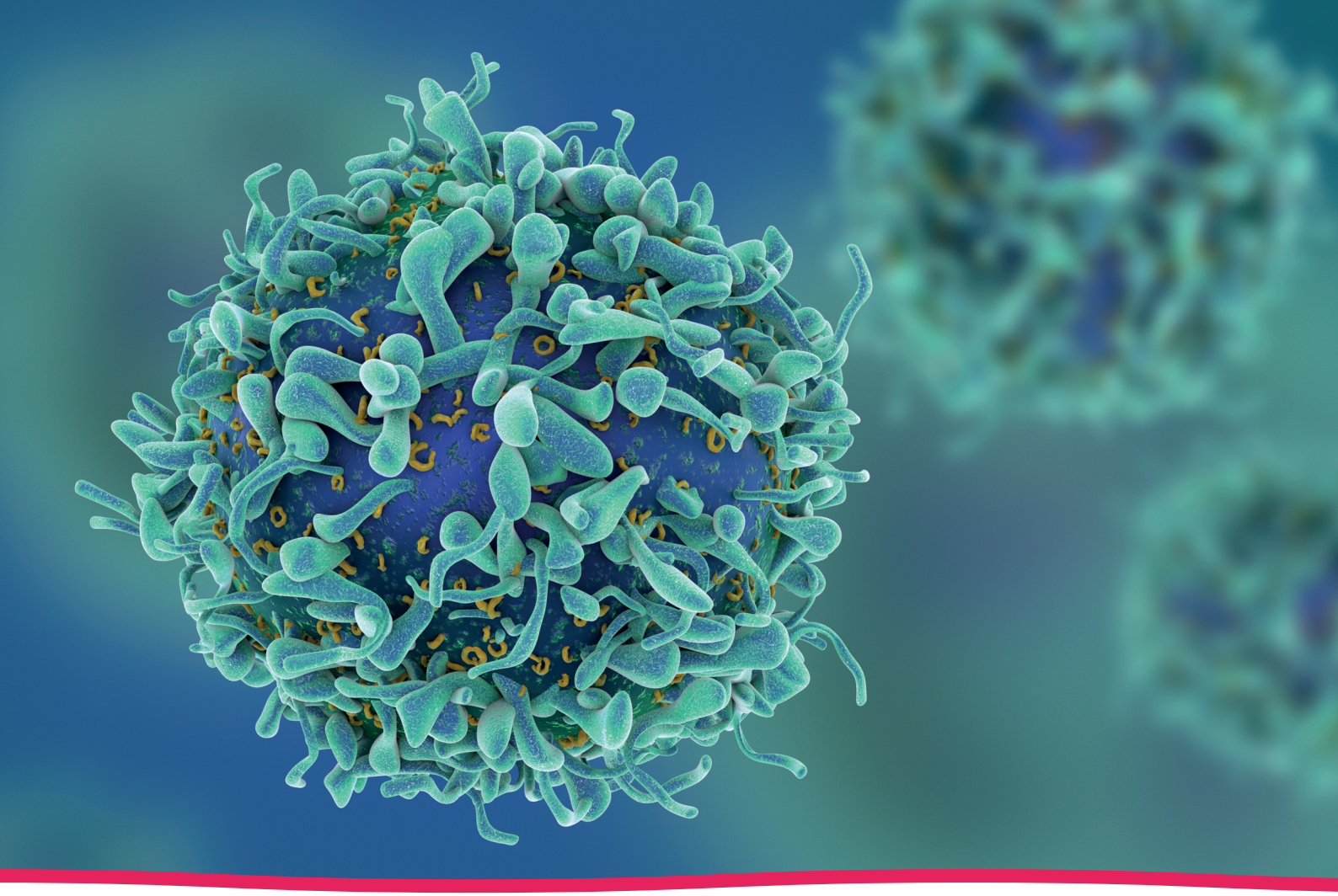


RESTORE

Health by Advanced Therapies

Position Paper

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 820292.

WHY must Europe invest more in Advanced Therapies?

The **increasing prevalence of chronic diseases** and multi-morbidity due to demographic factors represents a high socio-economic burden for Europe. The direct health costs increased by 50% during the last decade and reached €1,526bn in 2017, a staggering **9.6 % of Europe´s GDP** (EU Health at a Glance 2018) (Fig.1).

As current therapies rarely cure, but merely fight symptoms, life-long treatment is required. This results in potential adverse effects, limited quality-of-life, and increasing costs for society. Increasing health costs or restricting access to new therapies to a few wealthy patients are not solutions for a stable European society.

The ultimate approach therefore, is to tackle the problem of affordable medicine by disruptive research and breakthrough innovations. There is a high need to achieve sustainable improvements or even to cure chronic diseases. **Advanced Therapies**, in Europe categorized as Advanced Therapy Medicinal Products (ATMP), are often referred to as 'living drugs', and could be the solution to sustainable improvements in chronic disease treatment. They can be specifically produced for individual patients and if feasible, they can also be produced as off-the-shelf products from allogeneic donor sources.

Advanced Therapies are game changers that open up transforming therapeutic opportunities to "restore health" instead of just "treating symptoms" (Fig.1).

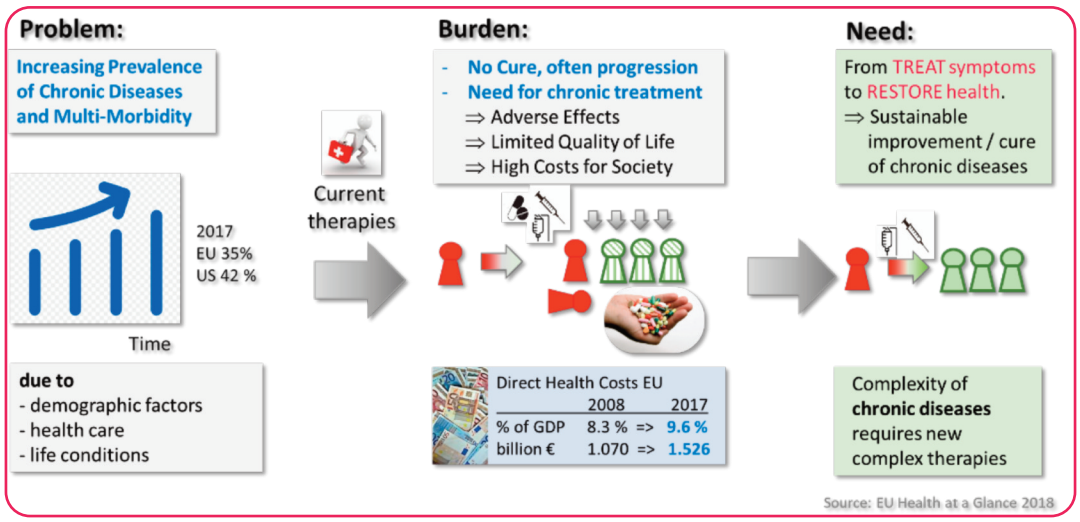


Fig.1
Chronic Diseases - A Burden for Patients & Society

Advanced Therapeutic are no longer merely fiction but becoming a reality - cures exist for rare genetic diseases as well as for common immune diseases, cancer, and tissue injury. Some products are already on the market, mostly for rare diseases and specific cancers. However, **up until now only a few thousand patients worldwide have benefitted from this new category of precision medicine.**

"Living" drugs challenge the "tried and tested" paradigm of drug development at almost all Technology Readiness Levels from drug discovery to reimbursement. At the dawn of such a trailblazing change, obstacles and roadblocks abound (Fig.2).

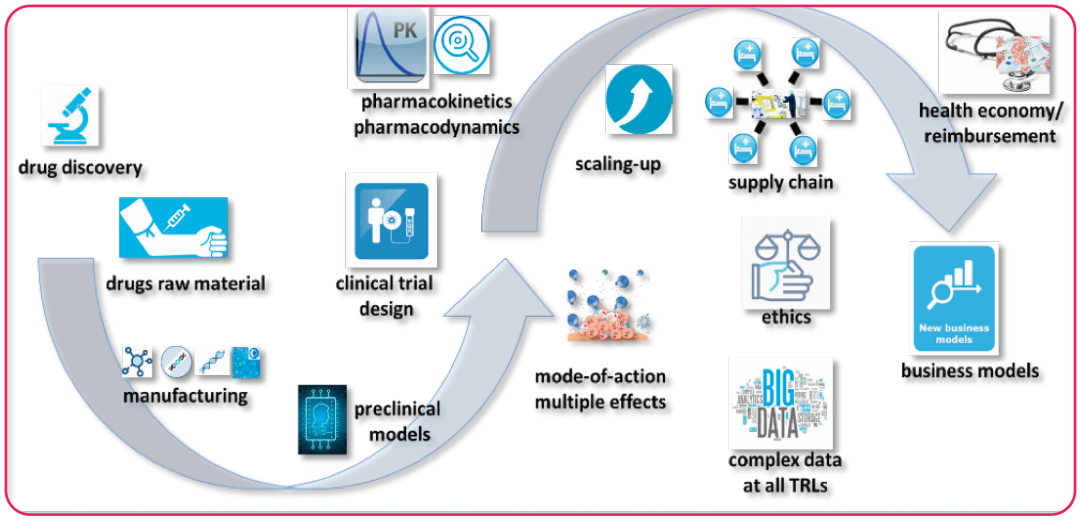


Fig.2
„Living" Drugs (ATMPs)
a disruptive innovation
shattering current paradigms

Consequently, it is not surprising that the recently approved ATMPs required a long (about 20 yrs each) and costly added-value chain and the complex manufacturing and development processes resulted in high product prices (Fig.3)

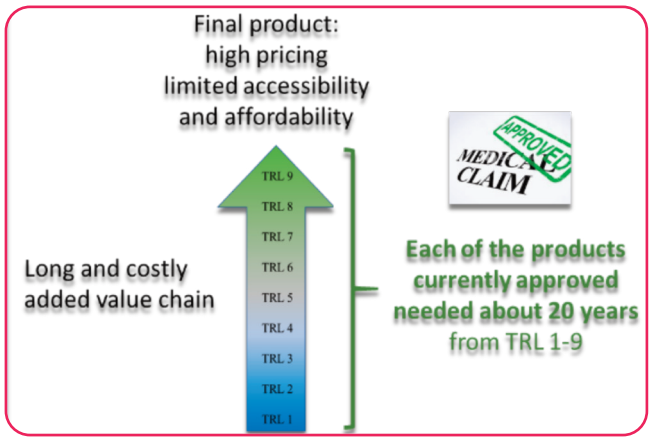


Fig.3
Long and costly added-value chain prevented no more than a dozen or so ATMPs from being approved to date

Some products are very successful and are revolutionary in their field; however, other products have shown disappointing market performance leading to their withdrawal. The available evidence for quality, safety, and efficacy at product launch can play a crucial rule in their market success (Elsallab M et al. Mitigating Deficiencies in Evidence during Regulatory Assessments of Advanced Therapies: A Comparative Study with Other Biologicals. Mol Ther Methods Clin Dev. 2020 Jun 3;18:269-279. doi: 10.1016/j.omtm.2020.05.035.).

There is a high demand for more Advanced Therapy products that can be developed cost-effectively and in a timely manner to enable the use of Advanced Therapies by millions of EU citizen.
The pace of progress has accelerated over the last few years, notably in the US and Asia **but much less so in Europe**, despite its high innovation potential and demonstrable success in the past. The EU can decide whether to be merely a **payer** for revolutionary (and expensive) drugs developed elsewhere that might not be affordable for all patients in need, or to become a **player**, by launching a virtuous circle where drug expenditures by the healthcare systems stimulate economic growth in a research and innovation intensive sector such as red biotechnology.
To reach the aim of being a significant player, clinical development needs de-risking and accelerating. Therefore, there is a need for a focused, determined and well-funded large-scale research initiative in Europe to create a true **European Research Area on Advanced Therapies**, combining the power of small, scattered teams for disruptive science and technology with larger structures for developing recent successes into innovation with impact (Wu L et al. Nature 2019, https://doi.org/10.1038/s41586-019-0941-9). That was the motivation to found **RESTORE**, a European, Horizon 2020 funded network from the former **FET-flagship competition**.

RESTORE aims to establish a sustainable European ecosystem integrating transdisciplinary research, clinical centers, pharma, biotech and enabling technology-providing industry, regulatory bodies, patients, and public society to overcome technological and regulatory roadblocks in Europe for the broad implementation of Advanced Therapies with wide-ranging impacts on patients and society (Fig.4).

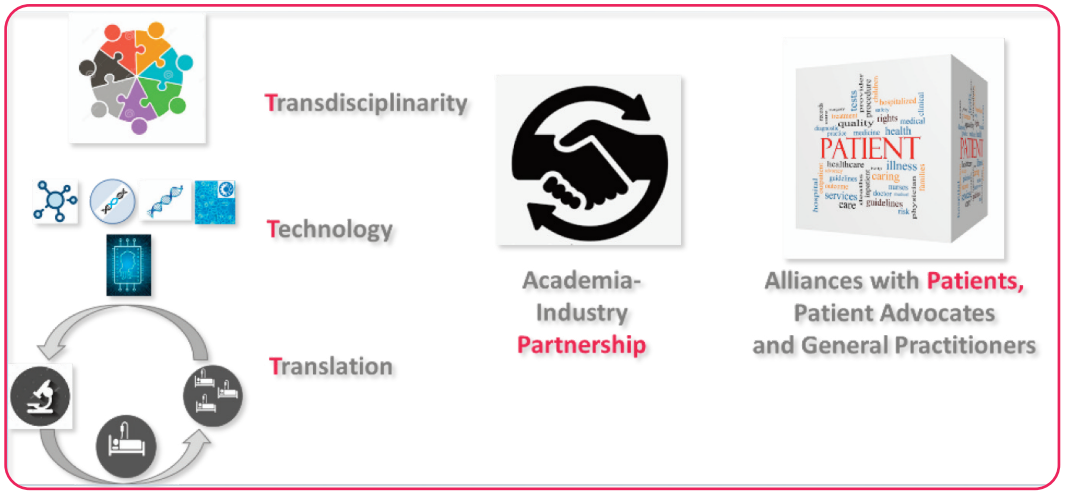
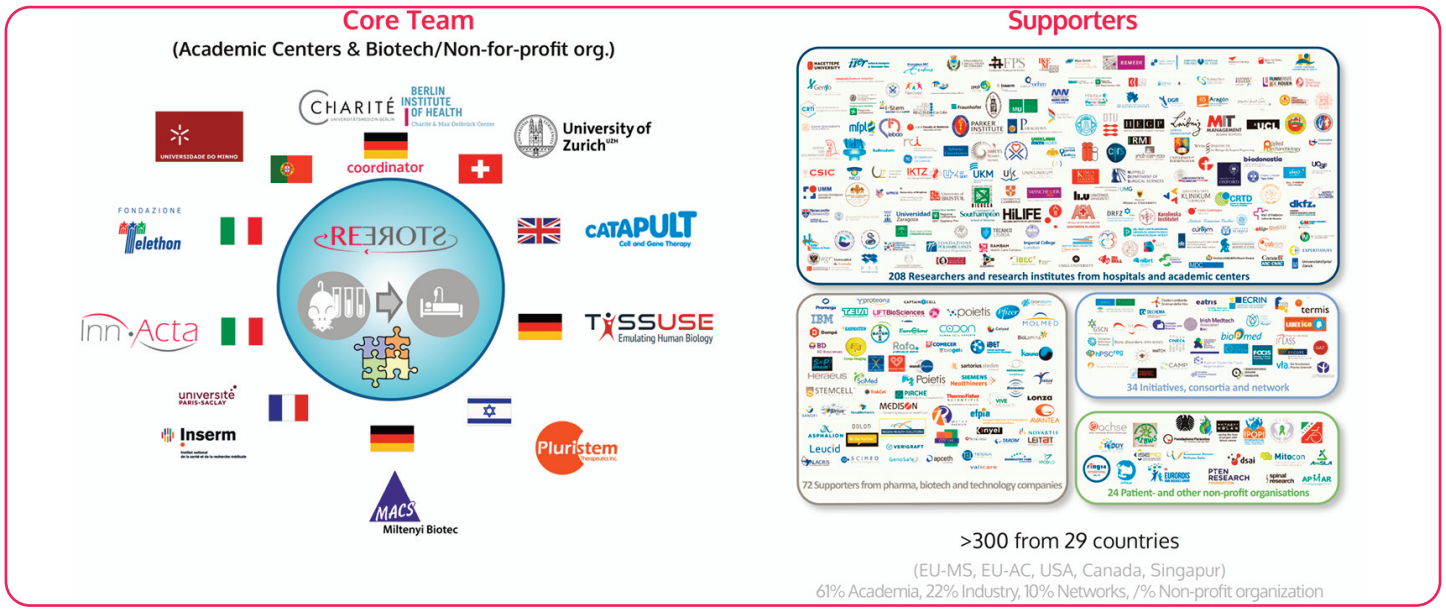


Fig.4
Need for broad networking and patient-centered approaches

WHO is behind RESTORE?

As part of WP1 of the preparatory phase of the H2020 large-scale research initiative (LSRI), we commenced in laying down the infrastructure necessary to establish such a European ecosystem: a broad RESTORE community with sufficient representation of all relevant stakeholder groups. This continued on-going effort has so far resulted in a pan-European network comprising 338 players with diverse expertise in the medical field in general and in Advanced Therapies in particular. RESTORE is currently coordinated by a core team of ten partners from academic translational centers, Biotech and non-for-profit organisations (https://restore-horizon.eu) (Fig.5).



The RESTORE network enthusiastically and actively engaged with the creation of the RESTORE roadmap for Horizon Europe. This resulted in participation of 256 supporters, 26-118 contributors in each of the 17 working groups, actively contributing to the groups via an online file sharing system and during numerous Face-to-Face (F2F) meetings. The results of this work are published as open access content on the RESTORE website, and further documents will follow as the team is continuing to work together even after finishing the official H2020-funded preparatory phase of the LSRI (https://restore-horizon.eu).

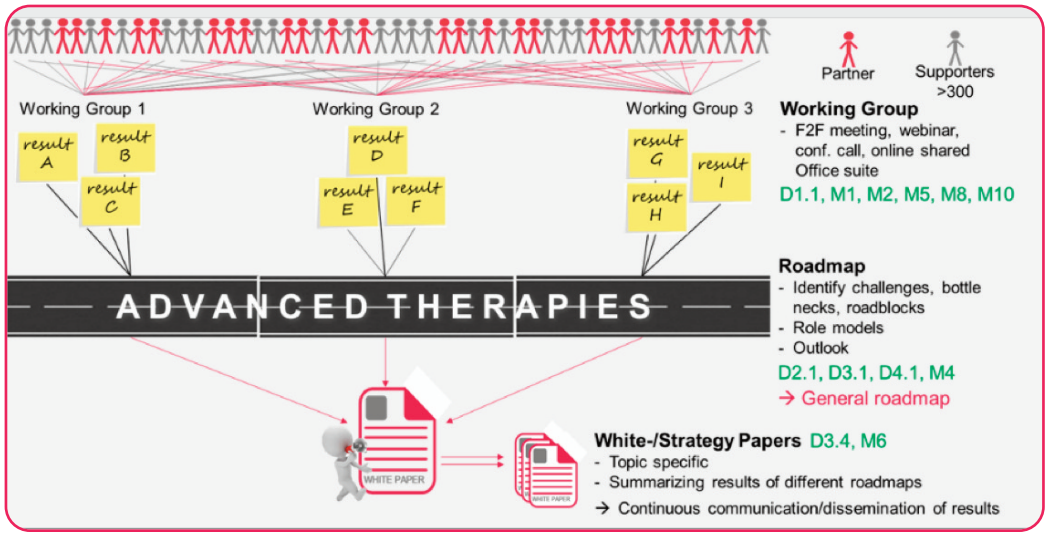


Fig. 6 Active contribution of the whole RESTORE community to the tasks of the 17 Working Groups in refining the roadmap.

This document presents the **key elements of WHAT RESTORE addresses and HOW.**

WHAT does RESTORE address?

Objectives:

- To deliver a pipeline of revolutionary Advanced Therapy Medicinal Products **"developed and made in Europe"** and transform the disruptive promise of Advanced Therapies into reality to cure chronic diseases
- To make them **accessible and affordable as "standard-of-care" for every patient in need**
- To make **Europe a spearhead** of Advanced Therapies in Science, Clinics and Biomedical Industry
- To make use of the **enormous socio-economic potential** of novel breakthrough-therapies in Europe

Key elements to achieve these aims and to overcome roadblocks are:

1. Coordination and support action for all efforts.
2. Combine the benefits of thinking SMALL and BIG to unify disrupting inventions and innovation.
3. Broadly accessible Technology Research and Innovation (TRI) platforms and Cross-theme platforms - Collaboration replaces competition.
4. A Network of Academic translation incubators (Hubs)
5. New forms of Private-Public-Partnerships (PPP) and support of SMEs

1.) Coordination & Support Action

RESTORE sees a strong need for a coordination and supporting structure. A consortium with transparent and dynamic governance should provide support, guidance, education, advice, networking, and expertise for the development of the field in Europe. It should be led by a board of max. 30 persons with representatives of academia, industry and patient advocates (Fig.7). The advantages would be:

- To have a sounding board for the European Commission and National Sponsors
- To interact with regulatory authorities to discuss challenges of new technologies early on
- To make European Research Area on Advanced Therapies visible to decision makers and the public as well as internationally visible
- To better realize patient interests
- To organize high-level education and training
- To better coordinate and interlink different activities at the levels of research and innovation actions (RIAs), Network of Hubs, Technology Research & Innovation platforms, and Public-Private-Partnership.

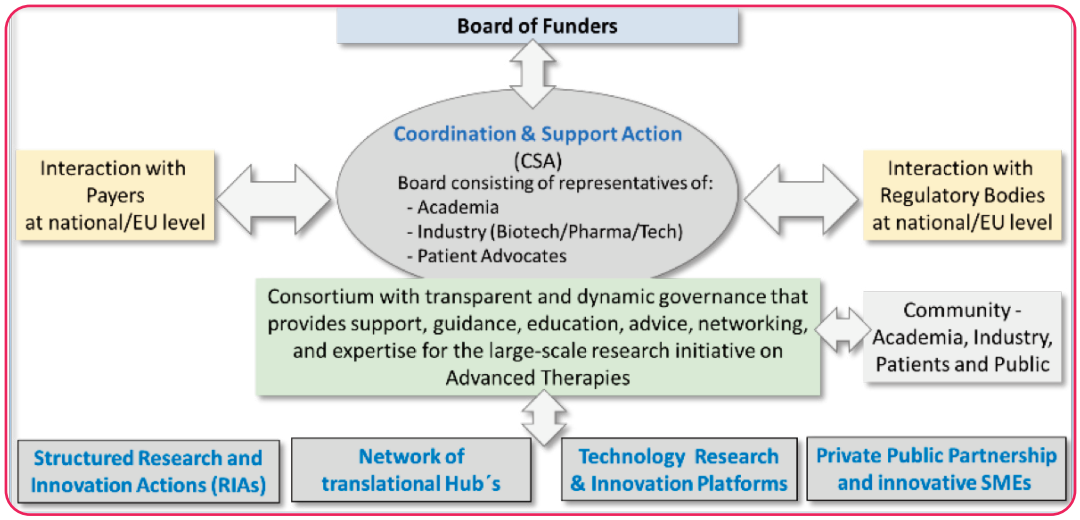


Fig.7
Coordination and Support Action (CSA) for Advanced Therapies in Europe

2.) Combine the benefits of thinking SMALL and BIG to unify disrupting inventions and innovation

It is well established (Wu L. et al., Large teams develop and small teams disrupt science and technology. Nature. 2019. PMID: 30760923) that creativity in the idea-creating sense is mostly related to small, independent teams - THINK SMALL! It might be an advantage of the scattered research landscape in Europe - this creativity should be supported and exploited by interlinking with the THINK BIG approach! Innovation in the action-producing sense is more effective in centralized large Hubs to translate innovation into measurable benefits for patients and society (Fig.8).

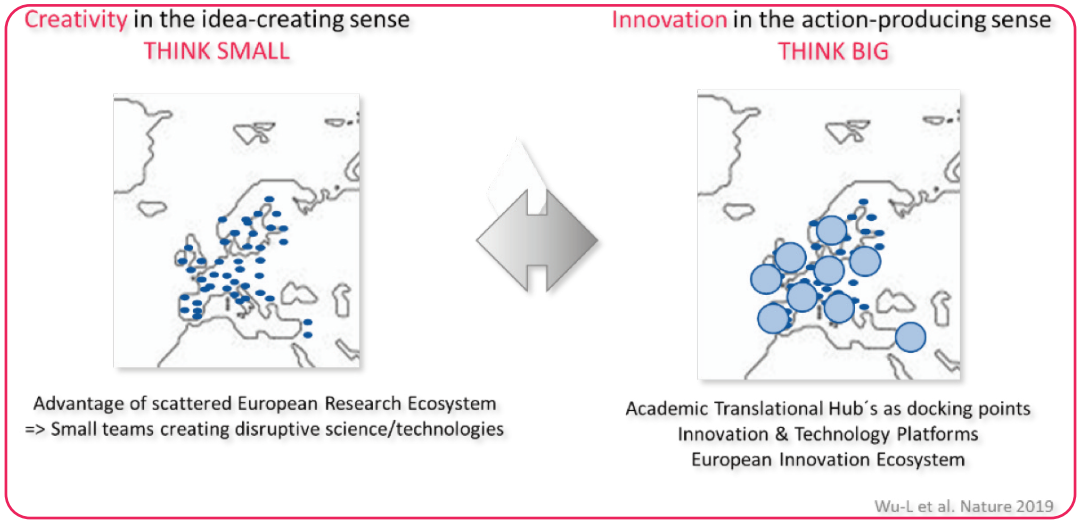


Fig.8
THINK SMALL-THINK Big Elements for de-risking and accelrating development of Advanced Therapies

To support creativity in scattered small teams around Europe, the tool of targeted Research and Innovation Actions (RIAs) according to the roadmap should be used to build-up a project pipeline as well as an enabling technology pipeline. The governance of RIAs should be flexible such that they can be halted or extended based on key performance indicators (Fig.9).

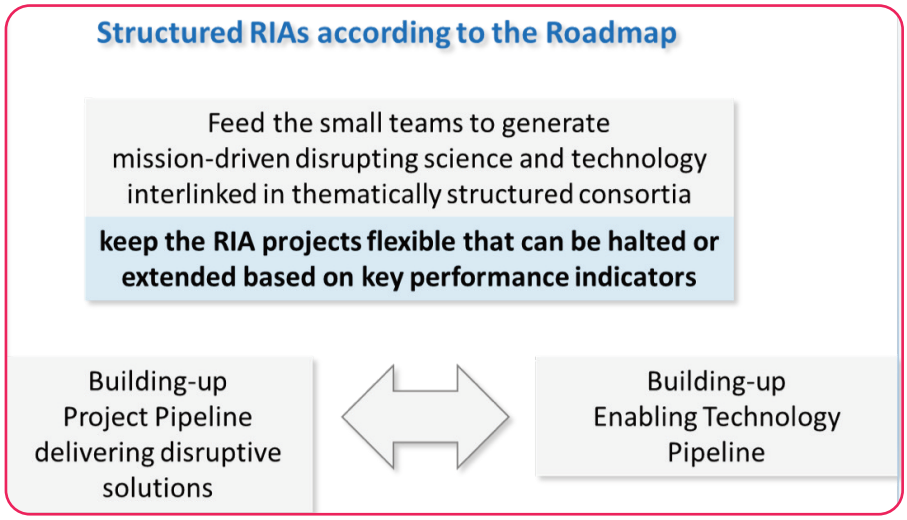
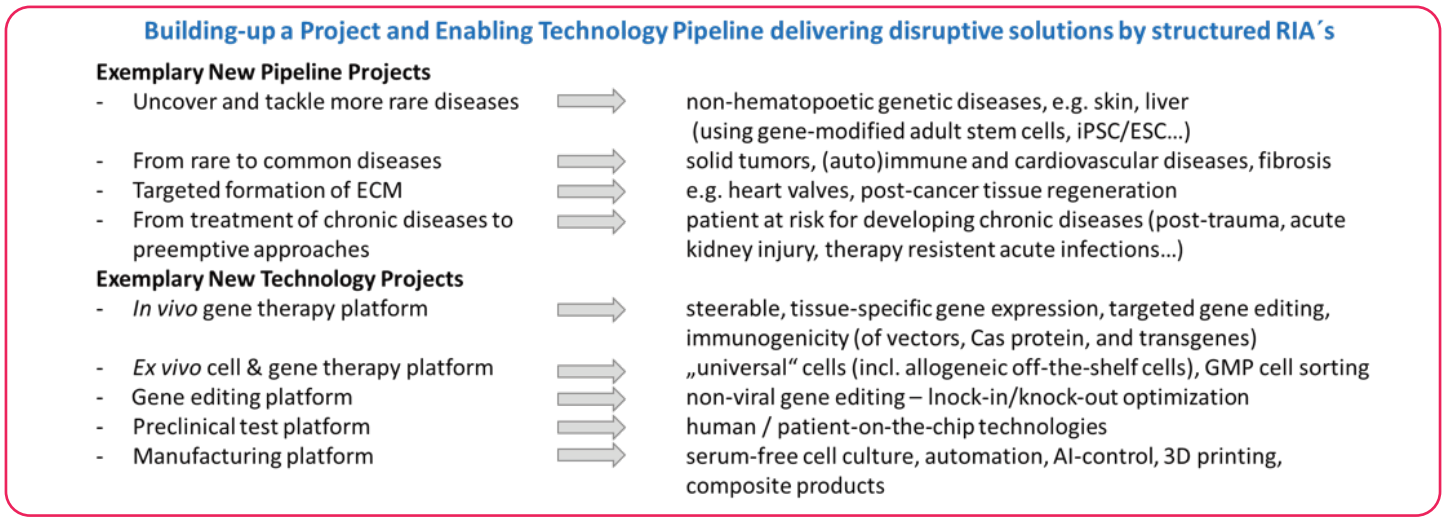


Fig. 9
Feed the small creative teams by structured RIAs according to the roadmap

Exemplary **pipeline projects** of near future might be:



Successful RIA projects should be encouraged to dock on the proposed Hub structures to drive innovation. To support innovation new structures are necessary (Hubs, Platforms) - see below.

3.) Broadly accessible Technology Research and Innovation (TRI) platforms and Cross-Theme platforms - Collaboration replaces competition

A key element for accelerating and de-risking of the development of Advanced Therapies is to replace strong competition by collaboration to prevent reinvention of the wheel in each new project and repetition of failures already done before. RESTORE proposes the support of broadly accessible Technology Research and Innovation (TRI) platforms (mission-driven basic science for discovering new targets and indications, technology development, manufacturing, product characterization, advanced preclinical models, biomarkers, early and late clinical development/regulatory affairs, scaling-up/automation, reimbursement etc.), and Cross-theme platforms (ethics, artificial intelligence, health economy) as core of this strategy (Fig.10).

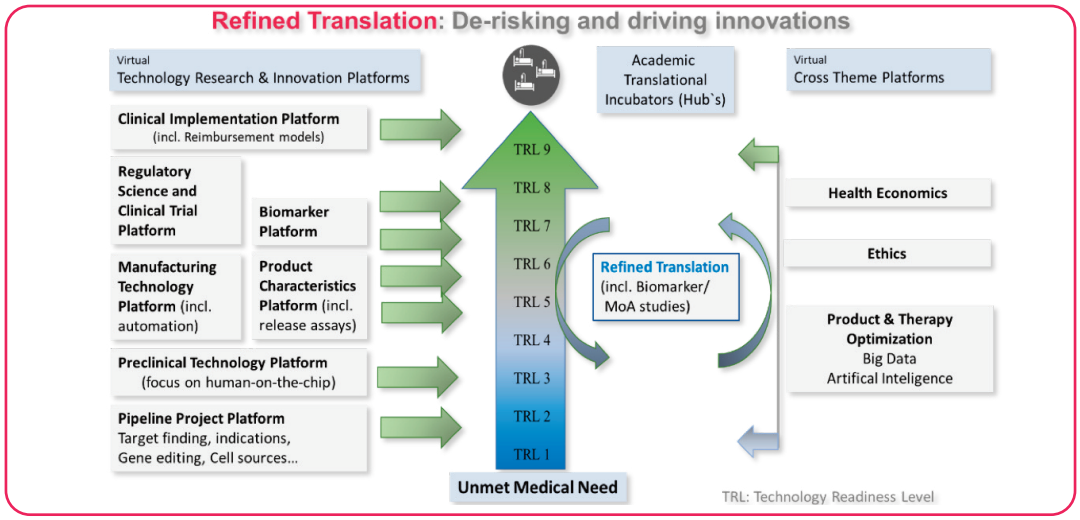


Fig.10
Accelerating and De-risking by Technology Research & Innovation as well as Cross-Theme platforms

Each platform follows its own TRL pipeline aiming to be ready for use in the clinical ATMP development TRL pipeline. The results could be commercialized as enabling technology products long before medical products using this technology are on the market. It is an attractive business model for enabling technology providers. Examples of potential platforms:

- Gene editing platform: new virus-free tools to optimize knock-out/knock-in targeting - applicable for almost all cell product but also basic research and non-medical approaches
- Human-on-a-chip platform: multiorgan models replacing animal experiments with closer relation to human diseases (disease models) – applicable for almost all ATMP developments but also for conventional drug development and pathophysiological research
- Biomarker platform: robust tests for safety, PK/PD, MoA studies - applicable for almost all ATMP developments but also for conventional drug development
- Target finding: to define new targets of therapy – applicable for new cell or gene therapies, e.g. cancer, but also for development of non-cellular biologics (e.g. bispecific antibodies)

4.) A Network of Academic Translation Incubators (Hubs)

A network of academic translation incubators (Hubs) is another key element of success as a place of mission-driven basic research, clinical studies, technology research and innovation platforms, and as docking points for projects from scattered small creative research teams, industry partners (enabling technology developers, biotech/pharma industry) and special interest venture funds (Fig. 11)

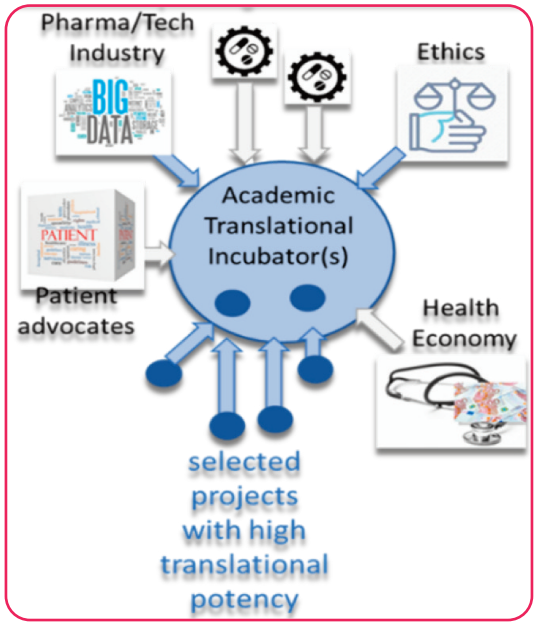


Fig. 11
Academic Translational Incubators (Hubs) - Putting ideas to work

To maximally exploit the Hub structures, they should be interlinked in a general network, but also topic-related (e.g. anti-cancer CAR-T cell, gene-modified stem cell therapy) and technology-related (e.g. coordinated Technology Research and Innovation and Cross-Theme platforms) networks.
RESTORE is part of several European initiatives in this direction.
RESTORE is actively involved in the leadership of the European University Hospital Alliance (EUHA) Initiative to form a network of academic centers focusing on anti-cancer immune cell therapy, called European Cellular Cancer Therapies (EuCAT). It aims to make cellular anti-cancer therapies developed at single centers available for the network by exchanging protocols and implementing joint supporting structures in order to bring product developments from clinical trials to routine treatment (hospital exemption/MA) with enhanced accessibility and affordability.
In the recently submitted new proposal of the European Paediatric Translational Research Infrastructure (EPTRI) initiative, a section for Advanced Therapies has been implemented under the leadership of RESTORE.

5.) New forms of Private-Public-Partnerships (PPP) and support of SMEs

The aimed for progress in the development of Advanced Therapies in Europe is only feasible with significant engagement of private capital. This arm is underdeveloped in Europe, partly due to the scattered landscape and the missing mindset for translation and commercialization at many academic centers as well as the complex regulatory framework for PPPs (Volk HD et al. Key elements for nourishing the translational research environment. Sci Transl Med. 2015, doi: 10.1126/scitranslmed.aaa2049. PMID: 25855490). To build-up successful incubators/accelerators such as those in Boston, San Francisco, Philadelphia, and the Centre for Commercialization of Regenerative Medicine (CCRM), RESTORE proposes new forms of PPP in Europe. Some positive examples for concentrating technology development in Europe are Catapult Gene and Cell therapy in the UK and Fraunhofer IZI in Germany. However, the proposed Hub structure with close links to academic translational incubators could further accelerate efficacy and output because of the link to basic science, clinical science, patients and medical need.

A second element to support higher innovation output and sustainability for EU-funded research projects are special interest venture funds (like in China and Israel) that are useful to promote the formation of spin-off companies in the Hub environment (Fig.12).

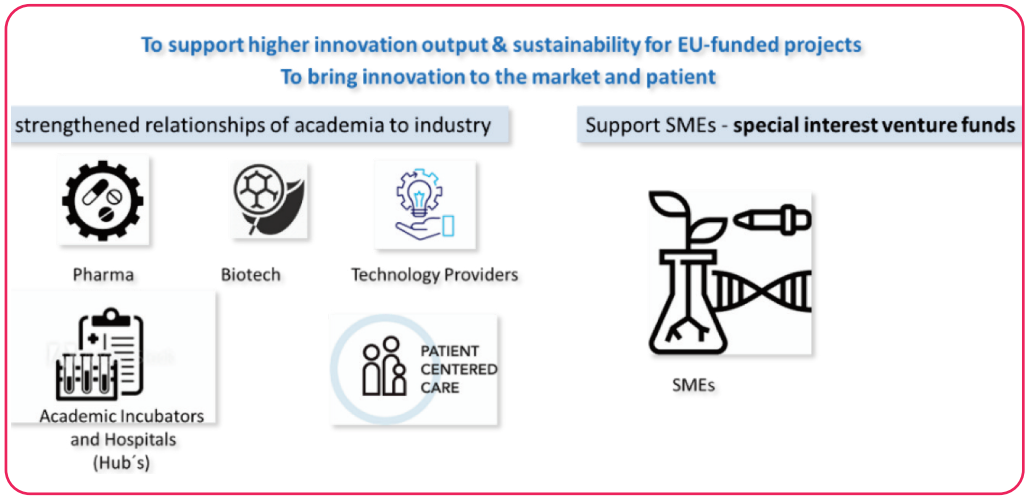


Fig. 12
To bring innovation to the market and patients

INTEREST in the RESTORE Initiative

The industry view

Discussions with partners from pharma industry resulted in the finding that there is a high interest of big pharma in contributing substantially to build-up efficient Hub structures in Europe. This requires Hub structures embedded in an adequate framework (e.g. adaption of the non-uniform regulatory and reimbursement rules, infrastructures, including space for incubator labs and GMP facilities) and a mindset for nourishing translation and innovation. We received only positive feedback for the RESTORE initiative and roadmap.

The EU citizens' survey

In collaboration with a professional company, we conducted an online survey in 13 European countries (Czech Republic, Germany, Denmark, UK, Spain, France, Italy, Lithuania, the Netherlands, Poland, Portugal, Romania and Sweden). We surveyed 7,062 European citizens in order to determine the extent to which European citizens' support public funding for innovations in the field of Advanced Therapies that may help to overcome technical and regulatory hurdles. In addition, the survey revealed to what extent the European citizen supports reimbursement of expensive therapies and related reimbursement topics unique to ATMPs. In addition, the results from the survey will be used to inform the EU- and national funding authorities about the views of EU citizens and hopefully to persuade them to provide adequate funding for research and innovation in healthcare and more specifically for Advanced Therapies in the future. Further, the results will be used to encourage policy makers to promote the establishment of reimbursement mechanisms unique to Advanced Therapies and rare diseases, such as cross-border healthcare.

The main findings of the survey are:

- The majority (58.6%) of the surveyed population in Europe has heard about Advanced Therapies.
- The clear majority (84%) of participants expressed support for using EU- and state-funding to help finance medical innovations
- Participants in all countries rated healthcare the number one most important topic among big political issues
- The majority of participants (62%) in all countries agreed that the state should pay very high prices for treatments that have been shown to be effective in the short term (up to two years), even though information for the long-term benefit of these drugs is still lacking.

In summary, the survey shows that it is the will of the surveyed European population that EU- and state-funding should be used to support Advanced Therapies (Fig.13). Further applications for EU-funding for Advanced Therapies should thus be made since it reflects the explicit interests of the European people.

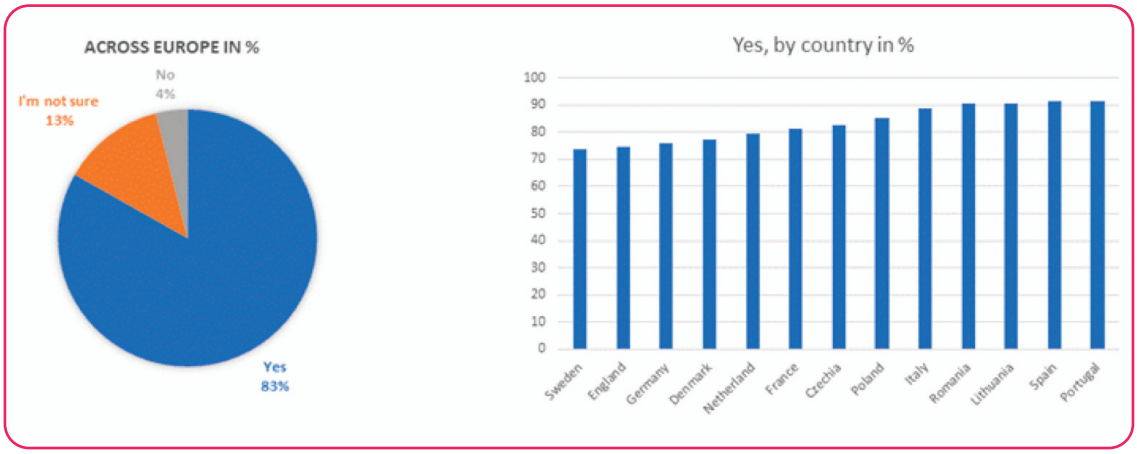


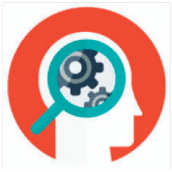
Fig. 13
Positive consensus that EU and member states should fund enabling technologies for cell and gene therapy

Further surveys performed by members of the RESTORE Core Team:

- On obstacles for translation of ATMP and especially CAR T cell therapies. The survey investigated the views of professionals on ethical, regulatory and technological obstacles (collaboration with CARAT). In summary, researchers mostly struggle with the cost issues for translation of ATMPs/GTMPs/Advanced Therapies. On the one hand, these issues are related to the high costs of commercially available cell products like the CAR T cell products Kymriah or Yescarta. On the other hand, the high manufacturing costs and costs for patient treatment represent a major obstacle for investigator-initiated trials (IITs) and there is a strong need for independent financial support through novel public funding programmes.
- An online questionnaire to assess the need of advance analytical tools such as Artificial intelligence (AI) and machine learning (ML) in the decision-making processes and management of RESTORE project. The majority of the respondents agreed that the use of BigData/AI/ML analytical tools will play a meaningful role in development of Advanced Therapies. The following main areas were pinpointed: identifying the target chronic diseases and selecting the "optimal" solutions; identifying the appropriate patient populations and relevant end-points to be used in clinical trials; improving monitoring of manu facturing, and quality control; reducing "time to market" and improving health economics.

IMPACT and RETURN of INVESTMENT

We see a high impact of pushing Advanced Therapies in Europe on:



Science and Technology

⇒ infrastructure and translational centers of excellence
⇒ boosting Europe´s competitiveness in the groundbreaking area of "living" drugs
⇒ fundamental knowledge and technology breakthroughs relevant for many areas
⇒ next generation of translational scientists with new mindset

Societal Benefits for Society and Economy

⇒ improved survival and quality-of-life for patients with chronic diseases
⇒ decreasing financial burden of the society by chronic diseases
⇒ innovative product pipeline for medtech/biotech/pharma industry and new players
⇒ generation of highly specialized workforces and expertise
⇒ setting ethical and quality standards for these new therapies

Based on experiences from the California Institute of Regenerative Medicine (CIRM) and the Centre for Commercialization of Regenerative Medicine (CCRM) in Canada, we would **project fast return on investment** from the support of the RESTORE initiative. Before any Advanced Therapy product was approved from the pipelines of these structures, every dollar invested by the public sector generated a return on investment of $5-8 through private investment in infrastructures, human resources and projects.

HOW to get there?

PROBLEM

Recent funding through research and innovation actions (RIAs) and support for SMEs as well as some single ERC grants under FP7 and Horizon 2020 programmes (around €150-200 million in total) has been beneficial in driving the new field forward, but it is **structurally and budget-wise not sufficient and competitive for the future. The originally planned new FET flagship programme would have provided a good opportunity to mobilise the various existing potentials and make Europe competitive for the future in this field - the question therefore arises, how to make alternative resources and organisational models available after the cancellation of FET-Flagships.**

RECOMMENDATIONS

- Tackle the rising problem of chronic diseases for patients and society by providing **accessible and affordable medicine** taking advantage of the disruptive research and breakthrough innovations on Advanced Therapies for conquering cancer and other chronic and degenerative diseases

- **Switch from the current focus on scattered, time limited, unconnected EU-funding to a concerted funding program for Advanced Therapies** integrating innovative elements supporting a creative and productive ecosystem and to build a true European Research Area on Advanced Therapies as a basis for attracting significant private investment

- **Take the momentum gained from the FET-Flagship initiative in bringing together stakeholders in the field and go in new directions** by supporting sustainable structural elements with sufficient budget according to the **achievement of key performance indicators** over the next seven years of the Horizon Europe programme as an adequate structural and financial alternative to the cancelled FET-flagship programme:

  - **Coordination and Support Action (CSA):** consortium with transparent and dynamic governance that provides support, guidance, education, advice, outreach, networking, and expertise for the large-scale research initiative on Advanced Therapies
    Budget: 5-6 Mio €/a (total for 7 years ca. 35-40 Mio €)

  - **Infrastructure:** Network of Academic Translational Incubators (Hubs) with adequate infrastructure (competitively selected, co-financing only, basic budget by national/regional funding organisations) as docking points for small teams with breakthrough projects, patients advocates, biotech, pharma and technology providing industry, policy makers, health insurers and special interest venture funds to accelerate and de-risk the development of Advanced Therapies by:
    i) implementing broadly accessible Research and Technology Innovation platforms,
    ii) performing high-quality clinical trials,
    iii) applying the Refined Translation Tool for de-risking late and costly clinical development
    iv) implementing incubators as docking points for start-ups, SME, industry and special interest venture funds
    Budget: calls for 15 centers, 3-4 Mio €/a each = 45-50 Mio €/a (total for 7 years ca. 300 Mio €)

  - **Research and Innovation Actions** (RIAs): Feed the small teams to generate mission-driven disrupting science and enabling technology interlinked in thematically structured consortia; keep the RIA projects flexible such that they can be halted or extended based on key performance indicators, for getting new pipeline projects and building-up European Research & Technology Innovation platforms (incl. smart manufacturing 4.0, health-economics, ethics); support docking of successful projects to the innovation Hubs
    Budget: coordinated, annual calls, about 20 consortia x 5-10 Mio €/each (total for 7 years ca. 150 Mio €)

  - **Private Public Partnership and SME support: To bring innovation to the market and patient** we need strengthened relationships of academia to industry and investors to support private funding and sustainability for EU-funded projects on Advanced Therapies, including support of SME/industry docked to the programme, notably through the **European Innovation Council** (EIC) and European Investment Bank (EIB).
    Budget: EIC /EIB tools (ca. 150-300 Mio €)

Most urgent

To take the momentum gained from RESTORE´s work during last 2 years, it would be urgent to implement at the beginning of the new Horizon Europe programme a Coordination & Support Action for Advanced Therapies as outlined above. In addition, the formation of the proposed Hubs is a key element to foster and build a European ecosystem, which attracts private investment to develop Europe as a player and not only a payer in this emerging field. This requires the support at regional, national, and European level. Recent experiences from the Covid-19 crisis demonstrate the contribution of innovative Hubs, Biotech and Pharma to support the efforts against Covid-19 and how important it is to keep innovative Hubs, Biotech and Pharma in Europe. The offers from overseas for such companies to leave Europe are attractive and can be only competed by a powerful ecosystem.

In addition, RESTORE suggests to adapt the rules for new RIAs in the direction mentioned (keep the RIA projects flexible such that they that can be halted or extended based on key performance indicators).

Acknowledgement

We thank the European commission for supporting the preparatory phase of the large-scale research initiative, RESTORE – Health by Advanced Therapies. We acknowledge the strong interaction with the supporters of RESTORE from academia, industry, non-for-profit organisations, and patient advocates. Finally, we thank the staff from the partner institutions for the great job they have done.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 820292.

Follow us

www.restore-horizon.eu

info@restore-horizon.eu