Health by Advanced Therapies

D 2.8
Strategy paper on new clinical indications
Public

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1. Deliverable's description

This deliverable outlines the RESTORE view on the most promising new indications in which Advanced Therapies can provide a huge benefit. Briefly these indications fall within the areas of i) improved genetic diagnostics of rare diseases and availability of stem cells for gene editing to cure, ii) new immunotherapeutic options, iii) tissue regeneration vs. tissue replacement approaches.

2. State of the Art

In principle, there are two ways of pursuing regenerative medicine: i) support of endogenous regeneration, and, if this is not feasible, ii) replacement strategies.
The support of endogenous regeneration can be addressed by direct support (recruitment, stimulation, reprogramming) of parenchymal stem/progenitor cells (growth factors etc.), and indirectly by reshaping undesired inflammation/immunity (immunoregulation/immune reconstitution) or modelling extracellular matrix (ECM "code").
Tools of advanced therapies for the endogenous regeneration approach (please note that non-ATMP approaches also exists that are not outlined here):

- cell therapy (MSC, MSC-like cells, Treg, Mreg …+/- gene modification) or cell-derivatives (extracellular vesicles/exosomes),
- combined products (e.g. cells + scaffold, theragnostic cellular devices for release of growth factor combinations),
- *in vivo* gene therapy (delivery of growth factors, RNAi…)
- Combination of *ex vivo* pre-grown micro tissues (tissue engineering) with *in situ* formation of larger tissue structures in the local environment together with additional support of endogenous regeneration ("triggered" endogenous regeneration)
- Replacement strategies of irreversibly injured or disturbed organs/tissues/cells reach from organ transplantation, and *in vitro* engineered tissues to *in vitro* (gene-manipulated adult stem cells) or *in vivo* gene therapy approaches.

Although few ATMP products have so far been approved (about one dozen in EU), mostly for rare diseases and haematological cancer, there are more than 1,000 clinical trials running covering a broad portfolio of medical indications (Fig.1).

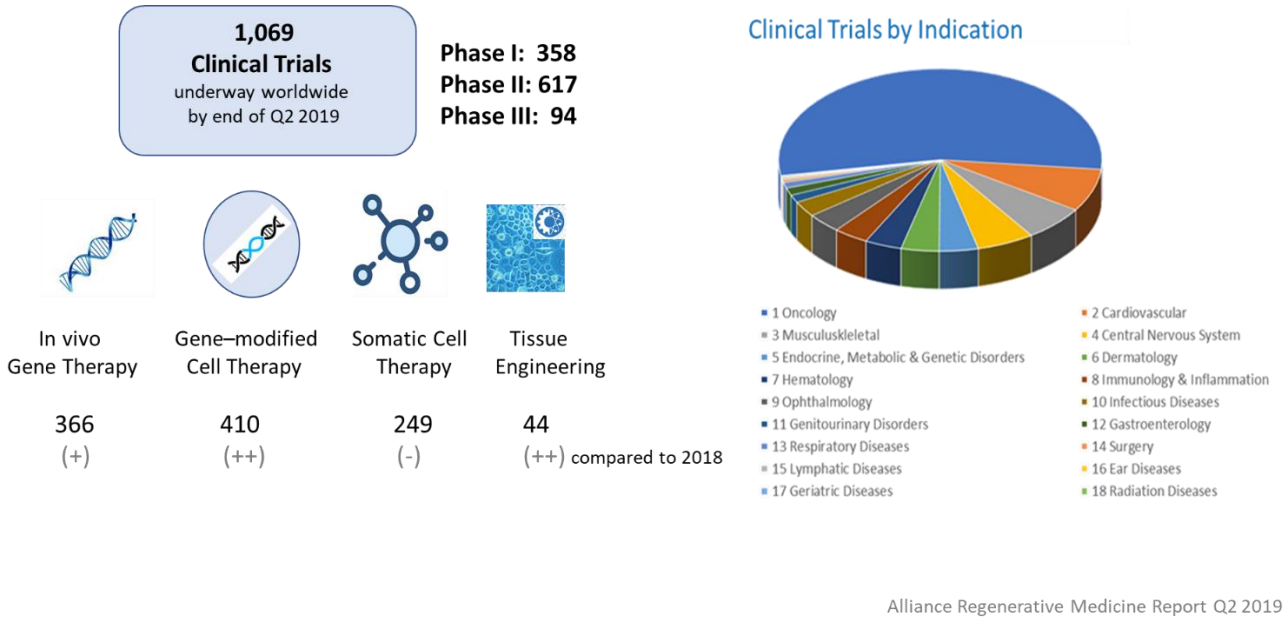

Fig. 1 Overview on ongoing clinical trials worldwide in Advanced Therapies

More than 60,000 patients worldwide have already received Advanced Therapy Products.

3. Challenges and Limitations

Although the recent few years were very successful in launching new products on the market, there still many challenges and limitations.

- The number of approval trials is quite low in comparison to early-stage trials (<10%)
- Late stage trials are increasingly biased for rare diseases and oncology

This is mainly due to:

- insufficient product supply chain and delivery for late stage trials
- lack of consistent manufacturing
- many developments driven by academia => limited resources for costly late-stage phase IIb/III
- common disease indications increase the challenge of manufacturing and supply chain
- industry is currently focusing on low hanging fruits (rare diseases, haematological cancer) to show PoC that advanced therapies are feasible as a business concept
- Mode-of-action for anti-cancer immune cell therapy is more clear than complex support of endogenous regeneration or multicomponent tissue engineering
- Lack of adequate source of stem cells for non-haematological diseases
- Less promising data from some early trials, e.g. solid cancer
- Negative health-economic assessment or business analysis mainly because of high costs of manufacturing

Moreover, several late stage clinical trials in distinct indications failed after promising early clinical stage or individual case treatment data, particularly in the field of mesenchymal stromal cell (MSC) therapy.
The lack of efficacy in later stage trials was partly due to:

- poor understanding of the mechanisms of insufficient endogenous regeneration, particularly in aged and diseased population

- missing biomarkers to identify patients where endogenous regeneration is still feasible and which approach might be the best one
- lack of using biomarkers to define the both right time point for therapy and also to monitor and predict response to treatment
- Imprecise concepts in biomaterial development for improved delivery, mechanical stress response etc.
- lack of predictive preclinical *in vitro* and *in vivo* models – currently used models have several limitations
- wrong targets , e.g. of anti-cancer therapy
- insufficient knowledge about the properties and functionality of the cell product in relation to the disease

4. Putative solutions

- Need for suitable medical indications with high medical need and clear understanding of the pathogenetic background
    - improved genetic diagnostics of rare diseases to identify new targets and availability of stem cells for gene editing to cure
    - new immunotherapeutic options for supporting regeneration in both directions - immune restoration (cancer, hematopoietic stem cell transplantation, infections) and immune modulation (targeting undesired immune reactions)
    - tissue regeneration vs. tissue replacement approaches
- Early health-technology assessment (HTA) to develop suitable business models
- Improved preclinical models with higher predictive value, e.g. human-on-the-chip technologies
- Centres of excellence with strong research capabilities to use the expertise from established Advanced Therapies for further improvement and for extension to other new indications and application of refined translation for de-risking
- Define “universal”/ “off the shelf” cell products applicable as “master” cell products with minor modification for different indications
- Strategy to maximize efficacy of cell derivatives (i.e. microvesicles/secretome) and combinations with biomaterials
- Smart manufacturing of “master” (“blueprint” backbone products) cell products

5. Where do we see the most promising medical indications?

a) Cancer

The promising data and first marketing authorizations for anti-haematological cancer cell products enormously boosted the field of cellular immunotherapy. Analysing the last two years of the clinical trial statistics show the most dramatic increase in this field. Remarkably, most early clinical trials using novel approaches are happening outside Europe – Europe is losing ground.
RESTORE sees the therapy of solid cancers as the most promising field due to the high unmet medical need, high incidence/prevalence, many adverse effects by gold-standard therapies, high financial burden of society by current therapies. However, this field has also several additional challenges:

- The most successful CAR-T therapy cannot be easily transferred from hematologic cancer to solid cancer as tumour-specific targets do not exist and current targets also target healthy tissue, which raises big safety issues (not comparable with e.g. targeting CD19 which eliminate only healthy B cells)
- The use of tumour epitope-specific TCR-transgenic T cells has limitations in the broad application to all patients (HLA restriction)
- The solid cancer microenvironment inhibits immune activation (immune evasion) – so targeting solid tumour antigens alone will not be sufficient
- Homing of T cells into the solid tumour is not automatically a given
- The delivery of sufficient number of products for "low incidence" haematological tumours is already a challenge - how can this issue be solved for a common tumour entity?

Therefore, this field need focused work in networks to address the challenges that are outlined in other deliverables, such as:

- Target antigen finding
- Improved fitness and homing of the cell products
- Improved and cost-effective manufacturing (point-of-care, autologous in automatic systems, serum-free conditions, off-the shelf production of allogeneic products, e.g. derived from iPSC)

b) Immunoregulation

There is an increasing prevalence of immune diseases (>10% of chronic diseases) with high financial burden: >100 billion €/a in the EU. In addition, undesired immune reactions are the critical roadblock for replacement interventions, such as organ and cell transplantation, *in vivo* gene therapy, and severe infections, like Covid-19.

Current therapies target both- the "bad and good guys" that results in the need for chronic immunosuppression with adverse effects at a high costs. Reshaping undesired immune reactivity by adoptive transfer of regulatory T cells (Treg) is a very promising new option (Fig.2).

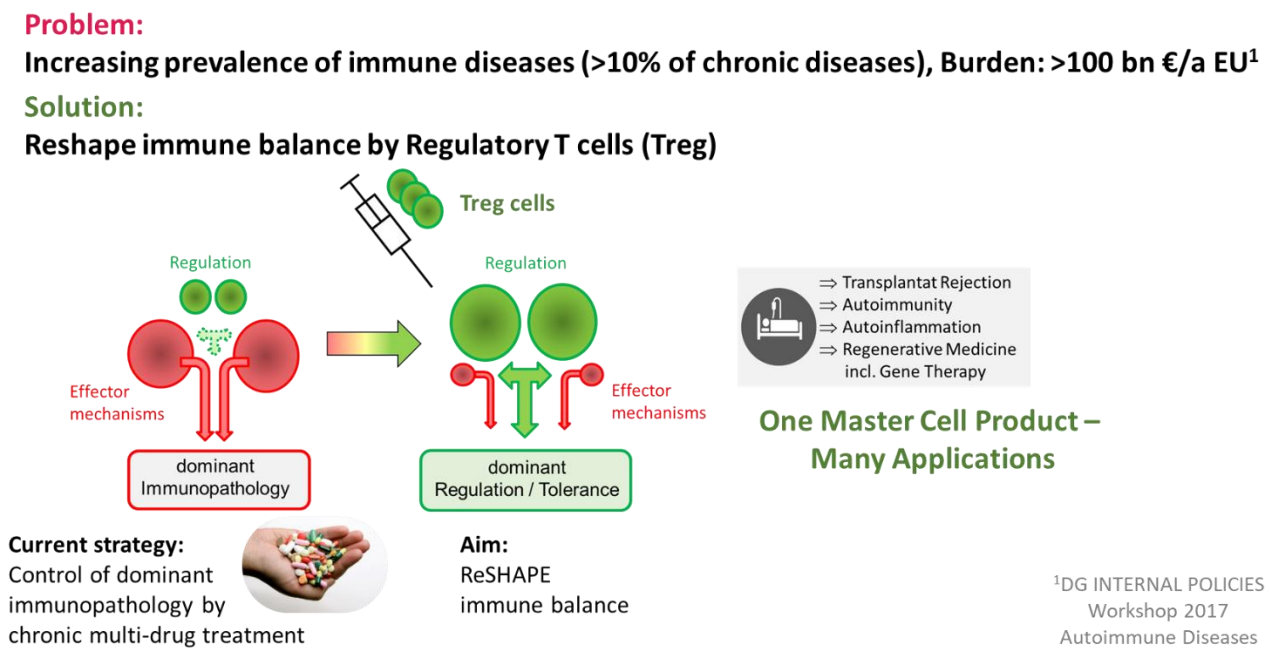

Fig. 3 Reshaping immune balance by regulatory T cells

After the encouraging data from first clinical trials using 1st generation Treg in transplantation and some other diseases and the progress in the development of next-generation Treg, RESTORE sees a big future in this field.

c) Rare Diseases

Rare diseases are not rare at all. Many patients are affected by a rare disease, but by different rare diseases. About 30 million people in Europe and 300 million people worldwide are affected by one of over 6,000 distinct a rare diseases (Fig.3)

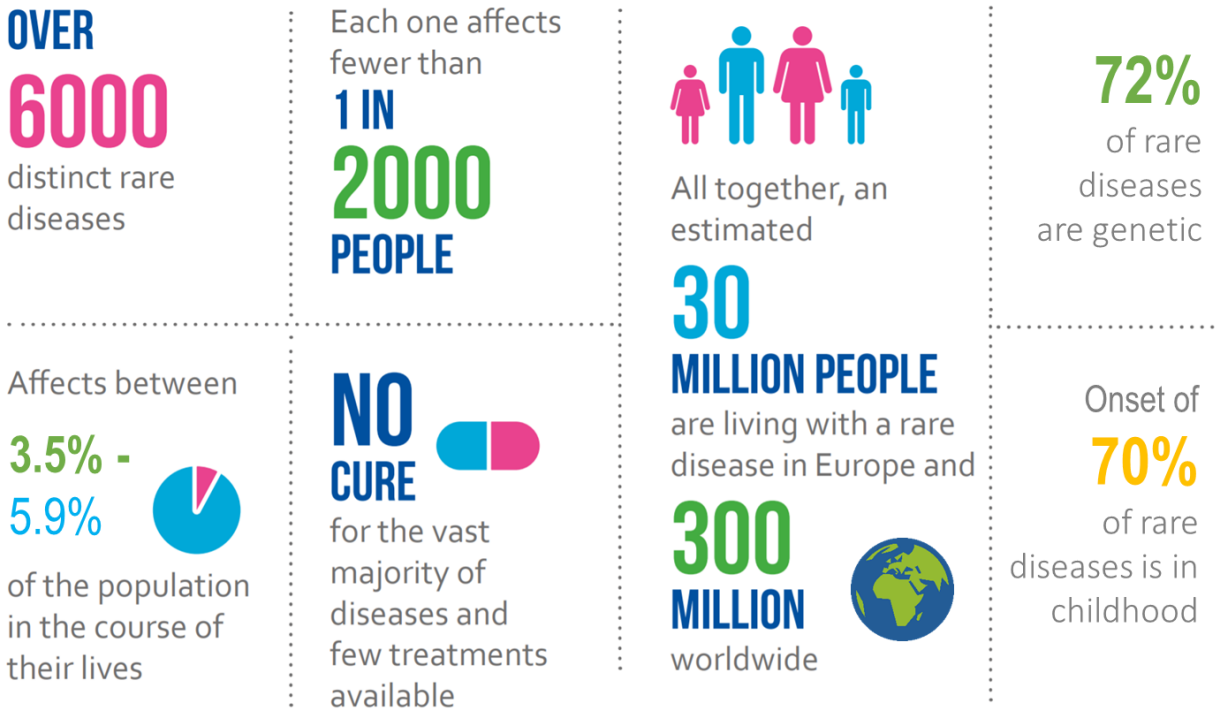

Fig. 3 Rare is not rare (provided by EURORDIS)

With the new tools of genetic analyses (whole exon, whole genome NGS etc.) the cause of more and more rare diseases can be decoded. This allows highly specific targeting of genetic deviations/errors in relevant adult stem cells to "cure" the involved tissue, e.g. haematopoiesis. The data for curing haematological diseases or some skin diseases by *ex vivo* "gene repair" are very promising. Limitations are related to the high costs of this procedure and the absence of GMP-compliant methods for isolation and expansion of adult stem cells from other tissues, but it is improving. Moreover, the iPSC approach allows for the generation of almost all tissue cells – a gene repair would be easily feasible (iPSC as a cell source are discussed in more detail in D2.2). Similarly, genetic diseases related to insufficient secretion of factors, e.g. for blood coagulation, can be corrected by *in vivo* gene therapy using AAV or gene editing.
RESTORE sees investment in cell-based gene therapy for further haematological diseases, liver and muscle diseases as well as a broader application of AAV gene therapy by solutions for the immunogenicity problem and steering of vector expression as a promising area.

d) *In Vitro* Tissue Engineering

Tissue Engineering has been in use for decades, particularly for mesenchymal tissue replacement. Recent progress in targeted *in vitro* tissue engineering combined with biomaterials, advanced imaging and highly personalized 3D-printing of matrix and cells offer new therapeutic options.
RESTORE see the most interesting fields in:

- Cardiosurgery (e.g. valves, vessels)
- Restoration of tissue injury post-cancer therapy
- Acute trauma to prevent chronification

6. Summary

There are a huge number of putative medical indications for Advanced Therapies. After intense discussion and analysis of literature, RESTORE favours the medical indications: solid cancer, undesired immune reactions (transplantation, autoimmunity, severe infections and beyond), selected rare diseases, combined tissue-engineering products. The success will be closely linked to technology developments (see other chapters).

7. References

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