Grant Agreement No. **602366**

AGORA

"ADVANCED THERAPY MEDICINAL PRODUCT GOOD MANUFACTURING PRACTICE OPEN ACCESS RESEARCH ALLIANCE"

SUMMARY OF AGORA ACHIEVEMENTS

Technical training and transfer

In accordance with the task of "*Designing courses with modules for basic and advanced training for target group and interest of expertise related to preclinical and translation to Phase I clinical trials"*, MHH organized and hosted a training course in GMP manufacturing which had been designed conjointly by all AGORA partners, and which was also linked to the EU Marie Curie Initial Training Network CELLEUROPE (www.celleurope.eu) and NATURIMMUN (www.naturimmun.eu).

The programme's purpose was to diversify over several target groups dependent on the depth of knowledge about ATMP, interest of expertise and stage of (pre)-clinical development. This allowed focus of specific course units on the needs of qualified pharmacists with established GMP knowledge wishing to diversify into ATMP manufacture as well as those of cell biology scientists with an understanding of ATMPs needing to learn GMP skills.

The training programme's followed the flow of events in trial design offering basic technical training to advanced training to bridge early to late stage clinical studies from phase I/II up to phase III/IV studies. Special care was given to those courses which are lacking in the GMP Academic area so far.

The training workshop addressed the necessity of different variables to explain how and why these may influence a specific manufacturing process with regard to time, cell viability, purity, recovery, enumeration of contaminating residual unwanted cells, expansion and transduction rate as well as cell functionality. The necessity to address these product variables within the preclinical development has been explained.

The training on GMP compliant manufacturing in generic terms explained the differences between research and development and GMP settings. The principles of documentation and qualification have been addressed. Furthermore, the bridge from preclinical research to clinical GMP compliant manufacturing procedures has been highlighted.

In a close cooperation between PharmaCell and MHH and all AGORA partners special effort has been made for late phase application advanced training with regard to the difficult point how to validate potency assays for phase III/IV trials. In addition for gene therapeutic ATMPs validation of both mycoplasma test according to EP2.6.7 and endotoxin test according to EP2.6.14. observing S2 conditions have been discussed in a training course.

These network wide GMP training workshops provided the trainees with knowledge which can be used for ATMPs in both regenerative medicine and cellular therapy. By pooling the resources of the clinical and industrial partners through the "Technical Training & Transfer" work package, AGORA provided a synergistic and complementary environment with training exceeding the whole linkage from basic manufacturing techniques up to large clinical trials.

By training academic trialists and new SMEs to improve their GMP compliance, AGORA greatly eased the transfer to contract manufacturer (CMO) of successful phase I/II products when picked up for commercialization, which are areas with substantial weakness in academic labs and many new biopharma SMEs. This programme established links for future collaborations for reverse translation of clinical trials but, more importantly, it ensured that academically led early phase clinical trials, manufacture products which can be easily translated to MOs for subsequent phase II and phase III studies, most of which are beyond the capacity and expertise of academic GMP units.

Furthermore, collaboration with the existing Cell Europe and NaturImmun Marie Curie Initial Research Training programmes enabled further dissemination of the project and of knowledge via interactive workshops and seminars to early stage and experienced researchers in the field of advanced therapeutic medicinal products.

Networking

The networking part of AGORA aimed to:
1. establish and maintain a communication structure within the Network of GMP facilities and practitioners created in the academic GMP environment,
2. provide an access to the AGORA Network, via a web based platform as a source of information and discussion forum for interested parties, stakeholders, researchers and the public,
3. design and establish the format needed for the development of a document "toolbox" to be provided for researchers use,
4. efficiently implement a comprehensive web-based project platform based on requirement analysis and specification.

The overall goal of the project was to establish a common platform for academic researchers, clinicians, quality managers, qualified persons, clinical trials coordinators, legal and regulatory advisors and regulators, the network was to provide essentially the infrastructure upon which this platform could be based. For the goals of

- explicit outreach and integration across Europe,
- linking academic researchers to existing expertise,
- contributing useful data to better assess the consequences of EU legislation,
- connecting research participants and stakeholders and by fostering dialogue,

the network can be seen as the skeleton, the portal and the frontpage of AGORA. All activities planned within the project build upon the use of this IT backbone; as such, WP3 was interwoven with all work packages, especially WP4 (toolbox) and WP 5 (outreach).

All deliverables and milestones were achieved in time, actually way before the timelines set by the project. A few statistics:

1. Number of visitors March 2014- July 2015: 5,391
2. Registered members (with access to the password protected area): 816
3. European map visitors: 306
4. Toolbox users (file manager): 533
5. Event calendar and blog are also popular pages

Significant Results

The outcomes of this task are presented in *Deliverable D3.1 – D3.5, submitted M3.1, 3.2, 3.3, 3.4, 3.5* and produced the following key results:

- Implementation of the AGORA_GMP.org web site.
- Maintenance of the web platform

- A plan for continuation of the web site beyond the period of AGORA funding

We have funded the web hosting agent for an additional year of support from within the AGORA grant to maintain availability of the data arising from AGORA. We will use this additional year of support to negotiate movement of the web data to a permanent host; probably EBMT.

An important function of the web-based project platform is to provide an access gate to researchers enquiring for all kinds of advice, project counselling and process development. AGORA wanted to offer the website as an entry portal to all GMP facilities and practitioners connected to the Network and pass requests on to competent European centres, engaging them to interact directly with researchers to ensure successful translation of projects into processes. The idea was to create an internal forum for communication within the Network, and a Discussion and Q&A forum to the public, with a minimum delay in replying to general or detailed requests, of scientific, technical or regulatory nature.
Databases were established and maintained: A networking and blog function for participants in the Network, A GMP library paving the way for the Document Toolbox, and an Interactive Map of Europe backed by a database with information specific to the member states, regarding national authorities, contacts, details on regulatory practices.

The following activities have been carried out in several sections of the AGORA IT platform:

1) "News": Regular announcement of important news for the GMP/ATMP community such as new regulations, draft documents published for comments, interesting events, etc., as news on the front page of the AGORA website. This section has been also used to communicate and promote the activities carried out and organized by the consortium, such as seminars, courses (including a QP Training), survey, etc.
2) "Blog articles": Publication of news as blog articles (including the quarterly AGORA Newsletter, sent previously to the AGORA distribution list), articles related with the GMP-ATMP environment, announcements of events and general information.
3) "Events Calendar": Addition and regular update of events including information such as link to the organizing institution, general information about the event (topic, location, registration, venue, etc.).
4) "Toolbox": Upload, download and creation of documents and training videos using the toolbox structure created for this purpose.
5) "Monthly poll": Upload of new questions every month for the visitors to answer and see other answers from other users.
6) General update of links, publications, etc.
7) Constant search for news, articles, events and information that could be published on the AGORA IT platform.
8) Promotion of the AGORA website:
   Publication of the "AGORA quarterly newsletter": 5 Newsletter have been sent by INSIGHT since the beginning of the project to a distribution list including more the 500 people related to the GMP/ATMP environment. One of the objectives of these newsletters was to promote the AGORA website and the activities carried by the project. The website was also presented in several conferences and meetings by the consortium members.

Development of Toolbox

The aims of the Toolbox were:

1. To create an on –line tool including a decision tree flow chart to assist product developers in deciding the likelihood that their product is an ATMP and to direct them to the correct contact in their Competent Authority to obtain formal classification
2. To create an on-line tool box of proven GMP-compliant documents for open access availability to end-users to facilitate development of new ATMPs for trial
3. Within the toolbox to provide a comprehensive list of manufacturing facilities with contact details across the EU able to provide some or all aspects of GMP manufacturing of ATMPs
4. To provide risk assessments of non-GMP compliant reagents/consumables which have been used in GMP manufacture to increase availability of critical reagents
5. To provide web-links to relevant European Medicines Agency (EMA) and European Directorate for the Quality of Medicines (EDQM) pages Focus of WP4

Documents have been collated from Partners and uploaded onto the toolbox. A comprehensive list of documents covering clinical trials application, EMA guidelines on GMP, pharmaceutical quality systems, QP release risk assessments and product development and release.

Training course materials have also been uploaded onto the portal. Any additional documents can be uploaded as requested. See attached 'toolbox review' for a summary of the documents currently available.

Within the objectives of the project as a whole was to establish a web-based platform for information exchange and the development of a documents "ToolBox" for use within the EU community for cell based therapies. This was achieved in Task 4.

The Toolbox part of the web site is well used and is more regularly accessed than the US-focussed version hosted on the ISCT website. We anticipate that this resource will remain valuable to the EU community for the next 12-24 months after completion of AGORA but will become increasingly redundant thereafter as the documents become too dated for valuable use. With the end of the project there will be no funds to add more documents to the site so only those from institutions which are prepared to anonymise their own documents or willing to post versions which are not anonymised will continue to contribute.
Additionally, examples of clinical trial applications have been uploaded into the web page for use by registered participants. A review has been conducted of clinical trial applications by academic groups across the EU and this was presented at ISCT EU in Seville in September 2015.

Representation

The aim of this part of the project was:

1. to represent the academic facilities within the GMP-network and make a direct link with the authorities/regulators in Europe.
2. To represent AGORA in front of policy makers including the European Parliament and the European Commission, European and national regulatory authorities, scientific organizations and the scientific community.
3. To communicate the objectives and structure of AGORA to interested parties.

The project led to representations by AGORA members at all relevant international meetings during the course of the project as well as hosting or co-hosting educational sessions and meetings including a product specific workshop at ISCT Paris 2015 and a second at ISCT Seville 2015.
AGORA was registered as an Interested Party at EMA CAT in 2012. The consortium was also represented at a meeting held at the European Parliament with MEPs entitled "MEPS against cancer" where we spoke against plans to reduce the product quality requirements for ATMPs in academic development which was proposed by another EU consortium. We believe that our intervention was a substantial contribution to the argument against

creation of a two-tier ATMP development process which would substantially undermine the delivery of safe and effective ATMPs across the EU.