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 the 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. Georg 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, biosafety 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 Biosafety (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 EUROBARO-METER 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

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

11.25 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)

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:

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

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:

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.

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).