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INNOVATIVE MEDICINES INITIATIVE CONSULTATION: FACILITATING THE TRANSLATION OF ADVANCED THERAPIES TO PATIENTS IN EUROPE

INTRODUCTION: EUROTECH UNIVERSITIES ALLIANCE

The EuroTech Universities Alliance is a strategic partnership of four leading universities of science and technology: Technical University of Denmark (DTU), École Polytechnique Fédérale de Lausanne (EPFL), Eindhoven University of Technology (TU/e) and Technical University of Munich (TUM). The Alliance builds upon and combines the excellence, expertise and capabilities of its partner universities to develop technical solutions which address grand societal challenges. The Alliance endeavors to create new approaches to and contribute to the development of research and scientific career paths, education, innovation, and entrepreneurship. EuroTech Universities Working Groups are active in a number of medical research fields, such as Ambient Assisted Living, Health Gaming, Soundcare as well as imaging technologies, ranging from In Vivo Imaging, Multi-Model Functional Bio-Photonic Imaging to Translational Brain Imaging and Integrating Imaging Processes.
At university level, all four EuroTech Universities develop extensive research within the field of Medicine:

TUM

TUM School of Medicine, together with the University Hospital, is one of the strongest medical research locations in Germany and its successes are internationally highly regarded. Medicine is one of the major areas that contribute to the TUM portfolio and is central for its further development. The guiding principle for the future of TUM School of Medicine is that of a confident and results-oriented synergy of research, teaching and patient care.
https://www.med.tum.de/en/welcome-tum-school-medicine

DTU

DTU Systems Biology is a major Danish research and teaching department in the field of systems biology and is involved in a wide range of research activities within its field. The academic profile covers the fields of cellular, molecular and structural biology, bioinformatics, computational biology, industrial biotechnology, biomedicine and health. DTU Systems Biology puts great emphasis on transforming scientific perceptions into advanced technical applications. This applies to its research as well as its study programmes.
http://www.bio.dtu.dk/english/About-the-Department

TU/e

TU/e was the first Dutch university to start the education programme in Biomedical engineering. Now, over 300 researchers from nine different departments have come together in the strategic area Health and are committed to the prevention, earlier diagnosis, and more effective treatment of diseases, as well as to promoting healthy lifestyles and living environments. Focused research in the theme Bio-molecular Health is being performed in collaboration with patient organizations and with clinical and industrial partners. The main applications lie in the cardiovascular, orthopedic and oncology fields.
https://www.tue.nl/en/research/strategic-area-health/research/bio-molecular-health/

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EPFL

The EPFL School of Life Sciences aims to foster a new generation of life scientists with strong expertise in quantitative and analytical biology. It offers a pluri-disciplinary training to students, providing them with the opportunity to study biology jointly with engineering, basic sciences, and computer sciences. The school's professors have diverse backgrounds – biology, chemistry, physics, engineering, computer science, psychology and medicine – bringing together their specific perspective and their passion to tackle fundamental questions in biological sciences and solve important biomedical problems to increase human knowledge and address key societal issues.
http://lmrp.epfl.ch/

Recent actions of the European Commission have attempted to ensure the development, provision and free movement of Advanced Therapy Medicinal Products (ATMPs) within the EU. However, we found substantial heterogeneity in the regulatory practice across member states which is leading to confusion and uncertainty, 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", a TUM-led FP7 study on the development and delivery of new advanced therapies for the treatment of cancers and regenerative medicine, concluded that a framework of support and training was needed to facilitate the implementation. AGORA, building on the work performed by "Academic GMP", has contributed to this framework 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 gratefully acknowledge the opportunity to comment on the Innovative Medicines Initiative consultation Document: "Facilitating the translation of advanced therapies to patients in Europe". The specific comments addressing the proposals and questions contained in the Consultation document are listed below. They will be circling around the topic of ATMP development and clinical use from an academic perspective, to complement and further expand the position laid down by the Innovative Medicines Initiative.

AD 1./2. INTRODUCTION/ TIME FOR ACTION IN EUROPE:

We agree that, in spite of growing numbers in clinical trials, the translation of ATMP concepts into clinical use remains disappointingly low. Germany, for instance, ranks second highest globally with regard to the number of clinical trials per country. In sharp contrast, it is embarrassing to see that, for chimaeric antigen receptor (CAR)- engineered T cells as one of the most promising developments in Biosciences, the number of clinical trials in the US is six fold higher than in Europe, with China scoring fivefold higher than the EU, stressing the urgent need for Action in Europe also from an academic point of view. It is our concern that this misbalance will lead to a drift of patients, scientists, know-how and investment out of Europe.
The regulatory framework, however, shows improvement in several ways: the EMA PRIME scheme, for instance, is hoped to offer early, concise and reliable guidance to ease the access to market, as will orphan drug designations and other concepts of early, supervised authorization schemes for clinical use. Similarly, the manufacturing process will hopefully benefit from the expected annex to the EU GMP guideline dedicated to ATMPs. Problems remain in the choice and availability of GMP-compliant starting materials, excipients and devices in early stages of clinical development. Also, Regulation 536/2014/EC on clinical trials will harmonize the approval of clinical trials in Europe, albeit at a high price especially

with regard to the development of ATMPs; deficiency reports to applicants Clinical Trial Applications can hardly be responded to in the time frame foreseen in the regulation (12 calendar days).
The Hospital Exemption Clause (HEC) laid down in Chapter 28 of Regulation 1394/2007/EC offers an opportunity to develop ATMPs for clinical use on a non-routine basis and on a national level. Products authorized under the HE clause lack the maturity of a fully developed medicinal product and should, therefore, not compete with an authorized product. On the other hand, ATMPs that lack commercial interest because of small numbers of affected patients or other reasons may still allow to respond to a clinical need, a scenario which is typical especially in Academia. It is important to point out that more than 90% of ATMPs are developed by academic centers, spinoffs and SMEs.
Products manufactured under the HE clause will have to comply with standards of GMP like any other product, and academic manufacturing processes may allow GMP upscaling to industry standards or act as an incentive for industry to develop these products further. To date there is no source of information on the products manufactured under the HE clause, nor are clinical data on safety and efficacy available as these products are by definition not used in clinical trials. For a better definition of the transition to (and collaboration with) industry, a **European registry for products manufactured under the HE clause is urgently needed**, including clinical data, safety issues and contact points. Ideally, this should be harbored by the **Qualified Persons and thus at the European QP Association (EQPA).**
Final reconstitution of an ATMP immediately prior to clinical use is a task that necessitates the availability of GMP facilities on site, i.e. in Academic centers and hospitals. For authorized ATMPs including IMPs, this may create a barrier to large-scale introduction into the clinic, given the scarcity of GMP facilities available to perform this final step which, in some cases, may be defined as a manufacturing step that requires a license. This is important mainly for Gene Transfer Medicinal Products. As for **Point of Care Devices**, the HE Clause could be used to define the interface between the Device and the product manufactured by the Device (under the premises that there is a QP, maybe employed by the manufacturer of the device?)

AD 3. DISCUSSION AND PRELIMINARY RECOMMENDATIONS

3.1 Preclinical Development

Model systems and Proof of Concept (PoC)

The need for demonstrating PoC in relevant animal models must be differentiated in terms of the type of ATMP: large animal models may be useful for Tissue engineered products and compositional products, but may be entirely missing or even misleading in genetically engineered T cells. Novel approaches of **Tissue screening, involving the use of biobanks** from industry and academia, should be exploited. Furthermore, especially due to the highly individualized nature of human cell products (HLA diversity, SNPs) substantial limitations of pre-clinical toxicity testing in animal models have to be accepted.

Vector systems

The problem of insertional mutagenesis has been addressed in depth; the problem lies rather with limited manufacturing capacities, expensive and cumbersome access for academia as a small customer, and a lack of **generic, mutually recognized vector systems** that allow for faster development and licensing of manufacturing processes.

Regulatory considerations

Academia will never have sufficient resources for GLP-like standards. Usually, subcontractors are employed to perform GLP or GLP-like studies; here, application-oriented, publicly funded institutions

may contribute to a successful cluster of Academia and Industry in ATMP development. In Germany, the Fraunhofer Society and Helmholtz Society might be capable to provide this bridging function.
As pointed out above, EMA has developed useful tools such as the PRIME scheme to respond to the need of early outreach and support. The efficacy of this approach awaits close observation and, if necessary, adaption of this interesting regulatory tool. Also, fast-track developments are being offered on a broader basis. We consider EMA's recent efforts as most promising and encouraging.
The idea of responding to the plentitude of challenges in a pre-competitive fashion, i.e. **joint platforms under the IMI umbrella, is strongly supported**. To better develop these platforms, we suggest to build upon certain **topics**, existing and emerging **regional clusters**, and **existing collaborations** between academia and industry in certain places. Also, incentives to establish such structures should be developed or, if existing, merged in joint funding schemes. An orientation towards the European Council of Region's funding and innovation schemes is encouraged.

3.2 Clinical development

The points raised by IMI are agreed to; some of these have been taken up already, some are hard to realize. Information technology needed for the individual disease conditions, clinical populations and outcome is needed but may be available once the **IT infrastructure for clinical trials** will be in place, as foreseen in Regulation EC/536/2014. Here, a **special registry for ATMPs** should be established and made accessible, preferably extended to include products manufactured under the HE clause.
IMI could act as the driving force for the creation of an IT environment where – within or beyond the EU CT database foreseen in Regulation EC/536/2014 - sample data, preclinical and clinical research data may be managed across various academic centres and hospitals. For this purpose, it is imperative that professional database and samples handling/tracking is set up possibly through an SME. It is equally important that research data across the study are linkable and queriable, and if patient records are to be involved, the biological/clinical questions and means to get to them should be clearly articulated.

3.3 Manufacturing

We agree that, especially in this highly complex field of ATMPs, common best practices and automated production platforms will enhance safety, comparability and suitability for tech transfer of these products. A database for existing systems, product descriptions and qualifications for ATMP developers would be most helpful, similar to existing databases like ISCT's Beacon database.
When considering raw materials, alternative sources for FCS, for instance platelet lysate, are needed but may come from non-EU countries where the source of origin is not compliant with EU regulatory requirements. The provision of raw materials manufactured in the EU or in accordance with EU standards should be fostered.
Academic Institutions face similar challenges in recruiting and training ATMP experts, and curricula for GMP Training in Biosciences are missing. We encourage to develop **joint incentives with Academia for courses, curricula and career development in GMP for biosciences**.

3.4 Pricing, reimbursement and access

Similar to Industry, academic institutions depend on payment and reimbursement models to allow for products with potential benefit for patients in need to be made available on a continuous basis. The costs for the GMP environment cannot be assumed to be covered by research funding alone, and products authorized under the HE clause must be brought to the attention of health insurance providers as well. Fast track structures for reimbursement should be developed by all stakeholders together, similar to fast track structures in marketing authorization.

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CONCLUSIONS

On behalf of the EuroTech Universities Alliance, we gratefully endorse IMI's Incentive and many of the opinions and proposals laid down in the IMI Consultation Document: **Facilitating the translation of advanced therapies to patients in Europe.** The IMI concept paper on Advanced Therapies incorporates many aspects that would indeed contribute to a faster development in the complex field of ATMPs, reflecting clinical requirements, manufacturing capacities especially in hospitals and academic institutions, and the variability inherent in the nature of these innovative products and the biological materials used. We would suggest to:

- promote the idea of developing the Hospital Exemption clause further, by establishing a registry and accessible database, for example together with the EU Clinical Trial Database and within a special section dedicated to ATMPs;
- foster the development of a pre-competitive IT environment within – or beyond – the EU CT Database for an exchange of pre-clinical, quality and clinical data across academic centres, hospitals and industry;
- use the hospital exemption clause to define the interface between the process and the product in Point of Care Devices;
- develop together new concepts of specificity testing in pre-clinical development, involving the use of biobanks established in Academia and Industry;
- promote the establishment of generic tools, vectors, platforms and processes in manufacture and quality control that can be used in a modular fashion and will speed up the developmental trajectory;
- establish a database of available materials, devices, active pharmaceutical ingredients and excipients with details on product information, sources of origin and quality, under the auspices for instance of the EQPA or similar institutions;
- encourage all stakeholders including health insurance providers to develop novel models for reimbursement in earlier stages of clinical use;
- establish joint training and career development opportunities in ATMP manufacture and GMP, involving both, Academia and Industry.

Most and above all, IMI's proposal of responding to the plentitude of challenges in a pre-competitive fashion, i.e. **joint platforms under the IMI umbrella, is strongly supported**. Here, we recommend to build upon, encourage and supervise existing structures, regional clusters of certain capacities, topics, and existing collaborations between Academia and Industry, and also to expand the networks by identifying new relevant partners. A one stop-shop concept will not be useful; rather, networks are needed (and available in Academia) that maybe more appropriate to bring ATMPs faster and more efficiently to the patients in need. Institutions to be involved may include:

- the Cell therapy working party (CTWP) of the European Blood and Marrow Transplantation Group (EBMT), together with the ISCT (International Society of Cell Therapy) Europe and the joint initiative JACIE (Joint Accreditation committee, ISCT and EBMT);
- the European Qualified Persons Association (EQPA);
- existing structures established by consortia funded under the EU's FP7 Programme (ACADEMIC GMP, AGORA);
- SMEs with a broad expertise in ATMP manufacture;

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- and regional or European Clusters. Here, an attempt to merge funding concepts between the EC DG Research and the European Council of Regions may be helpful to identify, establish and support existing and emerging structures more efficiently.

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