COST

Domain Committee Food and Agriculture

COST Action FA0804

Start Date 27/11/2008

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

MONITORING PROGRESS REPORT

Reporting Period: *from 1 March 2010 to 1 May 2011*

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, i.e. it is updated annually 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*.

Based on the monitoring results, the COST Office will decide on the following year's budget allocation.

Executive summary (max.250 words):

The objective for the Action is to co-ordinate European efforts in plant Molecular Farming (MF) to ensure rapid generation, development and commercialization of products that will sustain the industry. The scientific program is 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 will be a sustainable European plant MF community with clear frameworks for regulatory, bio-safety and IP issues. Eventually a European Committee 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 will take 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 are performed in close cooperation. To facilitate this Molecular farming Protein Expression database has been formulated and will be made fully operational during the coming year.

I. Management Report *prepared by the COST Office/Grant Holder*

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:	26/11/2012	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 is 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 will create new opportunities for European agriculture, horticulture and related technology sectors as the plants dedicated to Molecular Farming constitute new high-value crops. The Action brings the key players together and will increase European momentum, capacity and infrastructure. It will also expand activities to countries that have not thus far been able to participate, including developing countries. The concrete outcome will be 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
China	China Jiliang University

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
DISSEMINATION	FA	2010-08-26	2010-10-06	(n.a.)	(n.a.)	Leaflets	1416	**1416**
MEETING	FA	2010-06-17	2010-06-17	Brussels	Management Committee Meeting	MC meeting Brussels	9792.60	
MEETING	FA	2010-08-05	2010-08-05	London	Other COST relevant meeting	WP leaders	1496.17	
MEETING	FA	2010-10-06	2010-10-08	Vico Equense (Naples)	Management Committee Meeting, Working Group Meeting	Annual meeting with all WG, MC meeting	30396.88	
MEETING	FA	2011-03-23	2011-03-25	Plovdiv	Working Group Meeting	Meeting WG 1	18418.63	**60104.28**
OERSA	FA	2010-07-15	2010-06-17	(n.a.)	(n.a.)	Payment of the Action website	60	**60**
STSM		15/03/2010	25/03/2010	Norwich	STSM from Spain to United Kingdom	Chemical modification of viral capsids for high yield antibody production	1200	
STSM	FA	2010-01-11	2010-04-09	Espoo	STSM from Bulgaria to Finland	Production of recombinant proteins in plants and plant cell cultures	2500	
STSM	FA	2010-01-11	2010-04-11	Norwich	STSM from Lithuania to United Kingdom	Transient expression of heterologous proteins by LAB into plants using versatile expression vectors	2500	
STSM	FA	2010-03-15	2010-04-30	44316 Nantes Cedex 03	STSM from Germany to France	Spider silk variants from plants	1666	
STSM	FA	2010-04-12	2010-05-03	Louvain-la-Neuve	STSM from United Kingdom to Belgium	Mass Spectrometric analysis of recombinant protein proteolytic degradation in transgenic plants	1240	
STSM	FA	2010-07-15	2010-10-08	Gent	STSM from Czech Republic to Belgium	Molecular characterization of antibodies expressed in plants	2500	
STSM	FA	2010-11-01	2011-01-21	Aachen	STSM from Italy to Germany	Purification of GAD65mut from transgenic tobacco leaf tissue	2100	

Type	Domain	Start	End	City	Type	Title	Amount	Total EUR
STSM	FA	2011-02-10	2011-03-10	London	STSM from Switzerland to United Kingdom	Molecular farming: plants as a production platform for high value proteins	2000	**15706**

II. Scientific report during the period 27.11.2008 – 31.3.2011

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 following three 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 whole Action is to co-ordinate European efforts in Molecular Farming and to ensure the rapid development and commercialization of 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 will be a sustainable European plant Molecular Farming (MF) community with clear frameworks for regulatory, bio-safety and IP issues. Eventually the Action will allow the establishment of a **European Committee of Molecular Farming**. This Committee 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, also after this COST Action, in the fast developing field of complex recombinant proteins, including biopharmaceuticals.

One of the first activities of this Action was the establishment of a preliminary Road Map as a tool to facilitate productive joint research among the ± 35 groups from 21 European countries. An inventory of activities and fields of expertise of the participants to this Action show promising future trends in MF. A rich and diversified toolbox is available and at least half of the groups have a clear orientation toward a family of products and/or production systems.

The scientific program of the Action is pursued through three main topics. These show significant

overlap and interaction, and the overall success of the Action relies on strong interactions between the different topics.

Strategic development of Molecular Farming (WG1)

This WG aims to provide a broad and global overview of the state of MF in the world today. Its primary purpose is 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 will involve reciprocal interactions with the other WGs in the areas of production systems and processing strategies (WG2) and target molecules (WG3).

At the kick-off meeting in Athens (March, 2009) it was proposed that the implementation of WG1 activities could be through the formation of specialized focus groups (FGs), comprising academic and industrial members. This proposal was accepted and a list of about 10 different possible Focus Group (FG) themes was proposed to the participants for selection. During a WG1 follow-up meeting in Lleida (May, 2009) the following four FG were agreed upon:

- Regulatory framework
- Public perception/stakeholder interactions
- Developing country aspects
- IP licensing strategy

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 next two general Action meetings that was organized in Prague (October, 2009) and in Vico (October, 2010). From here on, Action members collaborated to achieve the defined short term objectives and measurable outputs. Finally a special workshop on WG1 was organized in Plovdiv (March, 2011).

FG1 (Regulatory Framework), current EU situation was compared to the situation in the US (contribution Elizabeth Hood, invited speaker, Prague meeting, 2009). Action members being part of EFSA GMO panel further brought Molecular Farming under the attention of the EU regulators. In addition, specific Action members participated at the 4th Meeting of the European Advisory Committees on Bio-safety (29-30 October 2009, Brussels), again with the aim to discuss specific regulatory MF issues.

FG2 (Public perception/stakeholder interactions)

The main success undoubtedly has been the increased visibility of our Action through refreshing the action website 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 now translated into at least 7 languages (German, Greek, Spanish, Italian, Dutch, French and Finnish) and these versions will be downloadable soon as Word file from our Action website as well.

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.

Based on the outcome of the Plovdiv workshop (March, 2011) cases were selected for targeted interaction with different stakeholders to overcome specific difficulties. This is planned in next year.

- Regulatory hurdles: interaction via specific members with EFSA, MEPs and other decision makers (activities of Joachim Schiemann, Inge Broer)
- IP training of Action members by experts – Workshop session Plovdiv (Harry Thangaraj)
- Continued funding: London brainstorm (August 2010) organised to define potential FP7 topics – interaction process with EPSO – description of outcome
- Better interaction with the companies: Synthon left and Protalix joined the Action.
- Specific questions for the EUROBAROMETER survey will be prepared.
- Contacts with possible beneficiary stakeholders (patient organizations) are being initiated.

FG3 (developing country aspects), ongoing activities focus 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 two non-COST country partners, China and India have been joining this Action.

FG4 (IP licensing strategy), an inventory of IP on MF within EU is one of the objective worked upon.

All these activities, set up during the first year and elaborated during the second year, will contribute to produce the outputs of WG1 during the rest of the Action. These will take 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)

WG2 aims 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 is 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 will carry out an inventory and literature study to summarize the state-of-the-art in MF and identify major bottlenecks hindering commercial exploitation. This will be supported by a database summarizing MF activities. This will be in a publishable form and will constitute 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 a 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. Therefore, the implementation of industrial partners including representatives from non-plant production platforms will be important 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 should carefully consider 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 workshop in Wageningen (January, 2010).

At the Prague meeting (2009) the structure of a database summarizing the various efforts in producing recombinant proteins in plants has been discussed. The database will be 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 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 (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 answered 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 include 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 comprises only a small sample its outcome reflects mainly the conclusion of the discussions during several COST Action meetings.

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 aims to deal the following issues of plant produced systems when choosing the best production system: i) Scalability, ii) Costs, iii) Adaptability, 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 is a starting point for the inventory to be made of molecules that potentially can be produced in a MF platform. It will also provide information of what the status quo is of various molecules that have been produced in plants using a MF platform. Taken together this information is 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. As a next step the database should be filled. Thereto, an inventory was made of relevant literature. Almost 600 papers were found describing proteins that are medically relevant. The proteins described in these papers will be added to the database in the third year of the project.

The Action is 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:

- CoMoPharm (coordinator: Stefan Schillberg)
- SmartCell (coodinator: Kirsi-Marja Oksman)
- PLAPROVA (coordinator: George Lomonossoff)

There are many ongoing 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 twelve accomplished STSMs is given in Annex 2. Moreover, there has been some interaction between plant scientists and communication scientists. Planning of Trans-Action Dialogue workshop to be held in Munich, Germany (3-4 November 2011) has been started and members of three COST Actions (FA0804, FA0806 and FP0905) will participate.

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 will further discuss with EPSO about the possibilities to influence the future topics of FP7 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. Moreover, currently two new non-COST country members have been approved by CSO from China and India, respectively, and one is pending (Australia). Their involvement so far has been rather minimal but in our upcoming annual meeting in Ghent, Belgium the partner from India will attend.

The total number of individual participants is approximately 110 from which 35% are female and 10% 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". Currently there are pending three more applications to obtain the ESR grant to

attend a scientific meeting.

Dissemination of results

The promotion through the publications and other outreach activities has become livelier during this second period of the Action. The Action has organized altogether five scientific 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 specialists. The scientific programs and reports can be found in Annex 1. Moreover, 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).

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 and it was refreshed during 2010 and has now better visibility to broader audience. It will be updated regularly with new content, news and links. It is also linked to the COST Office web site. The establishment and maintaining are performed by Dr. Tomas Vanek (Czech Republic) and the vice-chair Prof. Julian Ma (UK).

We have also published a leaflet – Molecular Farming: a field of opportunity - in autumn 2010, and it has now been translated besides English into six other languages. It is downloadable in the webpage of our Action. Action has already been mentioned in the acknowledgements of five joined publications. The number of the joined publications is increasing currently being about 25 (see Annex 3). To support the various communication and dissemination activities of the three working groups a series of perspective articles will be published in the journal Transgenic Research. One to two articles will be published per issue. A list of potential 9 articles have been discussed and lead authors with co-authors have been suggested. The article list and some guidelines to be considered when preparing these articles will be presented on the homepage. During the Plovdiv meeting (March, 2011) it was also discussed that the white papers for WG1 and WG2/3 may extract information from these perspective articles.

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, 8-10, 2011.

II.D. Self evaluation

The Molecular Farming COST Action has rapidly established itself into a lively and productive initiative. The priorities for the Action and the targets for our collaborative work were agreed and established unanimously at the first meeting in Athens. Since then, each Working Group has established its short and long term goals, and determined its membership. The ease and speed with which this has been achieved is testament to the collective will of the MC members to ensure a successful Action.

We have held extremely successful meetings for the entire Action in Athens (2009), Prague (2009) and Vico (2010), for WG1 in Lleida (2009) and Plovdiv (2011), and for WGs 2 and 3 in Wageningen (2010). All have been extremely well attended, with, gratifyingly, a large component of young scientists in attendance. The meetings have benefited from contributions from both academic and industrial participants and it is one of the strengths of the Action that industry feels that involvement is necessary and worthwhile.

With regards STSMs, an internal process for application and peer review was rapidly established, and the Action has already funded 12 STSMs till the end of March 2011. The reports and feedback on these will be important to audit the effectiveness of the STSM strategy of our Action. It was decided that in the next annual meeting in Ghent (September, 2011) each student or post-doc who have obtained the STSM grant will present his/her work in the form of a poster.

The Action website has been up and running and it has been refreshed in order to gain more public interest. We have purchased the domain name molecularfarming.org and we use the website, not just to identify ourselves, but also to make available reports and power point presentations from all of our meetings. The Action is still open for new members, and the "Join Us" page on the website clearly indicates the primary contacts for anyone interested.

Now that the Action is about in its half way, we will focus on publishable deliverables as our main output. The nature of these has been agreed. There is a considerable commitment and energy from a core group of members of the Action, and one of the tasks will be to ensure that we receive more input from a wider group of people. We still feel that less administrative burden from COST Office e.g. new grant holder system would allow us to focus on the Action itself much better and beneficial way.

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 Center 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 meeting), 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 mol farm products or proof-of-concept studies is very important.

- Deliverable – a positive declaration or endorsment of molecualr 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)

Introduction

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 groups dealt with IP licensing strategies. In his presentation, Antonia 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 documents 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 meeting), 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

08.50-9.10	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 ongoing 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 thouroghly discussed. The minutes of the MC meeting have been prepared separately.

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

Wednesday 23rd March 2011

Arrival during the afternoon - informal get together 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 Ongoing 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

18:10 End

Friday 25th March 2011

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

9.00 Introduction by *Harry Thangaraj- St George's University London, United Kingdom*

9.15 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

9.50 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*
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 provide 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". Given 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. Case studies of problematic issues of IP protection and management was 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.

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.

ANNEX 2

Short term scientific missions until 31.3.2011

The following twelve STSMs have so far 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

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/UGent, Gent, Belgium

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

Period: 20/04/2009 to 20/04/2009
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

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

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 Reserach Centre of Finland, Espoo, Finland

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

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

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), 06466 Gatersleben, Germany
STSM Topic: Spider silk variants from plants
Host: Jacques Guéguen, INRA, 44316 Nantes Cedex 03, France

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

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

Period: 15/07/2010 to 9/10/2010

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: Prof. Ann Depicker, Laboratory of Gene Regulation, Department of Plant Systems Biology, Flanders Institute for Biotechnology (VIB), Ghent University, Gent, Belgium

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

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

Period: Start Date: 10/02/2011 to 10/03/2011

STSM Applicant: Mr. Rodrigo Corredor, University of Bern

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

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

ANNEX 3

Lists of joined publications until 31.3.2011 (not yet complete)

With COST acknowledgement:

Pompa A, De Marchis F, Vitale A, Arcioni S, Bellucci M (2010): An engineered C-terminal disulfide bond can partially replace the phaseolin vacuolar sorting signal. The Plant Journal 61: 782 – 791.

De Marchis F, Pompa A, Mannucci R, Morosinotto T, Bellucci M (2010): A plant secretory signal peptide targets plastome-encoded recombinant proteins to the thylakoid membrane. Plant Molecular Biology DOI 10.1007/s11103-010-9676-6

Floss DM, Sack M, Arcalis E, Stadlmann J, Quendler H, Rademacher T, Stoger E, Scheller J, Fischer R, Conrad U (2009): Influence of elastin-like peptide fusions on the quantity and quality of a tobacco-derived human immunodeficiency virus-neutralizing antibody. Plant Biotechnology Journal 7: 899–913.

Cardi T, Lenzi P, Maliga P (2010): Chloroplasts as expression platforms for plant-produced vaccines Expert Review of Vaccines 9: 893–911.

Morandini F, Avesani L, Bortesi L, Van Droogenbroeck B, De Wilde K, Arcalis E, Bazzoni F, Santi L, Brozzetti L, Falorni A, Stoger E, Depicker A, Pezzotti M (2011): Non-food/feed seeds as biofactories for the high-yield production of recombinant pharmaceuticals. Plant Biotechnology Journal DOI: 10.1111/j.1467-7652.2011.00605.x

Without COST Acknowledgement:

Loos A, Van Droogenbroeck B, Hillmer S, Grass J, Kunert R, Cao J, Robinson DG, Depicker A, Steinkellner H (2011): Production of monoclonal antibodies with a controlled N-glycosylation pattern in seeds of *Arabidopsis thaliana*. Plant Biotechnol. J. 9: 179-192.

Loos A, Van Droogenbroeck B, Hillmer S, Grass J, Pabst M, Castilho A, Kunert R, Liang M, Arcalis E, Robinson DG, Depicker A, Steinkellner H (2011): Expression of antibody fragments with a controlled N-glycosylation pattern and induction of endoplasmic reticulum-derived vesicles in seeds of *Arabidopsis*. Plant Physiol. 155: 2036-2048.

Arcalis E, Stadlmann J, Marcel S, Drakakaki G, Winter V, Rodriguez J, Fischer R, Altmann F, Stoger E (2010): The changing fate of a secretory glycoprotein in developing maize endosperm. Plant Physiol. 153: 693-702.

Bosch D, Schots A (2010): Plant glycans: friend or foe in vaccine development? Expert Rev. Vaccines 9: 835-842.

Demeyer R, Ruttink T, Van Gulck E, Van Droogenbroeck B, Querci M, Taverniers I, De Loose M (2010): Molecular toolbox for the identification of unknown genetically modified organisms. Anal. Bioanal. Chem. 396: 2073-2089.

Farre G, Ramessar K, Twyman RM, Capell T, Christou P (2010): The humanitarian impact of plant biotechnology: recent breakthroughs vs bottlenecks for adoption Curr. Opin. Plant Biol. 13:219-225.

Henquet M, Heinhuis B, Borst JW, Eigenhuijsen J, Schreuder M, Bosch D, van der Krol A (2010): Differential effects of human and plant N-acetylglucosaminyltransferase I (GnTI) in plants. Transgenic Res. 19: 535-547.

Mandal MK, Fischer R, Schillberg S, Schiermeyer A (2010): Biochemical properties of the matrix-metalloproteinase NtMMP1 from *Nicotiana tabacum cv.* BY-2 suspension cells. Planta DOI 10.1007/s00425-010-1221-y.

Ramessar K, Capell T, Twyman RM, Christou P (2010): Going to ridiculous lengths—European coexistence regulations for GM crops. Nat. Biotechnol 28:133-136.

Ramessar K, Sabalza M, Miralpeix B, Capell T, Christou P (2010): Can microbicides turn the tide against HIV? Curr. Pharm. Design 16: 468-485.

Schiermeyer A, Schillberg S (2010): Pharmaceuticals. *In:* Genetic Modifications of Plants, Biotechnology in Agriculture and Forestry 64, Kempken F, Jung C (Eds), Springer-Verlag, Berlin - Heidelberg, pp. 221-235.

Berends E, Ohm RA, de Jong JF, Rouwendal G, Wösten HA, Lugones LG, Bosch D (2009): Genomic and biochemical analysis of N-glycosylation in the mushroom-forming basidiomycete *Schizophyllum* commune. Appl. Environ. Microbiol. 75: 4648-4652.

Berends E, Scholtmeijer K, Wösten HA, Bosch D, Lugones LG (2009): The use of mushroom-forming fungi for the production of N-glycosylated therapeutic proteins. Trends Microbiol. 17: 439-43.

Bortesi L, Rossato M, Schuster F, Raven N, Stadlmann J, Avesani L, Falorni A, Bazzoni F, Bock R, Schillberg S, Pezzotti M (2009): Viral and murine interleukin-10 are correctly processed and retain their biological activity when produced in tobacco. BMC Biotechnology 9:22, doi:10.1186/1472-6750-9-22.

Fischer R, Schillberg S, Twyman RM (2009): Molecular farming of antibodies in plants. *In:* Recent Advances in Biotechnology, Kirakosyan A, Kaufman PB (Eds), Springer-Verlag, Berlin - Heidelberg, pp. 35-64.

Floss DM, Kumlehn J, Conrad U, Saalbach I (2009): Haploid technology allows for the efficient and rapid generation of homozygous antibody-accumulating transgenic tobacco plants. Plant Biotech. J. 7: 593-601.

Ramessar K, Capell T, Twyman RM, Quemada H, Christou P (2009): Regulatory Harmony in the GE World? Information Systems for Biotechnology 9: 13-15.

Ramessar K, Capell T, Twyman RM, Quemada H, Christou P (2009): Calling the tunes on transgenic crops – the case for regulatory harmony. Mol. Breed. 23: 99-112.

Rouwendal GJ, Florack DE, Hesselink T, Cordewener JH, Helsper JP, Bosch D (2009): Synthesis of Lewis X epitopes on plant N-glycans. Carbohydr. Res. 344: 1487-1493.

Schiermeyer A, Hartenstein H, Mandal MK, Otte B, Wahner V, Schillberg S (2009): A membrane-

bound matrix-metalloproteinase from *Nicotiana tabacum* cv. BY-2 is induced by bacterial pathogens. BMC Plant Biology 9:83.

Sorrentino A, Schillberg S, Fischer R, Porta R, Mariniello L (2009): Molecular farming of human tissue transglutaminase in tobacco plants. Amino Acids 36: 765-772.

Twyman RM, Ramessar K, Quemada H, Capell T, Christou P (2009): Plant Biotechnology: The importance of being accurate. Trends Biotech. 27: 609-612.

Zhang M, Henquet M, Chen Z, Zhang H, Zhang Y, Ren X, van der Krol S, Gonneau M, Bosch D, Gong Z (2009): LEW3, encoding a putative alpha-1,2-mannosyltransferase (ALG11) in N-linked glycoprotein, plays vital roles in cell-wall biosynthesis and the abiotic stress response in *Arabidopsis thaliana*. Plant J. 60: 983-999.

III. Previous scientific report

Action FA0804: Molecular farming: plants as a production platform for high value proteins

II. Scientific Report

II. A. Results achieved during the period 27.11.2008 – 26.11.2009

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 following three 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 and 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 whole Action is to co-ordinate European efforts in Molecular Farming and to ensure the rapid development and commercialization of 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 will be a sustainable European plant Molecular Farming (MF) community with clear frameworks for regulatory, bio-safety and IP issues. Eventually the Action will allow the establishment of a **European Committee of Molecular Farming**. This Committee 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, also after this COST Action, in the fast developing field of complex recombinant proteins, including biopharmaceuticals.

One of the first activities of this Action was the establishment of a preliminary Road Map as a tool

to facilitate productive joint research among the ± 35 groups from 21 European countries. An inventory of activities and fields of expertise of the participants to this Action show promising future trends in MF. A rich and diversified toolbox is available and at least half of the groups have a clear orientation toward a family of products and/or production systems.

The scientific program of the Action is pursued through three main topics. These show significant overlap and interaction, and the overall success of the Action relies on strong interactions between the different topics.

Strategic development of Molecular Farming (WG1)

This WG aims to provide a broad and global overview of the state of MF in the world today. Its primary purpose is 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 will involve reciprocal interactions with the other WGs in the areas of production systems and processing strategies (WG2) and target molecules (WG3).

At the kick-off meeting in Athens (March, 2009) it was proposed that the implementation of WG1 activities could be through the formation of specialized focus groups, comprising academic and industrial members. This proposal was accepted and a list of about 10 different possible Focus Group (FG) themes was proposed to the participants for selection. During a WG1 follow-up meeting in Lleida (May, 2009) the following four FG were agreed upon:

- Regulatory framework
- Public perception/stakeholder interactions
- Developing country aspects
- IP licensing strategy

For each of these FGs 2 short term objectives and 2 measurable outputs were defined at the Lleida meeting. These were presented to all Action members on the next general Action meeting that was organized in Prague (October, 2009). In addition, during the second day of this meeting, selected speakers elaborated on themes directly related to the four FGs. From here on, Action members collaborated to achieve the defined short term objectives and measurable outputs.

FG1 (Regulatory Framework), current EU situation was compared to the situation in the US (contribution Elizabeth Hood, invited speaker, Prague meeting). Action members being part of

EFSA GMO panel further brought Molecular Farming under the attention of the EU regulators. In addition, specific Action members participated at the 4th Meeting of the European Advisory Committees on Bio-safety (October 29-30, Brussels), again with the aim to discuss specific regulatory MF issues.

FG2 (Public perception/stakeholder interactions), stakeholder interaction meetings are being planned currently. In addition, specific questions for the EUROBAROMETER survey are being prepared. Finally, contacts with possible beneficiary stakeholders (patient organizations) are being initiated.

FG3 (developing country aspects), ongoing activities focus 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 non-COST country partner, China has been joining this Action.

FG4 (IP licensing strategy), an inventory of IP on MF within EU is one of the objective worked upon.

All these activities, set up during the first year, will contribute to produce the outputs of WG1 during the rest of the Action. These will take 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)

This WG aims 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 is 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 will carry out an inventory and literature study to summarize the state-of-the-art in MF and identify major bottlenecks hindering commercial exploitation. This will be supported by a database summarizing MF activities. This will be in a publishable form and will constitute 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. At the kick-off meeting in Athens (March, 2009) different MF systems producing pharmaceutical and technical proteins have been presented by representative

from academia and industry. During the discussions two major conclusions were made: 1) The pharmaceutical industry, which currently uses conventional systems such as animal cell and microbes, will define the needs for a 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. Therefore, the implementation of industrial partners including representatives from non-plant production platforms will be important to evaluate the achievements of the MF community and to define process steps that have to be improved. 2) The success of specific plant production platforms is tightly interlinked with the features of specific protein products. Therefore, future activities should carefully consider 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).

At the Prague meeting the structure of a database summarizing the various efforts in producing recombinant proteins in plants has been discussed. The database will be interactive allowing the extraction of specific information and more than initially described in the proposal. A first version of the database will be presented and discussed during the next joint WG2/WG3 meeting in Wageningen (January, 2010).

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. This WG aims to deal the following issues of plant produced systems when choosing the best production system: i) Scalability, ii) Costs, iii) Adaptability, 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 (Athens, March 2009) expert opinions were presented by industry and academia followed by plenary discussions. 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). 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 the appendix). 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 that holds all kinds of specific data on proteins that have been expressed in plants. This would be a tangible output of the Actions and should allow more systematically addressing specific questions and finding answers on which (type of) proteins are best produced via plants.

Short term scientific missions (STSMs)

The following four STSMs took place in the frame of this COST Action:

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

Period: 15/04/2009 to 20/04/2009

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/UGent, Gent, Belgium

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

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

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

II.B. Dissemination of results

The Action has organized three scientific 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 specialists. The scientific programs can be found at the end of this chapter.

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 now and is also linked to the COST Office web site. The establishment and maintaining are performed by Dr. Tomas Vanek (Czech Republic) and the vice-chair Prof. Julian Ma (UK).

The Action is 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:

- CoMoPharm (coordinator: Stefan Schillberg)
- SmartCell (coodinator: Kirsi-Marja Oksman)
- PLAPROVA (coordinator: George Lomonossoff)

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.

COST FA0804 meeting, Athens 5.-6.3.2009

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

1. 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 pharming 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?"*

COST Action FA0804 WG1 meeting, Lleida May 27 - 28, 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

Cost Action FA0804 meeting, Prague 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 I□1 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

11.26 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*

14.30 Management committee meeting (only for MC members)

II.C. Self evaluation

The Molecular Farming COST Action has rapidly established itself into a lively and productive initiative. The priorities for the Action and the targets for our collaborative work were agreed and established unanimously at the first meeting in Athens. Since then, each Working Group has established its short and long term goals, and determined its membership. The ease and speed with which this has been achieved is testament to the collective will of the MC members to ensure a successful Action.

We have held extremely successful meetings for the entire Action in Athens and Prague, for WG1 in Lleida, and for WGs 2 and 3 in Wageningen. All have been extremely well attended, with, gratifyingly, a large component of young scientists in attendance. The meetings have benefited from contributions from both academic and industrial participants and it is one of the strengths of the

Action that industry feels that involvement is necessary and worthwhile.

With regards STSMs, an internal process for application and peer review was rapidly established, and the Action has already funded 4 STSMs till the end of 2009. The reports and feedback on these will be important to audit the effectiveness of the STSM strategy of our Action.

The Action website has been up and running for over 4 months. We have purchased the domain name molecularfarming.org and we use the website, not just to identify ourselves, but also to make available reports and powerpoint presentations from all of our meetings. The Action is still open for new members, and the "Join Us" page on the website clearly indicates the primary contacts for anyone interested.

Now that the Action is established, we will focus on publishable deliverables as our main output. The nature of these has been agreed. There is a considerable commitment and energy from a core group of members of the Action, and one of the tasks will be to ensure that we receive more input from a wider group of people. We hope that within the next few months, the administrative elements of the Action that were unexpectedly placed on us, will be resolved to the agreement both of the COST office and the Action members.

Appendix

Scientific Reports

Meeting in Athens, 5-6 March, 2009

The meeting took place at the Conference Center 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).

Meeting in 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:

3. 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.
4. 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

George 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 tolls 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 mol farm products or proof-of-concept studies is very important.
- Deliverable – a positive declaration or endorsment of molecualr 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:

4. 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).

5. 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).
6. 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.

Meeting in Prague, 5-6 October, 2009

Introduction

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 groups dealt with IP licensing strategies. In his presentation, Antonia 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 documents 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).