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Innovative Medicines Initiative (IMI) JU

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Re: Consultation on IMI Advanced Therapies Concept Paper

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Dear members of the IMI program committee,

we appreciate the opportunity for public consultation on the preliminary recommendations that have been made pursuant to the 1st IMI workshop and are pleased to provide the following answers and comments to the question provided in the concept paper.

1. Have the key challenges that can be addressed through collaborative, public-private initiatives been properly identified?

We believe that key challenges that can be addressed through public-private partnerships have been identified and would like to comment on each of the preliminary recommendations:

Pre-clinical development - Model systems

We do agree that testing in relevant animal models can inform clinical translation in genetic engineering, cell-based therapy and tissue engineered products. We would like to point out however, that large animal models such as pig and dog models as detailed in the preliminary recommendations may be of particular relevance in tissue engineering to model tissue and/or organ replacement where the scale and physiology needs to be close to that of humans. However, this does not apply to cell and gene therapies, and especially not to cancer immunotherapy with genetically engineered T cells (chimeric antigen receptors, CARs, or T-cell receptors, TCRs).

For this type of therapies, animal models in pigs and dogs are of very limited use. Preferable model systems in cancer immunotherapy are xenograft models that allow engraftment of human tumor cells and human immune cells, e.g. in immunodeficient mice (1,2). It is important, however, that xenograft models in immunodeficient mice need to be ameliorated, according to the principles of the three Rs (reduce, refine, replace): i) for example, by using non-invasive monitoring tools reducing the number and suffering of animals, e.g. bioluminescence; ii) by optimizing these models through further humanization, e.g. transgenic expression of human cytokine that better support human cells; iii) and by replacing them with in vitro tissue-engineered systems when, e.g. 3D human organoids, when feasible. Alternatively, non-human primate models may be considered, but are more laborious and associated with stronger ethical concerns.

We believe that particular emphasis should be placed on the development and refinement of non-animal models. As an example, 3D human organoid models based on synthetic or physiologic extracellular matrices subsequently populated with human cells are already well advanced in their development and are being utilized by members of our group to address issues related to safety and efficacy of cellular therapies, such as CAR T-cell cancer immunotherapy.

A critical advantage is that non-animal models do not depend on specific infrastructure for animal housing and are not bound by ethical concerns. Further, they are modular and can be adapted to address specific questions, and scaled-up to enable high-throughput testing. There is strong expertise for non-animal models in European academic institutions, so this would be ideal for refinement and scale-up in a public-private partnership.

A key objective that should be pursued is to develop a ‘consensus’ panel of normal human tissue organoids for safety testing, that becomes ‘industry standard’ and is accepted by EMA and national regulators. This could be complemented by a panel of human tumor organoids for efficacy testing.

Pre-clinical development - Vector systems

We do agree that development of enhanced vectors is critical, and that the risk of insertional mutagenesis needs to be better understood and mitigated. However, it must be emphasized that so far, all cases of malignant transformation have been reported after genetic modification of hematopoietic stem cells, and no single case has been reported after transfer of genetically modified lymphocytes (such as CAR T cells). Thus, this issue is much more related to the correction of genetic disorders rather than to cellular cancer immunotherapy.

We believe this challenge can be addressed through development of advanced viral vectors that incorporate additional safety features, including suicide genes, which are well advanced in clinical development. For example, members of our group have substantially contributed to the development of a gene-modified cellular product (Zalmoxis by Molmed Spa.) that incorporates a suicide gene and has recently been conditionally approved by the EMA, marking the milestone of the first gene therapy to be marketed for a cancer indication (3). Also, the recent introduction in the clinical arena of lentiviral vectors which are less biased for integration in genetic 'hot spots' compared to older gamma-retroviral vectors, are a major step forward and this development needs to be continued in public-private partnership to ensure that large patient populations will be able to benefit.

However we also believe that the refinement of non-viral gene transfer strategies and scale-up of non-viral vector production should be pursued intensively. We would like to point out that non-viral gene transfer strategies (e.g. Sleeping Beauty-mediated transposition from DNA vectors) have recently been significantly improved in efficacy through work by members of our group and others (4). A key advantage is that DNA vectors are much easier to produce and handle, and possess a safe integration profile and reduced risk for insertional mutagenesis than lentiviral and gamma-retroviral vectors.

Further, we believe that the development and implementation of technologies that allow rapid and standardized genome integration and copy number analyses need to be fostered. Criteria to better assess the risk for insertional mutagenesis, and to qualify gene-modified cell products that are acceptable for clinical use need to be established in liaison with EMA and national regulators. Advancements in ameliorating the safety of viral and non-viral vectors could be facilitated by a joint effort between academia (strong know-how and methodologic expertise) and industry (assays, equipment and software for rapid analysis and interpretation).

Additional technologies to be further investigated include systems for regulated gene expression. Nowadays viral and non-viral vectors are based on constant expression of therapeutic transgenes under the control of strong promoters. Although for certain applications, e.g. correction of a genetic defect in housekeeping metabolic pathways, this is near optimal, for applications such as cancer therapeutics, this may result in toxicity. Recently, different systems for regulated gene expression have been described, spanning from promoters selectively activated by signals in the tumor milieu, to chemical biology approaches whether transgenes are put under control of small molecules that can be administered to patients for timewise switch-on or switch-off of therapeutic expression.

Pre-clinical development - Targeted gene editing

We do agree that genome editing holds great promise in gene therapy, and would like to highlight that gene editing can also be used concomitantly and synergistically to enhance the therapeutic index of cell-based and tissue engineered products.

We would like to point out that targeted gene editing comprises i) the editing/correction of a specific gene – often in rare, exemplary diseases, so impact on society and health care is anticipated to be low. ii) the knock-out of genes to delete certain (negative) characteristics of a cell or tissue product – this enables a large number of applications, so impact will be high. iii) the knock-in of genes at a specific gene locus – e.g. in CAR or TCR gene transfer – this also enables a large number of applications, so impact will be high. Thus, in our view, knock-out and knock-in strategies should be prioritized.

In the field of cancer immune-gene therapy, a particularly important application of gene editing is represented be the genetic knock-out of the so-called immune checkpoints (CTLA-4, PD1). These checkpoints physiologically function as “hand-brake” blockers of T-cell activation, therefore reducing the ultimate efficacy of CAR and TCR gene therapies. Recently, the first application of immune checkpoint edited CAR-T cells has been cleared by regulatory bodies in the US, allowing patients to be treated with cells edited with the Crispr/Cas9 system.

A significant concern is related to off-target effects of genome editing tools and thus, emphasis should be placed on genome editing tools with highest specificity and lowest risk for off-target effects. In this regard, Zinc finger und TALEN-based genome editing tools are preferable to Crispr/Cas9 due to their higher specificity and lower off-target effects (5).

Pre-clinical development - Regulatory considerations

We do agree that translational academic work should be conducted, whenever possible, under GLP or GLP-like conditions, and instruments to facilitate interaction and scientific advice from national regulators and EMA should be implemented. We appreciate the recommendation to establish suitable platforms under the IMI umbrella. We also agree that a very close and productive interaction with the regulatory authorities at very early stages of development is important for defining proper experimental designs. It is advisable, for example, that similarly to the US situation, fast-track procedures for clinical approval are designed and implemented, allowing a rapid translation of cell and gene therapy from bench to bedside and ultimately raising the competitiveness of the EU research and development area.

We would like to point out that academic investigators often have specific methodologic expertise but don’t have the means and infrastructure to perform experiments under GLP conditions. In contrast, such specific know-how and expertise is often lacking in industry which in turn has the means and infrastructure to work under GLP. Thus, there is enormous potential to synergize and in our view, a program that establishes GLP laboratories at specialized academic centers that are operated as a public-private joint venture would be a preferable and effective way to address this challenge. It has also to be underlined that, through this interaction, the costs of GLP experimental work should be rendered more affordable for the academic institutions, since nowadays cost is extremely high and currently prevents academia from conducting experiments under GLP.

Clinical development

We do agree that clinical development and the ability to rapidly translate novel findings from bench to bedside in exploratory studies that demonstrate safety and efficacy is of critical importance. Fast-track procedures that enable expedited clinical testing and clinical approval of ATMPs need to be designed and implemented.

We would like to point out, that there is an unmet need to define appropriate study designs and novel, appropriate endpoints for clinical trials with cell-based products. The ‘classic’ concept of phase 1 – phase 2 – phase 3 clinical trials is of limited relevance for cell based therapies, e.g. cancer immunotherapy with CAR- or TCR-modified T cells, because even very low numbers of T cells can engraft after administration to the patient, proliferate substantially *in vivo* and persist long term. Thus, a phase 1 trial to assess safety with a low dose of CAR T cells is in fact also evaluating efficacy, which is conventionally not done until phase 2 and 3.

Further, ‘classic’ concepts of pharmacodynamic and pharmacokinetic do not apply to cellular therapies, e.g. because T cells can proliferate *in vivo* and are not metabolized or cleared from the body with a pre-defined half-life. Thus, novel concepts in immunopharmacodynamic, immunopharmacokinetic and monitoring need to be developed, and acceptable standards and regulatory frameworks defined jointly between academia, industry and regulators (6).

We would like to point out that clinical data bases and registries are already being developed, e.g. through the European Society for Bone Marrow Transplantation (EBMT, Cellular Therapy and Immunobiology Working Party, Chair: Prof. Chiara Bonini). Additional efforts under the umbrella of IMI are highly appreciated and should be designed to synergize with these existing efforts.

Manufacturing

We agree that manufacturing know-how and ability is critical and also agree that academia often has specific knowledge and know how that is missing in industry. Thus, we embrace the proposal to establish a technology platform as a joint effort between academia and industry, as as well as a biophorum initiative for raw materials.

We believe emphasis should be placed on tools and technologies that enable processing and culturing cell and tissue products in closed, exportable systems to provide point of care manufacturing devices (i.e. devices that can be installed at dedicated centers where patients are treated, to facilitate logistics and ensure that cell- or tissue-products are provided to the patient in the highest possible quality, e.g. without prior cryopreservation which affects their function).

We do agree that immunogenicity is an enormous problem with third-party products, and would like to point out that the immunogenic barrier with third-party donors is high and not easy to overcome by knocking-out single genes, but requires substantial modification. This is particularly the case for cancer immunotherapy with CAR- and TCR-modified T cells.

A misconception often associated with third-party cell products is that they can be amplified indefinitely to provide an unlimited supply – which is not the case. Also from an allogeneic third-party donor only a limited amount of e.g. T cells can be extracted, modified with a CAR and expanded before T cells reach a state of exhaustion and become dysfunctional. Thus, a large patient population will still demand producing third-party products from many individual donors. An important ethical concern is, that in contrast to the autologous setting, where a patient receives his own modified cells or tissue product, an allogeneic third-party donor carries a risk of (still undetected) infection and intrinsic disease – and this demands a joint dialogue and discussion between academia, industry, regulators and the society. Thus, we believe strong emphasis should be placed on both – the rapid and standardized manufacture of autologous products, and the development of universal allogeneic products.

The development of novel tools and technologies for quality assessment and monitoring, e.g. lab on-a-chip are welcome. A joint effort between academia, industry and regulators under the umbrella of IMI should be made to define what quality control analysis need to be done, and a consensus reached on what quality is acceptable for clinical use.

Pricing, reimbursement and access

We do agree with topics 1 through 4 that have been defined for prioritization.

We would like to comment that the 'hospital exemption' is an important instrument but should not become a way to bypass regulatory pathways and IP. Clearly, the focus should be on an expedited, fast-track approval process.

We would like to point out that there is a need to define novel reimbursement models for ATMPs: novel gene and cell therapies are complex and often entail years of preparative work and expensive manufacturing for which there is no reimbursement. Models are needed that provide reimbursement also during early clinical developmental phases, prior to clinical approval, to encourage the clinical development of such products.

Further, there is a need to build outcome databases that are rooted in pharmacoeconomics (see recent IMI backed by Celgene and others on new therapies for hematologic malignancies, myeloma, myelodysplasia). This will guide reimbursement based on outcome (reimburse per year of life extension).

2. Which of the proposed potential initiatives should be prioritized?

In our opinion, the following topics should be pursued with the **highest priority**:

-Pre-clinical development - Model systems (Non-animal models; Small animal xenograft models)

-Pre-clinical development - Vector systems (Non-viral; Lentiviral vectors with enhanced safety)

-Pre-clinical development - Regulatory (GLP – Joint academia-industry facilities)

-Manufacturing (Closed system; Point-of-care devices; Autologous products)

-Manufacturing (Genetic re-engineering of third party & universal allogeneic cells)

-Reimbursement (Long-term follow-up requirements & cost; Multi-year payment mechanisms)

In our opinion, the pre-clinical development of large-scale animal models (e.g. pigs and dogs) should be pursued with the **lowest priority**.

3. Are any areas missing?

We have identified 2 pre-clinical areas that should be included in to the work program and recommendations:

-Identification of target antigens for cell-based cancer immunotherapy.

The number of validated target antigens for CAR and TCR-modified T cells is limited and novel antigens could be rapidly identified and validated in a joint effort between academia (specific expertise in particular diseases, access to patient material) and industry (technology for high-throughput testing).

-Identification and validation of target genes for gene knock-out or gene editing approaches.

A joint effort between academia (specific know-how and expertise) and industry (technology for high-throughput sequencing and testing) could rapidly identify genes that if knocked-out lead to the highest gain-of-function in a gene-edited cell or tissue product.

4. What are the key European or national initiatives that IMI shall synergize with?

We recommend ensuring that IMI synergizes with existing efforts of establishing registers and databases on the use of ATMPs, e.g. the EBMT database.

Further, patient associations and advocacy groups should be involved in all efforts of IMI to ensure participation of all stakeholders in the EU.

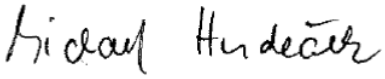
We are convinced that IMI has an excellent potential as a platform for enhancing ATMP research and development. We hope that our comments and suggestion are deemed beneficial and will be considered in the IMI ATMP portfolio of projects.

We would be delighted to join the 2nd IMI workshop later this year and contribute our expertise in one of the expert panels.

Should you have any questions, or desire any additional information, please do not hesitate to contact us.

On behalf of the group of contributors,

Sincerely,



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