UGent, Belgium): Evaluation of the Arabidopsis seed platform for the Production of recombinant proteins
12.45 – 13.00	Heribert Warzecha (Technische Universität Darmstadt, Germany): Evaluation of novel plant-made measures against Malaria
13.00 – 14.00	Lunch
14.00 – 14.15	Grazina Juodeikiene (Kaunas University of Technology, Lithuania): Antimicrobial activities of BLIS producing lactic acid bacteria against undesirable microorganisms in food industry
14.15 – 14.30	Valeska Hauptmann, Nicola Weichert (Leibniz-Institut für Pflanzengenetik und Kulturpflanzenforschung IPK, Germany): How to characterize high repetitive plant-produced spider silk proteins?

14.30 – 14.45	Vikram Virdi (VIB Department of Plant Systems Biology, UGent, Belgium): Simplified IgA antibodies produced in seeds protects from enterotoxigenic *Escherichia coli* infection in weaned piglets
14.45 – 15.00	Heike Mikschofsky (Biovativ GmbH, Germany): Open field cultivation of pharma plants focusing on transgene variability
15.00 – 15.15	Daniela Salgado (Fraunhofer Institute IME, Germany): Purification and characterization of the Plant-produced human Surfactant Protein D (hSP-D)
15.15 – 15.30	Paloma Juarez (Instituto de Biología Molecular y Celular de Plantas (CSIC-UPV), Spain): sIgA expression and glycosylation analysis
15.30 – 16.00	Coffee Break and posters viewing
16.00 – 18.30	Workshop Working Group 1 (Program organized by WG Leader)
19.00 – 21.30	Dinner at Osteria Restaurant (inside Radisson blue Hotel)

Friday February 8th

09.00 – 10.50	Working Group 2 (Program organized by WG Leader)
10.50 – 11.10	Coffee Break
11.10 – 13.00	Working Group 3 (Program organized by WG Leader)
13.00 – 14.30	Lunch
14.30	Departure all participants

Scientific report (Rostock, 6-8 February, 2013)

The workshop was organized by Prof. Dr. Inge Broer, University of Rostock. It was planned as a working platform for the working groups as well as a possibility to organize the completion of the deliverables. In addition the establishment of a Society for Plant Molecular Farming, which should succeed the COST Action in order to sustain the close contact between the COST members, was discussed. The number of participants was 33 in this meeting.

Since Mecklenburg Vorpommern hosts two important governmental scientific institutes on animal health, the Leibniz Institute for Farm Animal Biology in Dummerstorf (FBN) and the Friedrich Löffler Institut (FLI) (Federal Research Center for Animal Health), it was another goal of the meeting to introduce these institutes as possible cooperators to the COST members. Hence we visited the Farm Animal Biology in Dummerstorf, which is located close to Rostock, on Wednesday, February 6th. The director of the FBN, Prof. Dr. Schwerin, gave a short introduction into the work at the institute, subsequently the COST members visited the research unit Genetics and Biometry, the unit Muscle Biology and Growth, the unit Nutritional Physiology 'Oskar Kellner' and the pig breeding station. Both Institutes were additionally presented on Thursday morning either by the FBN director Prof. Schwerin or by Dr. Keil, representing the FLI director Prof. Dr. Dr. h.c. Mettenleiter.

The meeting fulfilled all the prospects, the talks were quite informative and especially the talks given by the STSM students exceeded expectation. The COST members decided to establish a Society for Plant Molecular Farming at the final meeting in Valencia. The working group sessions made clear that impressive work has been done. The last papers should be finalized in March.

ANNEX 2

Short term scientific missions until 22.3.2013

The following nineteen STSMs have taken place in the frame of this COST Action:

1. COST STSM Reference Number: COST-STSM-FA0804-04581

Period: 06/04/2009 to 05/05/2009
STSM Applicant: Mrs Gergana Zahmanova, University of Plovdiv, Department Plant Physiology and Molecular Biology, Bulgaria
STSM Topic: Expression of HBcAg-AIV chimaeras in plants using CPMV-HT technology
Host: George Lomonossoff, John Innes Centre, Norwich, UK
Sum: 2000 EURO

2. COST STSM Reference Number: COST-STSM-FA0804-4409

Period: 15/04/2009 to 13/05/2009
STSM Applicant: Mr Andreas Loos, Department for Applied Genetics and Cell Biology, Boku, Vienna, Austria
STSM Topic: Subcellular localization and N-glycosylation of seed-produced antibodies
Host: Ann Depicker, VIB/Universiy of Ghent, Ghent, Belgium
Sum: 400 EURO

3. COST STSM Reference Number: COST-STSM-FA0804-4376

Period: 20/04/2009 to 20/05/2009
STSM Applicant: Dr Jitka Folwarczna, Institute of Experimental Botany v.v.i., Academy of Sciences of the Czech Republic, Prague, Czech Republic
STSM Topic: Aim of the work is to learn various methods connected to plant molecular farming.
Host: Agnieszka Sirko, Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland
Sum: 2000 EURO

4. COST STSM Reference Number: COST-STSM-FA0804-4569

Period: 01/06/2009 to 31/08/2009
STSM Applicant: Dr Mathilde Francin-Allami, INRA, France
STSM Topic: Study of wheat prolamins traffic in plant cell model
Host: Chris Hawes, Oxford Brookes University, UK
Sum: 3500 EURO

5. COST STSM Reference Number: COST-STSM-FA0804-5451

Period: 11/01/2010 to 09/04/2010
STSM Applicant: Ms Mariya Petrova, Institute of Genetics "Acad. D. Kostoff", Bulgarian Academy of Sciences, Sofia, Bulgaria
STSM Topic: Production of recombinant proteins in plants and plant cell cultures
Host: Anneli Ritala-Nurmi, VTT Technical Research Centre of Finland, Espoo, Finland
Sum: 2500 EURO

6. COST STSM Reference Number: COST-STSM-FA0804-5503

Period: 11/01/2010 to 11/04/2010
STSM Applicant: Ms Vilma Narbutaite, Kaunas University of Technology, Kaunas, Lithuania
STSM Topic: Transient expression of heterologous proteins by LAB into plants using versatile expression vectors
Host: George Lomonossoff, John Innes Centre (JIC), Norwich, UK
Sum: 2500 EURO

7. COST STSM Reference Number: COST-STSM-FA0804-5906

Period: 15/03/2010 to 25/03/2010
STSM Applicant: Mr César Feliciano Cruz Fernández, Centro de Biotecnología y Genómica de plantas (CBGP), UPM-INIA, Madrid, Spain
STSM Topic: Chemical modification of viral capsids for high yield antibody production
Host: David Evans, John Innes Centre (JIC), Norwich, UK
Sum: 1200 EURO

8. COST STSM Reference Number: COST-STSM-FA0804-5542

Period: 15/03/2010 to 30/04/2010
STSM Applicant: Ms Valeska Hauptmann, Leibniz Institute of Plant Genetics and Crop Plant Research

(IPK), Gatersleben, Germany
STSM Topic: Spider silk variants from plants
Host: Jacques Guéguen, INRA, Nantes, France
Sum: 1666 EURO

9. COST STSM Reference Number: COST-STSM-FA0804-5907

Period: 12/04/2010 to 03/05/2010
STSM Applicant: Ms Verena Hehle, St. George's Hospital Medical School, London, UK
STSM Topic: Mass Spectrometric analysis of recombinant protein proteolytic degradation in transgenic plants
Host: Marc Boutry, Université Catholique de Louvain, Louvain-la-Neuve, Belgium
Sum: 1240 EURO

10. COST STSM Reference Number: COST-STSM-FA0804-6771

Period: 15/07/2010 to 8/10/2010
STSM Applicant: Dr. Hana Hoffmeisterova, Institute of Experimental Botany v.v.i., Academy of Sciences of the Czech Republic
STSM Topic: Molecular Characterization of Antibodies Expressed in Plants
Host: Ann Depicker, VIB, Ghent University, Ghent, Belgium
Sum: 2500 EURO

11. COST STSM Reference Number: COST-STSM-FA0804-7040

Period: 18/10/2010 to 21/01/2011
STSM Applicant: Dr Elisa Gecchele, University of Verona, Verona, Italy
STSM Topic: Purification of GAD65mut from transgenic tobacco leaf tissue
Host: Stefan Schillberg, Fraunhofer Institute, Aachen, Germany
Sum: 2100 EURO

12. COST STSM Reference Number: COST-STSM-FA0804-7607

Period: 10/02/2011 to 10/03/2011 and 9/11/2011 to 16/11/2011
STSM Applicant: Mr. Rodrigo Corredor, University of Bern, Switzerland
STSM Topic: Addressing global access and affordability of molecular farming products through responsible licensing of intellectual property.

Host: Harry Thangaraj, St George's University of London, UK
Sum: 2000 EURO

13. COST STSM Reference Number: COST-STSM-FA0804-8805

Period: 29/08/2011 to 23/09/2011
STSM Applicant: Mr Vikram Virdi, VIB, Ghent University, Ghent, Belgium
STSM Topic: Evaluation of a phaseolin promoter driven expression cassette in pea seeds
Host: Inge Broer, University of Rostock, Germany
Sum: 2060 EURO

14. COST STSM Reference Number COST-STSM- FA0804-9951

Period: 01/03/2012 to 31/3/2012
STSM Applicant : Ms. Linda Rafeld, University of Rostock, Germany
STSM Topic: Characterisation of pea seed derived CTB::VP60
Host: Eva Stöger, University of Natural Resources and Life Sciences, Vienna, Austria
Sum: 2500 EURO

15. COST STSM Reference Number: COST-STSM-FA0804-9899

Period: 16/04/2012 to 15/06/2012
STSM Applicant: Ms Daniela Alejandra Salgado Bustos, Fraunhofer IME, Aachen, Germany
STSM Topic: Purification and characterization of the plant-produced human Surfactant Protein D (hSP-D)
Host: Grith Lykke Sørensen, Institute for Medical Biology, University of Southern Denmark, Odense, Denmark
Sum: 1500 EURO

16. COST STSM Reference Number COST-STSM- FA0804-10370

Period: 11/05/2012 to 04/06/2012
STSM Applicant: Mr Henning Pennekamp, Technische Universitaet Darmstadt, Germany
STSM Topic: Generation of plant-derived nanobodies inhibiting plasmodium development
Host: Stefan Magez, Vrije Universiteit Brussel, Belgium
Sum: 2000 EURO

17. COST STSM Reference Number: COST-STSM-FA0804-10752

Period: 01/10/2012 to 14/10/2012
STSM Applicant: Ms Paloma Juarez Ortega, IBMCP (UPV-CSIC), Valencia, Spain
STSM Topic: Glycosylation profiling of IgA
Host: Friedrich Altmann, Department of Chemistry at BOKU University, Vienna, Austria
Sum: 1100 EURO

18. COST STSM Reference Number: COST-STSM-FA0804-11153

Period: 1/10/2012 to 22/12/2012
STSM Applicant: Ms Rita Santos, Universidade Nova de Lisboa, Oeiras, Portugal
STSM Topic: Characterization of a putative substrate for the tobacco matrix-metalloproteinase NtMMP1
Host: Andreas Schiermeyer, Fraunhofer IME, Aachen, Germany
Sum: 2500 EURO

19. COST STSM Reference Number: COST-STSM-FA0804-11044

Period: 01/10/2012 to 16/11/2012
STSM Applicant: Mr Lauri Reuter, VTT Technical Research Centre of Finland, Espoo, Finland
STSM Topic: Production of recombinant proteases in tobacco BY-2 cell line and a crash course on flow cytometry
Host: Stefan Schillberg, Faunhofer IME, Aachen, Germany
Sum: 2500 EURO

ANNEX 3

Lists of joined publications until 31.3.2013

With COST acknowledgement:

2013

Berman J, Zhu C, Pérez-Massot E, Arjó G, Zorrilla-López U, Masip G, Banakar R, Sanahuja G, Farré G, Miralpeix B, Bai C, Vamvaka E, Sabalza M, Twyman RM, Bassié L, Capell T, Christou P (2013): Can the world afford to ignore biotechnology solutions that address food insecurity? Plant Mol. Biol. (in press). DOI: 10.1007/s11103-013-0027-2.

Bosch D, Castilho A, Loos A, Schots A, Steinkellner H (2013): N-Glycosylation of plant-produced recombinant proteins. Curr. Pharm. Design 19: 000-000. (in press).

Buiatti M, Christou P, Pastore G (2013): The application of GMOs in agriculture and in food production for a better nutrition: two different scientific points of view. Genes Nutr. (in press). DOI: 10.1007/s12263-012-0316-4.

Christou P (2013): Plant genetic engineering and agricultural biotechnology 1983-2013. Trends Biotechnol. 31: 125-127.

De Marchis F, Bellucci M, Pompa A (2013): Traffic of human α-mannosidase in plant cells suggests the presence of a new endoplasmic reticulum to vacuole pathway without involving the Golgi complex. Plant Physiol. (in press).

De Wilde K, De Buck S, Vanneste K, Depicker A (2013): Recombinant antibody production in Arabidopsis seeds triggers an unfolded protein response. Plant Physiol. 161: 1021-1033.

Fischer R, Schillberg S, Buyel JF, Twyman RM (2013): Commercial aspects of pharmaceutical production in plants. Curr Pharm. Design (in press).

Hauptmann V, Weichert N, Menzel M, Knoch D, Paege N, Scheller J, Spohn U, Conrad U, Gils M (2013): Native-sized spider silk proteins synthesized in planta via intein-based multimerization. Transgenic Res. (in press). dx.doi.org/10.1007/s11248-012-9655-6.

Lössl AG, Clarke JL (2013): Molecular pharming: manufacturing medicines in plants. Immunotherapy 5(1): 9-12.

Miralpeix B, Rischer H, Häkkinen ST, Ritala A, Seppänen-Laakso T, Oksman-Caldentey K-M, Capell T, Christou P (2013): Metabolic engineering of plant secondary products: which way forward? Curr. Pharm. Design (in press).

Phan HT, Pohl J, Floss DM, Rabenstein F, Veits J, Le BT, Chu HH, Hause G, Mettenleiter T, Conrad U (2013): ELPylated haemagglutinins produced in tobacco plants induce potentially neutralizing antibodies against H5N1 viruses in mice. Plant Biotechnol. J. (in press).

Phan HT, Floss DM, Conrad U (2013): Veterinary vaccines from transgenic plants: highlights of two decades of research and a promising example. Curr. Pharm. Design (in press).

Sabalza M, Vamvaka E, Christou P, Capell T (2013): Seeds as a production system for molecular farming applications: status and prospects. Curr. Pharm. Design (in press).

Schillberg S, Raven N, Fischer R, Twyman RM, Schiermeyer A (2013): Molecular farming of pharmaceutical proteins using plant suspension cell and tissue cultures. Curr. Pharm. Design (in press).

Sparrow P, Broer I, Hood E, Eversole K, Hartung F, Schiemann J (2013): Risk assessment and regulation of molecular farming – A comparison between Europa and US. Curr. Pharm. Design (in press).

Rischer H, Häkkinen ST, Ritala A, Seppänen-Laakso T, Miralpeix B, Capell T, Christou P, Oksman-Caldentey K-M (2013): Plant cells as pharmaceutical factories. Curr. Pharm. Design (in press).

Twyman RM, Schillberg S, Fischer R (2013): Optimizing the yield of recombinant pharmaceutical proteins in plants. Curr. Pharm. Design (in press).

Waheed MT, Lössl AG, Martinussen I, Daniell H, Clarke JL (2013): Managing animal health by cost-effective and safe production of animal vaccines in plants through plastid genetic engineering: present status and future perspectives. Plant Mol. Biol. Special Issue (in press).

Zhu C, Sanahuja G, Yuan D, Farre G, Arjo G, Berman J, Zorrilla-Lopez U, Banakar R, Bai C, Perez-Massot E, Bassie L, Capell T, Christou P (2013): Biofortification of plants with altered antioxidant content and composition: genetic engineering strategies Plant Biotech. J. 11: 129-141.

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Bortesi L, Rademacher T, Schiermeyer S, Schuster F, Pezzotti M, Schillberg S (2012): Development of an optimized tetracycline-inducible expression system to increase the accumulation of interleukin-10 in tobacco BY-2 suspension cells. BMC Biotechnol. 12: 40.

De Marchis F, Pompa A, Bellucci M (2012): Plastid proteostasis and heterologous protein accumulation in transplastomic plants. Plant Physiol. 160: 571-581.

Demeyer R, De Loose M, Van Bockstaele E, Van Droogenbroeck B (2012): Exploiting the natural variation of *Arabidopsis thaliana* for the seed-specific production of proteins. Euphytica 183: 83–93.

Farré G, Zorrilla U, Berman J, Zhu C, Christou P, Capell T (2012): Increasing the vitamin E content of food by in-plant production. CAB Rev. 7: 1-10.

Farré G, Zorrilla-Lopez U, Capell T, Berman J, Zhu C, Christou P (2012): Multi-gene engineering for reconstruction and extension of complex plant biosynthetic pathways and sociopolitical constraints limiting the transition from the laboratory to the market place. *In:* Hot topics in cell biology. Becerra J, Santos-Ruiz L (Eds). Chartridge Books, Oxford, pp. 75-85.

Gomez-Galera S, Twyman RM, Sparrow PAC, Van Droogenbroeck B, Custers R, Capell T, Christou P (2012): Field trials and tribulations-making sense of the regulations for experimental field trials of transgenic crops in Europe. Plant Biotech. J. 10: 511–523.

Sabalza M, Madeira L, van Dolleweerd C, Ma JK-C, Capell T, Christou P (2012): Functional characterisation of the recombinant HIV-neutralizing monoclonal antibody 2F5 produced in maize seeds. Plant Mol. Biol. 80: 477–488.

Ullisch D, Müller CA, Maibaum S, Kirchhoff J, Schiermeyer A, Schillberg S, Roberts JL, Treffenfeldt W, Büchs J (2012): Comprehensive characterization of two different *Nicotiana tabacum* cell lines leads to doubled GFP and HA protein production by media optimization. J. Biosci. Bioeng. 113: 242-248.

2011

Chao B, Twyman RM, Farré G, Sanahuja G, Christou P, Capell T, Zhu C (2011): A golden era-pro-vitamin A enhancement in diverse crops. In Vitro Cell. Dev. Biol. Plant 47: 205–221.

Conrad U, Plagmann I, Malchow S, Sack M, Floss DM, Kruglov AA, Nedospasov SA, Rose-John S, Scheller J (2011): ELPylated anti-human TNF therapeutic single-domain antibodies for prevention of lethal septic shock. Plant Biotechnol. J. 9: 22–31.

De Marchis F, Balducci C, Pompa A, Stensland HM, Guaragno M, Pagiotti R, Menghini AR, Persichetti E, Beccari T, Bellucci M (2011): Human α-mannosidase produced in transgenic tobacco plants is processed in human α-mannosidosis cell-lines. Plant Biotech. J. 9: 1061-1073.

De Marchis F, Pompa A, Mannucci R, Morosinotto T, Bellucci M (2011): A plant secretory signal peptide targets plastome-encoded recombinant proteins to the thylakoid membrane. Plant Mol. Biol. 76: 427–441.

Farre G, Bai C, Twyman RM, Capell T, Christou P, Zhu C (2011): Nutritious crops producing multiple carotenoids – a metabolic balancing act. Trends Plant Sci. 16: 532-540.

Farre G, Twyman RM, Zhu C, Capell T, Christou P (2011): Nutritionally enhanced crops and food security: Scientific achievements versus political expediency. Curr. Opin. Biotechnol. 22: 245-251.

Henquet M, Eigenhuijsen J, Hesselink T, Spiegel H, Schreuder M, van Duijn E, Cordewener J, Depicker A, van der Krol A, Bosch D (2011): Characterization of the single-chain Fv-Fc antibody MBP10 produced in *Arabidopsis* alg3 mutant seeds. Transgenic Res. 20: 1033-1042.

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