Health by Advanced Therapies

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Strategy paper on the benefit and requirements of mechanistic side studies

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1. Deliverable's description

This document outlines the importance of mechanistic side studies and monitoring of therapy response, i.e. biomarkers, in patients for a better understanding of Advanced Therapies. This is important not only for the future development of better therapies, particularly in the area of clinical trials, but also, crucially, to ensure the safety of the therapy-receiving patient. Further outlined in the document are the strategies by which RESTORE plans to ensure refined translation, through implementation of a biomarker research and technology platform as a means to de-risk Advanced Therapy development.

2. State of the Art

Advanced Therapies are a disruptive innovation challenging the traditional added-value chain of drug development at all stages from drug discovery to the supply of products to patients and business models. This also includes the challenges in product characterization, including product release criteria, as well as pharmacodynamics and pharmacokinetics.

There are no well-defined standards on how to characterize the products and patient responses to ATMPs. In other words, the biomarker program is changing from product-to-product. Both the product release criteria and patient monitoring markers require high quality standards, must be robust and well validated.
Currently, cellular products are – in addition to traditional QC criteria (sterility, vitality etc.) - mostly characterized by common flow cytometry, and some functional assays adapted to the proposed mode-of-action (e.g. cytokine secretion, specific killing of target cells, cell differentiation). These release parameters are rarely published by the manufacturers, at least not in detail. Some information can be found in a few papers from academic groups.

Although the majority of cell and gene therapy studies are accompanied by mechanistic side studies, such as immune monitoring, the data are hard to compare between the studies.
In addition to standard safety parameters, the majority of biomarker studies focus on the fate of adoptively transferred cells, surrogate biomarkers of clinical response, and markers of adverse effects (e.g. cytokine release), and detection of immunogenicity of the cell or gene product. As is the case for product characteristics, academic groups publish most of the data on mechanistic side studies.

3. Challenges and Limitations

There is a high need for biomarker studies – both for ATMP product characteristics and patient responses.

Why do we need biomarker analyses?

In contrast to conventional drugs, ATMP are frequently living drugs with complex, multiple biological activities, which can change depending on the in vivo conditions. As a result neither conventional simple product characteristics, such as purity, sterility etc., nor are conventional pharmacokinetic and pharmacodynamic (PK/PD) and safety tests sufficient.
Currently used routine tests have several limitations with respect to addressing the following challenges:

- Analysis of cell product functionality - when superficially characterized, apparently identical products can show completely different PK/PD in vivo, and level and duration of response to the ATMP can be due to variability in product quality and not only to patient responsiveness.
- Safety data – Advanced Therapy products raise several challenges regarding safety, which are dependent on the individual product category, such as cytokine release, immunogenicity, over-immunosuppression, and tumorgenicity to name a few.
- PK/PD data – "living" drugs have completely different dose-related effects, PK, and a complex PD. For mode-of-action a deeper knowledge of PD is essential, also to better understand the level and duration of response
- Surrogate markers – Advanced Therapies make the claim of sustained effectiveness or even curing diseases, however, this can only be proven by extremely long follow-up observations. Well validated surrogate markers could provide faster, at least preliminary results
- Stratification marker – As Advanced therapies are costly, the selection of the right patient and the right time point of therapy is a key for cost-effective therapy

Because of these limitations, many questions relating to surprising results of clinical trials cannot be answered. Some examples:

- Why did almost all pivotal phase 3 trials applying MSC products fail despite promising data from early clinical trials? The hypothesis: scaling-up of manufacturing is not sufficient to produce comparable products, and product characterisation by consensus parameters do not guarantee functional identity. Moreover, patient responses were also poorly characterized.
- Why do MSC products show effects in so many clinical indications? Are the proposed immunomodulatory properties the key mode-of-action and should we optimize the MSC products for this? The hypothesis: the anti-proliferative effects of MSC on immune cells in vitro is less relevant to the observed in vivo effects. The mode-of-action is mostly poorly understood
- Why do the results of autologous T cell products, including CAR-T cells, show high variability of clinical response in patients? The hypothesis: the composition of the individual (CAR) T-cell product strongly varies with respect to the proportion of less and more differentiated T-cell subsets, which has a major impact on the sustainability of biological effectiveness.
- Why does in vivo gene therapy using AAV technology fail in some patients even if they are screened for seronegativity against the respective AAV strain? The hypothesis: some patients have preformed T-cell immunity to the AAV (in absence of humoral sensitization) resulting in stimulation of memory T-cell response.

An adequate biomarker program can help to guide the decision after early clinical trials to move forward into risky and expansive late-stage trials or to return to the bench and back to bed in an iterative way in order to improve the product and approach, called "refined translation" – a key element of de-risking and accelerating clinical development of Advanced Therapies. (Fig.1)

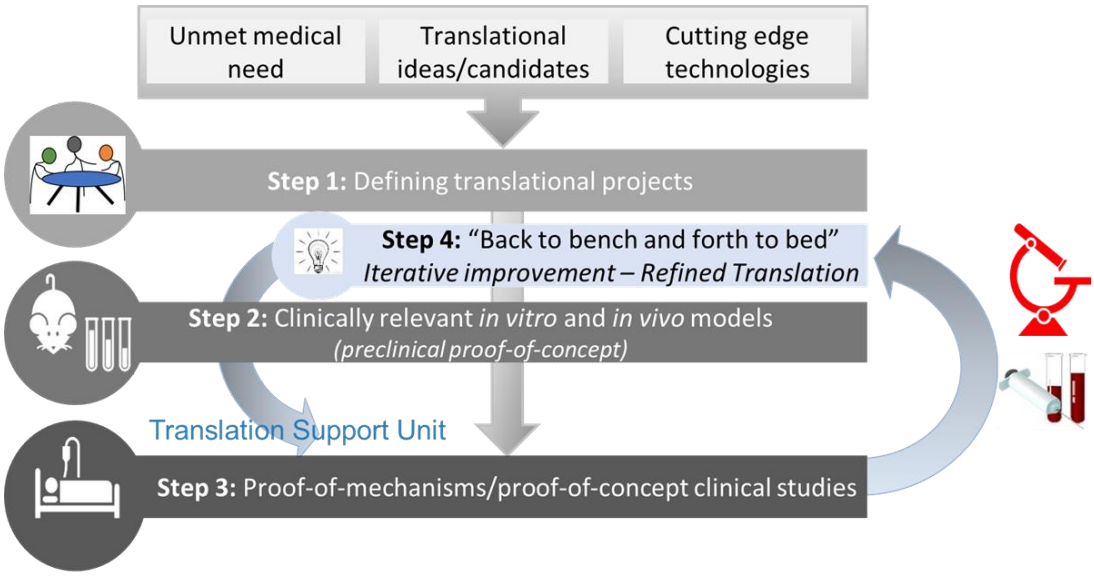

Figure 1 Biomarker Analyses play a key role for successful Refined Translation to de-risk and accelerate Clinical Development of Advanced Therapies

4. Putative solutions

Recent technology developments, such as molecular analysis tools using Next-Generation Sequencing (genomics, transcriptomics, epigenomics, T-cell receptor sequencing single-cell analyses), multiscale proteomics (MS, DIGI-West, multi-parameter flow cytometry and mass cytometry) and metabolomics, as well as new functional assays, have opened new opportunities to address these issues. This offers many opportunities but also result in even higher hurdles to harmonize the test systems.

RESTORE recommends:

- To build-up a biomarker research & technology innovation platform for Advanced Therapies in Europe linked to the Academic Translational Hub structure mentioned elsewhere (D4.2).
- Generate a tool box of biomarkers for cell product analysis (with high relevance for mode-of-action) and patient response monitoring (PK/PD, safety, MoA, surrogate) (Fig.2).
- One-stop-service offering off-the-shelf validated biomarker panels and advice for the development of new biomarkers for monitoring therapy response and patient stratification (in collaboration with translational centers of excellence and industry partners)
- Refined Translation (iterative improvement at early clinical trial stage based on mechanistic side studies)
- Publishing open-access data for understanding failures and success and offering opportunities to develop targeted assays

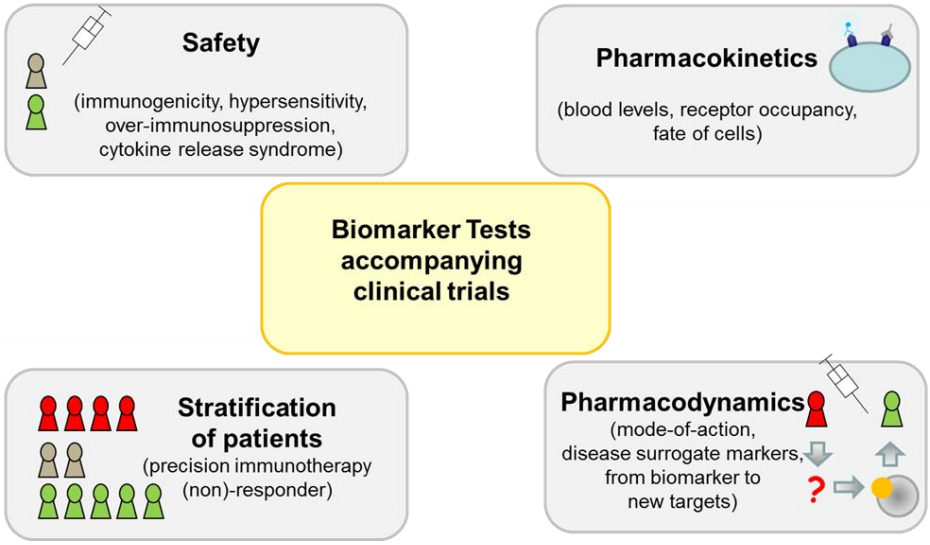

Figure 2 Biomarker portfolio for mechanistic side studies

5. Challenges for RESTORE

- Need for a virtual biomarker expert team supporting the building-up tool box available for RESTORE
- Engagement of diagnostic and technology industry as well as contact research organisations (CRO) with a focus on biomarkers is needed

6. Summary

There is a high need for in-depth Advanced Therapy product analyses as well as patient response monitoring to de-risk and accelerate the clinical development of novel ATMPs. RESTORE propose the implementation of a Technology and Research platform "Biomarkers" within the network of Hubs to bring Europe in the position of a world-wide leader in this field.

7. References

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