Grant Agreement No. **602366**

AGORA

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

Final Report on the achievements over the 26 month extended project

1. EXECUTIVE SUMMARY

The aim of this project was undertake a series of specific actions to address each of the current unmet needs and critical issues arising from the regulation of cell therapies derived from human cells and tissues across the EC. Advanced Therapy Medicinal Products (ATMPs) are medicinal products based on gene therapy, somatic cell therapy or tissue engineering. AGORA planned to create a resource to boost biomedical and clinical research through provision of a platform to facilitate consultation with biomedical researchers in the field and to support academic ATMP developers comply with legislation whilst promoting the development of these medicines from early phase to commercial later phase trials. AGORA has achieved its planned objectives through the establishment of a technology transfer network, training programmes, an interactive web-site, representation and provision of information on pathways, regulations, technologies and resources across the European Union.

We have generated new knowledge on the impact of advanced therapies regulations by:

- comparing the experience of partners and invited stakeholders;
- conducting a European survey of non-industry facilities in this sector;
- organising workshops, a major conference and a joint meeting with the EBMT for targeted, collaborative discourse;
- establishing a web-based platform for information exchange including the development of a document “tool-box”
- analysing publications and guidance from the perspective of better regulation principles;
- analysing innovation statistics in relation to advanced therapies.

In combination, we have obtained comprehensive feedback, data and evidence which has led to a very considered report that assesses how the new ATMP regulations are impacting on the academic sector and we have presented concrete suggestions to policy makers in response to the consultation document published by the Commission. We have directly addressed the future needs by establishing the technology transfer critical to the innovative development of ATMPs and disseminate improved awareness of EU regulations. We have strengthened the growing European translational network by training programmes, an interactive web-site, representation and provision of information on pathways, regulations, technologies and resources across the European Union.

Moreover, the project has established a common platform that brings together academic researchers, clinicians, quality managers, qualified persons, clinical trials coordinators, legal and regulatory advisors and regulators. The project has reached out across the EU MS to facilitate integration across Europe and links academic researchers to existing expertise and highlight the particular issues that can arise when the academic research culture encounters the requirements of ATMP regulations.

Finally we secured on-going support for the WEB-based resource created by AGORA which provides a toolbox of documents and information for ATMP developers across the EU and beyond.

2. SUMMARY DESCRIPTION – CONTEXT & MAIN OBJECTIVES

The aim of this project was undertake a series of specific actions to address each of the current unmet needs and critical issues arising from our previous FP7 Academic Good Manufacturing Practise (GMP) study on the development and delivery of new advanced therapies for the treatment of cancers and regenerative medicine.

Advanced Therapy Medicinal Products (ATMPs) are medicinal products based on gene therapy, somatic cell therapy or tissue engineering. AGORA planned to create a resource to boost biomedical and clinical research through provision of a platform to facilitate consultation with biomedical researchers in the field.

Recent EC actions have attempted to ensure the development, provision and free movement of ATMPs within the EU. However, FP7-funded research found substantial heterogeneity in the regulatory practice across member states which is leading to confusion and uncertainty and creating a severe barrier to development and delivery of these novel medicines which was weakening the position of EU academics and industry to collaborate and compete globally in this expanding field.

The outcome of the current impact assessment by "Academic GMP" did not conclude that the current EU legislation needed revision but that a framework of support and training was needed to facilitate the implementation. AGORA has contributed to this framework substantially through the establishment of a technology transfer network, training programmes, an interactive web-site, representation and provision of information on pathways, regulations, technologies and resources across the European Union.

At the outset of the project we set ourselves twenty five deliverable objectives across five work packages with eighteen milestones.

Description of the work performed since the beginning of the project and the main results achieved so far (M1-M26)

We have generated new knowledge on the impact of advanced therapies regulations by:

- comparing the experience of partners and invited stakeholders;
- conducting a European survey of non-industry facilities in this sector;
- organising workshops, a major conference and a joint meeting with the EBMT for targeted, collaborative discourse;
- establishing a web-based platform for information exchange including the development of a document "tool-box"
- analysing publications and guidance from the perspective of better regulation principles;
- analysing innovation statistics in relation to advanced therapies.

Work Package 2: TECHNICAL TRAINING & TRANSFER

Data from our previous FP7-funded project consistently showed that GMP manufacturing knowledge remains a barrier for academic trialists aiming to perform the full cycle from pre-clinical investigations to early and subsequent late stage clinical trials. The early phase training programmes for academic trialists will be compiled to explain the design of preclinical programme to the principle concepts of GMP compliant manufacturing. Aspects addressed will vary from building-up a product dossier in order to present data needed for a GMP manufacturing unit to facilitate the translation to variables needed for validation of the ATMP at the different phases of clinical trial programmes. Both academic and industrial partners will participate in designing this training, aiming to provide confidence to the end users that they can work with either type of GMP supplier to develop their product.

The training work package was designed by the different members of AGORA, headed by Ulrike Koehl 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 us to focus 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 programmes which were developed 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. 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 AGORA we provided a synergistic and complementary environment with training exceeding the whole linkage from basic manufacturing techniques up to large clinical trials.
We planned for course units of the established Cell & Gene Therapy program (MHH) to be made available as diplomas in ATMP manufacturing with training programmes designed to be applied as on-line learning available via the AGORA website. In addition training courses in manufacturing were organised to link where applicable to the EU Marie Curie Initial Training Network CELLEUROPE (www.celleurope.eu).
Both academic and industrial partners participated in designing this training to provide confidence to the end users that they can work with either type of GMP supplier to develop their product.
Clinical development of Advanced Therapeutic Medicinal Products (ATMPs) can be sub-divided in preclinical development, Phase I, -II, -III and commercialization of the product. Between each clinical phase additional development was addressed.

Work Package 3: Network

WP3 involved the communication strategy for AGORA and the objectives over the 24 months of the project were to:
1. to establish and maintain a communication structure within the Network of GMP facilities and practitioners created in the academic GMP environment,
2. to 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. to design and establish the format needed for the development of a document “toolbox” to be provided for researchers use,
4. to efficiently implement a comprehensive web-based project platform based on requirement analysis and specification.

Key objectives in this WP were:

Design and implementation of IT platform, maintenance and updating of IT platform

Based on the requirement and specification analysis, a subcontractor was to be sourced to perform the design and implementation of the web-based project portal.

Creation of Internal and Public forum, Databases

Provision of an access gate to researchers enquiring for all kinds of advice, project counselling and process development. We intended AGORA to function as

1. 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.
2. A database of participants in the Network,
3. A GMP library that will pave the way for the Document Toolbox emerging from our project, and an Interactive Map of Europe that is backed by a database with information specific to the member states, regarding national authorities, contacts, details on regulatory practices.

Work Package 4: Development of Toolbox

WP4 included the development of a virtual toolbox of documents to be shared across the ATMP GMP community. The objectives of WP4 were to:

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

Work Package 5: Representation

The objective was to represent the academic facilities within the GMP-network and make a direct link with the authorities/regulators in Europe through the following pre-determined tasks

Representation

- Registration at EMA-CAT as 'Interested Party'
- Participation at EMA, EU workshops and incentives relevant to ATMPs
- Representation at meetings of relevant professional societies (EBMT, ESGCT - European Society of Gene and Cell Therapy, EHA - European Hematology Association, TERMIS-- Tissue Engineering and Regenerative Medicine International Society and ISCT- International Society of Cellular Therapy when in Europe).

Communication

- Establishment of a Scientific and Technical Blog as a Discussion forum on the Consortium's Internet Platform
- Maintenance and Adjustment of the "Interactive Map of Europe"
- Publication and dissemination of a quarterly newsletter

Harmonisation in the ATMP classification

- We performed a survey on the classifications of ATMPs in the clinical trials and under the hospital exemption scheme.
- We studied the differences in these classifications and their regulatory framework. These results were published and sent to the Competent Authorities involved in the classification of ATMP and presented in workshops/international meetings

Final results and their potential impact and use

ATMP development is probably the fastest moving field of translational medicine at the moment and keeping up with developments has been an on-going challenge for the consortium. Nonetheless we have been able to make significant contributions with respect to training, exchange of relevant information and valuable GMP documentation and the formation of a network of scientists and clinicians across the EU who are using the website and the on-line tools.

The project hosted more than ten meetings of members of the executive or the wider consortium and the regular communication led to delivery of new training resources, both physical and virtual. Basic

traiing courses were set up at MHH and UCL. A one day course hosed at UCL provded a completely new on-line accesible videos of all of the CPD lectures and a series of presentations were made at consortium hosted meetings to raise awareness of QC issues related to ATMP GMP. AGORA was invited to attend a one-day meeting at EDQM on this issue which was an essential contribution to the EU decision making process. AGORA has hosted one-day meetings on QC issues at ISCT annual international conference in Paris 2015 and in Las Vegas 2016 plus sessions at ISCT EU regional meeting in Seville 2016.
In view of the tools provided with the web-based platform, the variety of folders and the tool-box (cf. WP 4), the potential of the network has not been explored in its entirety, due to submaximal feedback from the consortium. However, the toolbox continues to receive contributions from consortium members and is well used by the community.

Impact:

This project:

- Has resulted in additional collaboration between experts and researchers across geographical boundaries, and made heterogeneous qualitative and quantitative data and balance models internationally available.
- The web based Toolbox has already facilitated the development of GMP compliance in academic GMP units across the EU and will continue to do so now that we have secured it for a further year.
- The AGORA consortium has become a point of reference for EU CA in ATMP regulation and the opinions of consortium members are now sought regularly as key opinion leaders in regulation of ATMP GMP
- Each WP leader submitted a comprehensive reply to the recent EC consultation document on ATMP GMP standards.
- Three peer-reviewed full publications arose from this project together with over 50 presentations at scientific and/or open public meetings including a TEDX talk by the consortium leader.

3. SCIENTIFIC & TECHNINCAL RESULTS / FOREGROUNDS

The scientific and technical deliverables from this project arose from work packages 2 – 5 which are presented below.

Work Package 2: TECHNICAL TRAINING & TRANSFER

Data from our previous FP7-funded project consistently showed that GMP manufacturing knowledge remains a barrier for academic trialists aiming to perform the full cycle from pre-clinical investigations to early and subsequent late stage clinical trials. The early phase training programmes for academic trialists will be compiled to explain the design of preclinical programme to the principle concepts of GMP compliant manufacturing. Aspects addressed will vary from building-up a product dossier in order to present data needed for a GMP manufacturing unit to facilitate the translation to variables needed for validation of the ATMP at the different phases of clinical trial programmes. Both academic and industrial partners will participate in designing this training, aiming to provide confidence to the end users that they can work with either type of GMP supplier to develop their product.

The training work package will be designed by the different members of AGORA, headed by Ulrike Koehl to diversify over several target groups dependent on the depth of knowledge about ATMP, interest of expertise and stage of (pre)-clinical development. This will allow 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 programmes to be developed will follow 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 will be given to those courses which are lacking in the GMP Academic area so far. In summary, these network wide GMP training workshops will provide 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 AGORA will provide a synergistic and complementary environment with training exceeding the whole linkage from basic manufacturing techniques up to large clinical trials.
We planned for course units of the established Cell & Gene Therapy programs (UCL/MHH) and Regenerative Medicine & Nanotechnology MSc programmes at UCL to be made available as diplomas in ATMP manufacturing with training programmes designed to be applied as on-line learning available via Moodle (all UCL lectures are now video recorded for on-line teaching). Students registering for these courses will pay fees which will allow the training WP to be sustained beyond the period of the FP7 funding. In addition training courses in manufacturing will be organised to link where applicable to the EU Marie Curie Initial Training Network CELLEUROPE (www.celleurope.eu).
Both academic and industrial partners were to participate in designing this training, aiming to provide confidence to the end users that they can work with either type of GMP supplier to develop their product.
Clinical development of Advanced Therapeutic Medicinal Products (ATMPs) can be sub-divided in preclinical development, Phase I, -II, -III and commercialization of the product. Between each clinical phase additional development will need to be addressed.

Work package 2 Objectives & Achievements
Objectives

The focus of this WP was to provide access to information and education, both academic and industrial partners collaborated to design the Work Package 2 “Technical Training & Transfer” headed by Prof. Ulrike Köhl.

Achievements

Task 2.1 Product development. UCL, MHH and UNEW all created one and two day training programmes including a specialist training session for EU Qualified Persons held at the ISCT Europe annual scientific meeting; thus extending the dissemination of AGORA training beyond the EU to attendees from Asia and the USA.

Task 2.3 Manufacturing process and robustness and Task 2.4 Regulatory aspects: UCL organised and hosted a course in spring 2015 which included training in all of these areas as did a programme hosted at MHH. The UCL course included 5 AGORA members as speakers and the entire day was video recorded and those videos are freely available on-line on the AGORA website.

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.

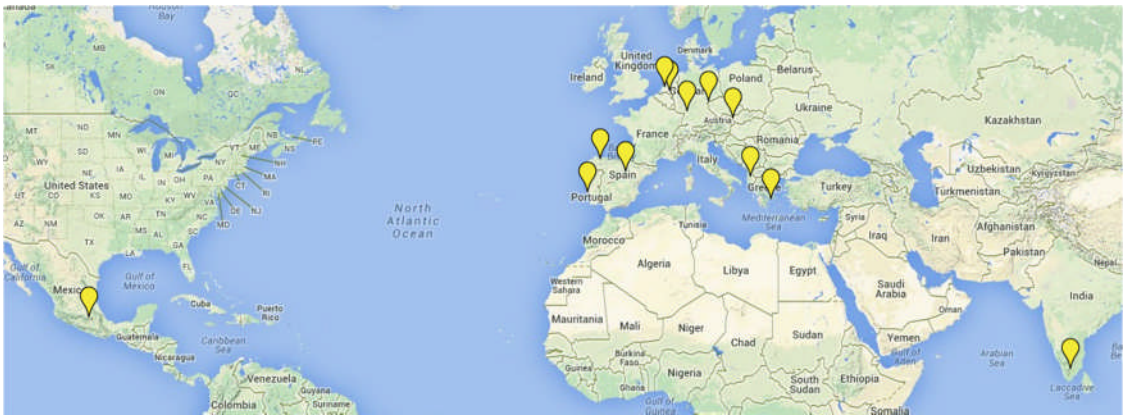
Expected final results, potential impacts and use

The training courses 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 was also explained.

Moreover, GMP compliant manufacturing was addressed in generic terms to explain the differences between research and development and GMP settings. The principles of documentation and

qualification were thereby addressed as well. Furthermore, it was aimed to highlight the bridge from preclinical research to clinical GMP compliant manufacturing procedures. The manufacturing workshop was highly successful. 20 participants, 5 from southern Europe, 13 from middle/northern Europe and 2 from southern countries of other continents were present. Participation was credited with 5 ECTS and a certificate was handed out.

Countries of origin of the participants



The Consortium, which is a closely associated group of European experts all with proven track records in the development and delivery of ATMPs to early and late clinical trial, brought together industrial and academic partners with exclusive capabilities in new cellular therapy technologies and processes, experience in R&D and with an aim to develop a unique capability across Europe in order to facilitate training and implementation in ATMP manufacture. The inclusion of PharmaCell, a specialist SME with contract manufacturing expertise, was an essential aspect of this project.

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.

Significant Results

A series of presentations have been made at consortium hosted meetings to raise awareness of QC issues related to ATMP GMP. AGORA was invited to attend a one-day meeting at EDQM on this issue which was an essential contribution to the EU decision making process. AGORA has hosted one-day meetings on QC issues at ISCT annual international conference in Paris 2015 and in Las Vegas 2016 plus sessions at ISCT EU regional meeting in Seville 2016.

A one day course held at Pharmacell for academic ATMP developers to explain the demands of process development to robustness for transfer to CMO manufacture for late phase trials and commercial delivery

WP2 successfully completed all of the objectives set for it in the description of work of the AGORA project.

Work Package 3: NETWORK

The aims of this WP were to establish the requirements of all partners for web based communication and dissemination to create detailed specifications for the web-based platform, including the following segments:

- an informative part accessible to the public
- a section for members of the consortium, protected by a password
- a blog for open communication on issues related to the practice of ATMP Development and Manufacture, intended as a counselling tool
- a GMP library that will grant access to a deposit of standard operating procedures, directives for production and quality control and other GMP-related documents deposited in a GMP library.
- An interactive Map of Europe related to issues of ATMP Development and Regulation as developed in the FP7 Consortium "Academic GMP"
- A development toolbox that will emerge as a result of the work of the AGORA Consortium for the establishment of translational trajectories and pathways for ATMP product development within the European Network of GMP practitioners.

Based on the requirement and specification analysis, a subcontractor was to be sourced to perform the design and implementation of the web-based project portal. We planned to provide an access gate to researchers enquiring for all kinds of advice, project counselling and process development. We intended AGORA to function as

1. 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.
2. A database of participants in the Network,
3. A GMP library that could pave the way for the Document Toolbox emerging from our project, and an Interactive Map of Europe that is backed by a database with information specific to the member states, regarding national authorities, contacts, details on regulatory practices.

Objectives

Work package 3 covered the networking part of AGORA. The objectives were:
1. to establish and maintain a communication structure within the Network of GMP facilities and practitioners created in the academic GMP environment,
2. to 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. to design and establish the format needed for the development of a document "toolbox" to be provided for researchers use,
4. to efficiently implement a comprehensive web-based project platform based on requirement analysis and specification.

Achievements

In view of the overall goal of the project, i.e. 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 were built 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

A requirement and specification analysis for the web site had been drafted by Martin Hildebrandt, circulated among Drs. Lowdell and Slaper-Cortenbach, and the other partners, and used to ask for offers from three European subcontractors. The best proposal was presented to the General assembly on September 30, 2013, and Insight publishers Inc., a company based in Bristol, UK, chosen to become subcontractor for AGORA's website as described above. The web-based platform was completed n time and now includes the following segments which remain accessible beyond the completion of the project:

- an informative part accessible to the public
- a section for members of the consortium, protected by a password
- a blog for open communication on issues related to the practice of ATMP Development and Manufacture,
- a GMP library that grants access to a deposit of standard operating procedures, directives for production and quality control and other GMP-related documents deposited in a GMP library,
- An interactive Map of Europe related to issues of ATMP Development and Regulation as developed in the FP7 Consortium "Academic GMP", in an improved, user-friendly and updated version,
- An ATMP toolbox (cf. WP 4) that was replenished more and more with documents in the weeks prior to the **Joint ECA – ISCT – AGORA Training Workshop for QPs in ATMPs** (cf. WP 5) in Seville, Spain, September 2015. The AGORA Consortium hoped here to make a contribution to the establishment of translational trajectories and pathways for ATMP product development within the European Network of GMP practitioners.

Based on the requirement and specification analysis, INSIGHT made proposals for the design and implementation of the web-based project portal. The final web appearance agreed upon should make it attractive for visitors to use the website frequently, to navigate easily among the different parts and to contribute themselves to a growing network of stakeholders and registered users. The full version of the website was available ahead of time, with all features specified and required by the project. The interaction between AGORA and INSIGHT via Roxana Laviña and Martin Hildebrandt allowed for an optimum performance with minimum down-time. Ineke Slaper-Cortenbach and Roeland Wasmann (WP 5) contributed both substantially to enhance the outreach of AGORA via the use of the website.

The AGORA website has been so widely used (especially in respect of the Toolbox – see below) that we have extended the contract with 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 has been and remains provision of 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.

The AGORA IT platform was established successfully and on time, updated and expanded continuously in the course of the project as planned. The statistics reflect that the project objectives regarding the AGORA website have been fulfilled, and that there is a good public acceptance that is presumed to grow further with the expansion of the toolbox. The project has created a tool that can help to further promote the field, develop new therapies and to contribute to the development of and access to innovative medicines in Europe. It is foreseen to maintain the website, especially the document toolbox, available for stakeholders for a minimum of three years, and to perpetualize the website via a renowned European professional society.

WP 3 Contributions to other Work packages:

WP 4 -Toolbox

- Task 4.2: Creation of a document tool box via AGORA web site: A toolbox structure with different folders has been created and is online. Several documents are available for registered members, with a confidential folder only accessible for consortium members and a general folder for all registered members of the AGORA website.

WP 5 - Representation

- Task 5.2: Communication: Four editions of the quarterly AGORA Newsletter had been drafted, finalized and distributed via email to more than 600 people related with the GMP- ATMP community. The newsletters are available on the website as well.

Work package 4 DEVELOPMENT OF TOOLBOX

Objectives

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

Achievements

The Consortium established at the first meeting that the provision of source documents such as IMPDs, SOPs and BMRs, by academic or commercial partners came with a risk which had been unforeseen at the time that the grant application was submitted. Provision of GMP compliant documents to new users might be taken by the end user as a statement that the documents were fit-for-purpose and thus the supplying organisation might indirectly accept some liability for the products arising from the use of the SOP or BMR. To avoid this it was agreed that all documents submitted to the Toolbox would be sent to the co-ordinator at UCL and converted to a standardised “AGORA format” which prevented tracing of the document to the originating organisation.
All of the documents submitted by the Partners have been collated 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 has been created for open access and is available on the AGORA website.

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. Completion of the project means that there are 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.
We are seeking a permanent host for this toolbox and negotiations are continuing with the EBMT Cell Processing Working Party as a potential permanent host.

We were able to host a version of this template immediately that the Toolbox went live and we have successfully updated the Toolbox with several product specific templates. These have been readily accessed by site users. D4.3 was submitted on time
In conclusion, WP 4 has been central to the aims of the entire project with the resources created being a major part of the training in WP2 and the website created in WP3.

The complete output of the Toolbox created in WP4 can be viewed on-line but the list is presented below:

AGORA Toolbox Review

Folder Title	Sub folder	File Names	Comment
Clinical Trials Application	IMPD	-EMA Guidelines on the requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials -IMPD Template -Manual to write an Investigational Medicinal Product Dossier for a (Somatic) Cell Therapy Medicinal product	
	Investigators Brochures		
	Other Documents	-IMP Product Specification Document -New Process Tracking Form	
	Study Protocol		
	Study Synopsis		
Draft Documents for Review			
GMP	Contracts Questionnaires		
	Documentation	-EMA Guidelines on the requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials -IMPD Template -Manual to write an Investigational Medicinal Product Dossier for a (Somatic) Cell Therapy Medicinal product	
	Outsourced Activities		
	Personnel		
	Pharmaceutical Quality System	-Agora Mandatory Quality Documents -Change Control Form -Adverse Events Procedure	

		-Product Quality Review -CAPA RootCause document -Change Proposal Form -Adverse Event Report Form - 8 further QA forms	
	Premises and Production	-Process for approval of Raw Material suppliers -Quarantine and release of consumable material - 4 further QA Forms	
	Production		
	QP Release	-Certification of IMP by QP -QP Certificate of Batch Release -QP Checklist -QP Log of Batches Certified	
	Qualification and Validation	-Import Qualification SOP for third party suppliers	
	Quality Control		
	Quality Manual Pharmaceutical Quality System		
	Risk	-AGORA Product Development Risk Assessment Matrix -Risk Assessment Form -2 further QA forms	
Product Development		-Product Development Document 01: Characterization Matrix CAR -Product Development Document 01: Characterization Matrix TCR Constructs	
Folder Title	**Sub folder**	**File Names**	
Production Protocols, Tissues and Medicinal Products	Blood products		
	CBMPs		
	Combined Products		
	General		
	GTMPs		
	TEPs		

	Tissues and Cells	-Receipt and Storage of Cells and Tissues	
Raw Materials and Excipients	Documentation		
	Pictures		
	Supplier Lists		
Regulatory Guidelines	EMA Guidelines		
	EU Directives & regulations		
	ICH Guidelines		
	Ph. Eur Pharmacopoieia Europea		
	PICS Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation		
Templates		EMA Guidelines	
		IMPD Template	
		Manual IMPD for CTMP	
		Prep Doc	
		Project Master File	
		Target Product Profile	
Training	Webinar	-UCL ATMPs Course Introduction -Martin Hildebrant -Dr Mark Lowdell -Anne Black AM -Anne Black PM -Andrea Hauser -Edward Samuel -Kim Champion -Pauline Meij	

Work package 5 Objectives & Achievements

Objectives

1. To represent the academic facilities within the GMP-network and make a direct link with the authorities/regulators in Europe.
2. Representation of 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. Communication of the objectives and structure of AGORA to interested parties.

Achievements

Ineke Slaper-Cortenbach (Utrecht, the Netherlands) lead this work package, the scope of which was to provide a constant and expanding representation of the AGORA Network in Europe. WP 5 leader worked with the secretariat of the Committee on Advanced Therapeutics (CAT) to take over the previous registration of the Academic GMP Consortium as an interested party at CAT. AGORA was represented at the 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. WP5 led the representation of AGORA at meetings of relevant professional societies (EBMT, ESGCT - European Society of Gene and Cell Therapy, EHA - European Hematology Association, TERMIS-- Tissue Engineering and Regenerative Medicine International Society and ISCT- International Society of Cellular Therapy when in Europe) throughout the 2 years of the project and has provided a framework for a direct interaction between interested parties, policy makers and stakeholders with members of the AGORA Network (WP 3) for requests, team formation and project formation. A particularly important output of this WP was participation as an invited speaker at the EDQM expert advice meeting on raw material standards for ATMPs.

This WP also established a Scientific and Technical Blog as a Discussion forum on the Consortium's Internet Platform and took responsibility for the maintenance and updating of the "Interactive Map of Europe" which had been established in the course of the "Academic GMP" Research Project. Finally, WP5 facilitated the publication and dissemination of a quarterly newsletter which summarised the activities of AGORA and acted as a source of education and information.

Harmonisation of ATMP classification

The classification of ATMP in clinical trials and under the hospital exemption is currently being done at the member state level and there was anecdotal evidence at the outset of AGORA that this was leading to inconsistencies in advice given to academic and commercial ATMP developers and adversely impacting on development across the EU. WP aimed to gather data to determine truth of these anecdotes and assess the impact. Within WP5 we performed a survey of the classifications of ATMPs in the clinical trials and under the hospital exemption scheme. The survey was performed successfully of current academic ATMP trials across the EU with responses from over 50 different sites. The outcome confirmed the lack of harmonisation of classifications and the detrimental impact those have on development of safe and effective ATMPs for the wider EU community. We summarised the differences in these classifications and their regulatory framework and the results were presented at ISCT Europe and will be published shortly and sent to the Competent Authorities involved in the classification of ATMP and presented in future workshops and international meetings.

The work performed as part of WP5 throughout the project has had significant impact with 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 held at ISCT Seville 2015 in M25 of the project.
The following publications have arisen from WP5:

- **M Hildebrandt**, C Bollard, K Peggs, L Uharek, HE Heslop. Immunotherapy: Opportunities, Risks, and future Perspectives. Cytotherapy, 2014 Apr;16(4 Suppl):S120-9. doi: 10.1016/j.jcyt.2014.02.001.
- C Chabannon, **M Hildebrandt**, S Scheding, A Humpe, M Lowdell, I Slaper-Cortenbach. Regulation of advanced therapy medicinal products will affect the practice of haematopoietic SCT in the near future: a perspective from the EBMT cell-processing committee. Bone Marrow Transplant. 2015 Mar;50(3):321-3. doi: 10.1038/bmt.2014.271. Epub 2014 Dec 15.

- N Cuende, C Boniface, C Bravery, M Forte, R Giordano, **M Hildebrandt,** A Izeta, M Dominici. The puzzling situation of hospital exemption for advanced therapy medicinal products in Europe and stakeholders' concerns. Cytotherapy 2014 Oct 4. pii: S1465-3249(14)00719-1. doi: 10.1016/j.jcyt.2014.08.007. Epub ahead of print

- AGORA Newsletters 1 (Feb 2014), 2 (June 2014), 3 (Nov 2014) and 4 (Feb 2015): published and distributed via email to more than 600 people related with the GMP- ATMP community.

In conclusion, WP5 was central to the dissemination of the outputs of much of AGORA although it was hampered by the industry-focussed activities of EMA. This is understandable in some respects given the EMA role is mostly in assessing marketing authorisation applications and these will always emanate from industry. Nonetheless, ATMPs are still developed predominantly in academic settings and it is disappointing that EMA did not want to engage with AGORA in facilitating the academic role in developing these novel medicines from early phase trial to late phase delivery.

4. POTENTIAL IMPACT - main dissemination activities and the exploitation of results

The project management activities conducted during the 26 months of the project have been essential to the successful delivery of AGORA. Throughout this reporting period, the project progress and results were disseminated to stakeholders and national and European policy makers to foster a high business take-up of the final AGORA outcomes. The dissemination activities enabled by WP1 has ensured that AGORA is renowned across the field and will lead to the partners remaining as key opinion leaders to regulators and ATMP developers beyond the period of the project.

Significant Results

The Consortium completed the Project Consortium Agreement on time and created the Executive Management team which has co-ordinated the remainder of the project to meet the milestones as described below. A Press Release by each of the Partners was co-ordinated and delivered on time. Throughout the project the co-ordinator has held regular telephone and face-to-face meetings with the Partners to ensure that the project remained focussed on its deliverables and could respond to changes in the field which impacted upon the aims of the project. Specifically the M12 co-ordination meeting of all partners was held in Amsterdam on 30th September 2014 to plan the remaining deliverables for the final year and to ensure that the on-line training workshop was planned. This was delivered in March 2015. A final report on the exploitation of the AGORA output is in preparation and will be submitted on or before the 30th October 2015.

ATMP development is probably the fastest moving field of translational medicine at the moment and keeping up with developments has been an on-going challenge for the consortium. Nonetheless we have been able to make significant contributions with respect to training, exchange of relevant information and valuable GMP documentation and the formation of a network of scientists and clinicians across the EU who are using the website and the on-line tools.

The project has been delivered within budget despite extending the duration by 2 months to accommodate an international meeting and two additional workshops.

Development of the Project website

The AGORA website has been one of the most significant achievements of this project. It is a very dynamic site which is accessed regularly by scientists who have signed up to the free membership and it has become a source of exemplar GMP documents for academic GMP labs across the EU. In collaboration with WP 5, the toolbox has been announced to other stakeholders in the field and received attention by the European compliance Association (ECA), the European QP Association (EQPA) and National Competent authorities. In fact, the regulators are aware of the projects Academic GMP and AGORA, and they have used national and international stakeholder meetings to mention favourably AGORA and policy of transparency, open exchange and mutual support. As it seems, Europe is moving here forward faster than many of the member states, where Academia is continues to be coined by competition rather than collaboration, and national authorities would find themselves in a hitherto unknown role of driving the field and, by doing so, offering alliance to consortia such as AGORA. As an example, AGORA members have hosted a first QP Training workshop in Sevilla, Spain, dedicated to the field of ATMPs, together with ECA and EQPA on the occasion of the Annual Meeting of ISCT Europe, where the toolbox was presented. A similar event is scheduled for February 2, 2016, with the Paul Ehrlich Institute, Germany, hosting a workshop together with members of AGORA for the topic of Quality Assurance Systems in Academic Institutions for the manufacture of ATMPs thus demonstrating the extension of the value of AGORA beyond the funding period.

For the purpose of providing information on events like these, as for the provision of the toolbox, the website is seen as an indispensable platform. The project participants have therefore decided to maintain and further develop the website for at least another three years, and to continue by all means to provide the researchers and stakeholders with the information collected in the course of AGORA.

Describe of the expected final results and potential impacts and use

The statistics show a good acceptance of the AGORA website and confirm that it could support the development of the area, since it satisfies some of the key needs from the ATMP/GMP community, especially in the context of a European Network.

In view of the tools provided with the web-based platform, the variety of folders and the tool-box (cf. WP 4), the potential of the network has not been explored in its entirety, due to submaximal feedback from the consortium. However, the toolbox continues to receive contributions from consortium members and is well used by the community. The closure of the project twill limit the ability to add documents since there is no resource for anonymising the contributors.

Dissemination of project results

This has been a horizontal activity throughout the project in order to disseminate the concept, vision and results of the project with a worldwide perspective. There were three main aims:

- To communicate the project's results to society and the broadest audience
- To transfer the methodologies used and the experience obtained to a wide range of stakeholders and researchers

Significant dissemination events

1. *Deliverable D1.2 – Project press release, lay summary submitted M1*
2. *Deliverable D2.3 – On line training resource.*
3. *Deliverable D3.3 – Implementation of the full IT platform*
4. *Deliverable D4.2 – Initiation of on-line toolbox*
5. *Deliverable D5.5 – Publication of first monthly newsletter*

List of project meetings, dates and venues;

- Initial meeting – 30/09/2013 Amsterdam, Netherlands
- Interim meeting – 14/03/2014 Lucca, Italy
- Interim meeting – 15/05/2014 Paris, France (whilst attending ISCT 2014)
- Interim meeting – 26/06/2014 Teleconference
- Interim M12 meeting 30/09/2014 Amsterdam, Netherlands
- Interim meeting – 01/06/2015 Amsterdam, Netherlands
- Interim meeting – 12/03/2015 Teleconference
- Closure meeting – 28/09/2015 Seville, Spain

Summary of important dissemination activities

Type of dissemination	Lead Partner	Title	Date delivered	Location	Type of audience
Press Release	UCL	The Agora Consortium	30/09/2013	Press	Media
Oral Presentation – Scientific event	UCL	ATMP Regulation across the EU	02/09/2013	Marseille	Cell Society Europe
Oral Presentation – Scientific event	UCL	QC of ATMPs in transplantation	09/09/2013	Paris	Patients, fellow researchers, hospital staff
Oral Presentation – Scientific event	UCL	Regulation of ATMPs in EU	07/012014	San Diego USA	ATMP manufacturers
Oral Presentation – wider public	UCL	The new world of personalised medicines - ATMPs	20/03/2014	Exeter UK	Lay persons
Oral Presentation – Scientific event	UCMU	ATMP clinical trials	01/05/2014	EBMT Milan	Medics and scientists
Oral Presentation – Scientific event	UCL	QC in ATMP manufacture	23/04/2014	ISCT Paris	Scientists
Oral Presentation – Scientific event	UCL	Delivery of DC vaccines for late phase clinical trials	26/04/2014	ISCT Paris	Scientific community
Oral Presentation – Scientific event	TUM	Academic GMP in EU,	25/04/2014	ISCT Paris	Scientific community
Oral Presentation – Scientific event	UCL	Regulation of ATMPs in the EU	17/06/2014	Sweden	Cell and medicines regulators
Oral Presentation – Scientific event	UCL	Production of TEP as ATMPs to GMP	03/10/2014	Lund Sweden	Scientists and clinicians
Oral Presentation – Scientific event	UCL	IQ.OQ and QC of ATMPs	21/05/2015	Stockholm Sweden	Scientists and clinicians
Oral Presentation –	UCL	Technology transfer	30/05/2015	Las Vegas USA	ISCT conference

Scientific event		of academic GMP to a CMO			
Oral Presentation – Scientific event	UCL	The role of the pharmacist in delivery of ATMPs	13/09/2015	Birmingham UK	AGM of Royal Pharmaceutical Society
Oral Presentation – Scientific event	TUM-Med	ATMPs, GMP and Risk Management	June 30, 2014	Vienna, Austria	Academia
Oral Presentation – Scientific event	TUM-Med	Cell Therapy	Sept 27, 2014	Innsbruck, Austria	Academia
Oral Presentation – Scientific event	TUM-Med	ATMPs: Manufacture in Academia	Nov 3, 2014	Munich, Germany	Industry leaders
Oral Presentation – Scientific event	TUM-Med	3rd Wildbad Kreuth Forum on Hemotherapy; Round-table on challenges in ATMP Manufacture in Academia	Jan 30, 2015	Wildbad Kreuth, Germany	Academia, Industry
Oral Presentation – Scientific event	UCL TUM-Med UKR LUMC	Course: Introduction to ATMPs Lecture: Gene Therapy Medicinal Products – Development and Clinical Trials in the EU	March 4, 2015	London, UK	Pharmacists, Researchers
Poster presentation, oral presentation and panel discussion	TUM-Med	EUCelLEX 1st International consensus Conference	March 30, 2015	Toulouse, France	Pharmacists, Researchers
Oral Presentation – Scientific event	TUM-Med	REMEDIC 2nd Interdisci-plinary Summit Conference 2015 on Regenerative Medicine in Europe	June 29, 2015	Berlin, Germany	Industry, Academia, Political Europe
Oral Presentation – Scientific event	TUM-Med	ECA-ISCT-AGORA joint training session for QPs in ATMPs	September 24, 2015	Sevilla, Spain	Pharmacists, Academia and Industry, Regulators
Poster presentation	LUMC	Clinical implementation of ATMP	September 24,25 2014	ISCT, Paris, France	Academia, Industry, Regulators and Pharmacists

Webinar	LUMC, UCL, TUM-MED, UK	Cell therapy Clinical trials in the EU	November 2014	ISCT Webinar	Academia, Pharmacists and Industry
Oral Presentation – Scientific event	LUMC	Clinical implementation of ATMP	September 26, 2015	ISCT Sevilla, Spain	Academia, Industry, Regulators and Pharmacists
Oral Presentation – Scientific event	LUMC	Documentation in early phase clinical trials of ATMPs	June 1st, 2015	AGORA workshop, PDA, Amsterdam, The Netherlands	Pharmacists, Academia and Industry, Regulators
Oral Presentation – Scientific event	LUMC	ZonMw project leader day	October 29, 2015	Utrecht, The Netherlands	Academia Pharmacists, Industry, and Regulators
Communication, Other Consortium Meeting	UNEW	Celleurope Consortium Meeting	27.09.2013	Gottingen, Germany	Scientific Community
Communication, Other Consortium Meeting	UNEW	Celleurope Consortium Meeting	26.03.2014	Regensburg, Germany	Scientific Community
Other- Conference Workshop	UNEW	Tissue Centre Engineering Society Conference	04.07.2014	Newcastle UK	Scientific Community
Communication, Other Consortium Meeting	UNEW	Celleurope Consortium Meeting	17.07.2014	Newcastle UK	Scientific Community
Oral Presentation – Scientific event	UNEW	Course: Introduction to ATMPs Lecture: What is different about Advanced Therapy Medicinal Products- a Pharmacists Perspective	04.03.2015	London UK	Pharmacists, Researchers
Oral Presentation – Scientific event	UNEW	Course: Introduction to ATMPs Lecture: Advanced Therapy Medicinal Products : QP Release and Practicalities for Pharmacy	04.03.2015	London UK	Pharmacists, Researchers
Workshop Participation	UNEW	ECA-ISCT-AGORA joint training session for QPs in	24.09.2015	Seville, Spain	Pharmacists, Academia and Industry,

		ATMPs			Regulators
Communication, Other Consortium Meeting	UNEW	Celleurope Consortium Meeting	27.09.2013	Gottingen, Germany	Scientific Community
Communication, Other Consortium Meeting	UNEW	Celleurope Consortium Meeting	26.03.2014	Regensburg, Germany	Scientific Community
Other- Conference Workshop	UNEW	Tissue Centre Engineering Society Conference	04.07.2014	Newcastle UK	Scientific Community
lecture	MHH	Natural Killer Cells for adoptive immunotherapy in high risk patients with leukemia and tumors	20.3.2014	DG-GT Annual Meeting in Ulm, Germany	Clinicians, scientists, industry, GMP, GCP practicioners gene therapy researchers
lecture	MHH	Advantage in stem cell purification: From handmade to fully automated manufacturing		ISCT Annual Meeting in Paris, France	Clinicians, scientists, industry, GMP, GCP, GTP practicioners
Training course	MHH	Manufacturing of cell-based therapies: From bench to bedside	12.9.2014	Medical School Hannover	Scientific community
lecture	MHH	Alpharetroviral vectors for the transduction of primary human natural killer cells: selective enhancement of tumor cytotoxic activity by chimeric antigen receptors	17.9.2014	Helsinki	Scientific community
Lecture	MHH	Zelltherapeutika zur individualisierten Medizin: Translationale Hürden	10.10.2014	Medical School Hannover	Scientific community
Lecture and training course	MHH	Harnessing NK cells for cancer immunotherapy:	16.12.2014	University Cologne	Scientific community

		From bench to bedside and back again			
lecture	MHH	Herausforderungen bei der Herstellung von ATMPs	24.02.2015	Cologne	Scientific community
lecture	MHH	Presentation of the AGORA project	23.03.2015	EBMT meeting in Istanbul, Turkey	Scientific community
lecture	MHH	Identification of distinct immune effector cell populations	23.03.2015	EBMT meeting in Istanbul, Turkey	Scientific community
lecture	MHH	Functional assays for product quality control of ATMPs	2.06.2015	PDA meeting in Amsterdam, Netherlands	Clinicians, scientists, industry, GMP, GCP, GTP practicioners
lecture	MHH	From activated to CAR expressing NK cells: improvement for future clinical studies?	28.08.2015	Karolinska University, Stockholm, Sweden	Scientific community

Problems which have occurred and how they were solved or envisaged solutions

The Consortium faced remarkably few problems; none of which substantially impacted on the overall aims of the project although four planned deliverables were not met. Our plan to integrate the AGORA website with the existing database of members held by the UK-based group "amc" (Advanced Manufacturing Community) (D1.4) and the linkage of the AGORA web-based "Toolbox" (D4.2) were not achieved due to a change in management direction by the amc and an increased focus on the UK industrial development space to the detriment of a broader EU-wide approach. The Executive team agreed that this was contrary to the spirit of AGORA and in conflict with the intention of an EU funded project and so redirected the funds to enhancing the AGORA web site and to other aspects of the dissemination work package. The Toolbox was created and hosted successfully on the AGORA website (D4.2) but was not linked to the amc web page as planned.

A second minor problem was caused by the substantial delays in publishing the revised EU directive on GCP and clinical trials. A survey of the impact of changes to the Clinical Trials Regulation on ATMP manufacturers was a planned deliverable (D4.4) followed by a report on the survey but none were possible within the duration of the project once the publication of the directive was delayed.

Finally, D5.8 was not achieved due to the absence of EU policy makers at the EBMT Annual Meeting and the consequent failure to meet with them as planned.

Conclusions

Whilst keeping well within a modest budget we have met each of the planned milestones and made all of the critical deliverables presented at the outset of the project application. The consortium has created long lasting professional partnerships across the EU and has already led to three applications to H2020; one of which was successful and will lead to the first ***multicentre***, ***multinational***, clinical trial of a tissue engineered ATMP in the World. This is exactly the sort of outcome hoped for when we conceived AGORA; namely the demonstration that academic ATMP developers can deliver high quality, complex ATMPs for clinical trial with industry to lead to substantial, long term benefits for patients across the EU. The continued availability of the website and the Toolbox is helping other academic groups to develop these complex medicines and will continue to do so.