Report on the Second Regenerative medicine workshop

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Abstract

Regenerative medicine aims to transform the current practice of medicine by treating the root causes of disease and disorders, through gene/cell therapies, and tissue-engineered products. As a consultancy active in various regenerative-medicine related research project on a European scale, AMIRES organized the 2nd edition of the regenerative medicine "from Project to market" workshop to exchange outcomes and experiences in the development of novel technologies and solutions in this field by EU-funded[1] initiatives and European companies. The event featured individual presentations of EU-funded research and innovation projects in addition to a round table with all speakers, where challenges and hurdles of practical deployment of the new technologies in regenerative medicine were discussed. The key takeaways from the event are summarised below:

- It is crucial to keep close to the patient and understand their needs in any technology development for health applications. Although it is a challenge to carry out necessary follow-up with patients, especially after they have recovered (new MDR requires 10 years follow-up), many patient organisations are happy to engage in the research and development of solutions that might benefit them. However, it is important to be careful and not to overpromise and share immature results and ambitions to avoid false hopes and expectations.
- It is essential to keep innovations simple and practical. Researchers tend to overcomplicate, but often solutions needed are not too complex. The more disruptive a technology is, the bigger the risk of scepticism and hesitancy for its wide uptake.
- Standardisation and automatization should be pursued wherever possible. Unfortunately, standardisation is difficult for personalised medicine as it requires comparability.
- Panellists agreed that fundamental research and technology development are the "easy" part of regenerative medicine projects. In contrast, successful entry to the market is a real challenge in innovation projects, which many fail to overcome.
- A Health Technology Assessment (HTA) should be considered at early stages to support technology development and increase the chances for successful fundraising from investors and transfer to market. Ideally, HTA should be launched before any development, with periodic follow-up, e.g. after market entry of a competitor or emergence of new technology.
- It is crucial to start thinking about regulatory and legal aspects early and collect all necessary documentation depending on the regulations need to be complied with. Innovators should make use of workshops/scientific advice/consulting offered by the regulators (European Medicine Agency - EMA, US Food and Drug Administration - FDA).
- Engagement with notified bodies (NB) might be helpful, although added value strongly depends on country and NB, many have a big backlog, especially after the entry into force of the new Medical Device Regulation (MDR) and Regulation of *in vitro* diagnostic medical devices (IVDR). Audits by NBs often focus mostly on successful implementation of quality and risk management procedures.
- Engagement with clinicians is strongly recommended since they are the "ambassadors" of the technology and key decision makers for adoption into clinical practice.
- Reimbursement of products by health insurance should be considered for a pricing analysis when preparing business plans.
- In project consortia that include industrial partners and research or academic organisations, the issue of protection vs publication of results should be discussed early and regularly revised as the project evolves.
- Patenting is expensive and not always a possibility, enforcement of intellectual property (IP) rights is often a challenge. Collaboration with universities might help, although systems differ between countries.
- Informal contacts should not be underestimated, as they often lead to successful collaborations, e.g. in public funded project consortia.
- In order to measure success, it is essential to define acceptance criteria. A challenge in many projects is to define them early on, when partners are still unable or hesitant to define Key Performance Indicators (KPIs) and prefer to keep it open. Nevertheless, an initial definition of acceptance criteria is key, they can be adapted during the process.

[1] Projects funded by the European Commission through the Horizon 2020 programme.

Introduction

According to Nature magazine, regenerative medicine "is the branch of medicine that develops methods to regrow, repair or replace damaged or diseased cells, organs, or tissues". The field develops, among others, methods and technologies for the generation and use of therapeutic stem cells as well as processes and solutions for tissue engineering and the production of artificial organs[2]. Owing to the rising need and demand for new solutions (for instance, in the light of increase of chronic diseases, longevity and organ/tissue donors' shortage) as well as unprecedented technological possibilities and procedures, this field of medicine has seen big advancements in the last years. The use of regenerative medicine solutions has the potential to greatly improve the quality of life for people with chronic conditions and reduce the burden on healthcare systems.

Recent developments such as stem cell therapies, cellular therapies, gene therapies, tissue engineering, direct cell reprogramming, exosome therapies, cellular scaffolds and matrices, 3D bioprinting and new biomaterials, combination products all fall under the umbrella of regenerative medicine. In the last 10 years, the number of scientific publications in this field has been steadily increasing, apart from a drop in 2022, likely influenced by the focus on the more urgent issue of the COVID19 pandemic. Similar dynamics are observed in the number of patents filed and granted related to regenerative medicine, which had the highest peak in 2019, and remained steady until 2021, before decreasing during 2022 (see figure 1B, data from PatSnap Discovery).

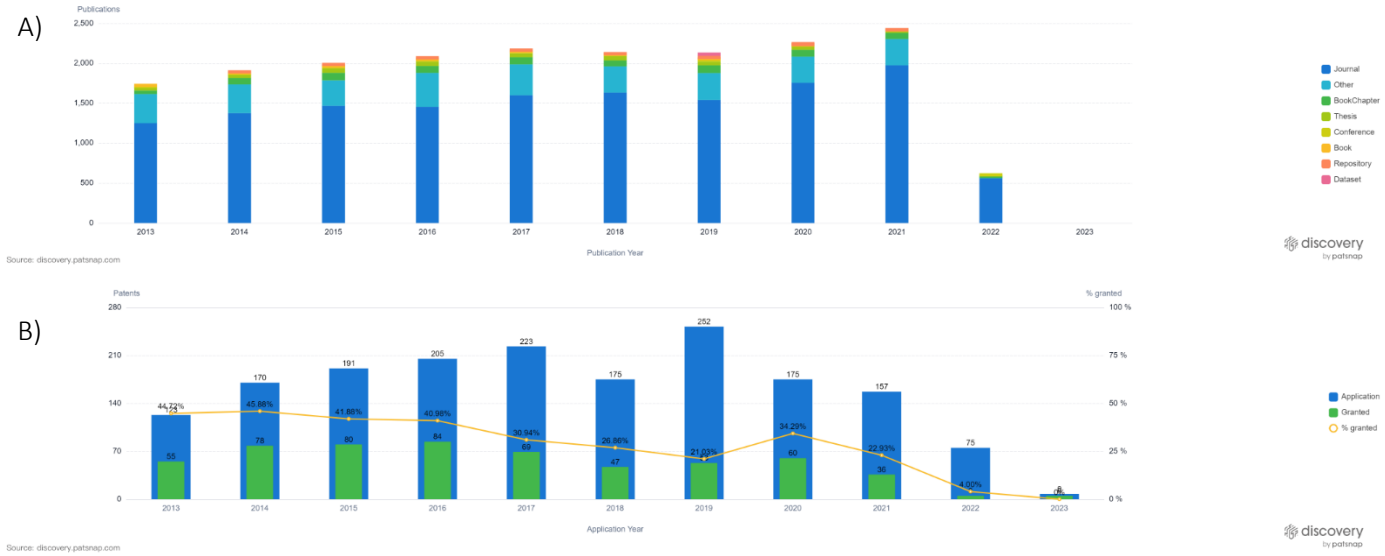

Figure 1. Scientific Publications (in different channels, e.g. journals, book chapters) (A) and patents in the regenerative medicine field (B). (PatSnap Discovery).

Regenerative medicine has also received considerable investments from the public domain: overall, 254 projects were funded in this field within the EU's research and innovation funding programme Horizon 2020, which was running between 2014 and 2020. In contrast, in the current framework programme - Horizon Europe - only 8 related projects were funded since programme launch in 2021 (information from AMI Plexus visualization engine). Venture Capital (VC) investments have not been constant in the last years, with a peak of investments in 2017 and 2021 (figure 2). While this tendency is seen worldwide, bigger investments take place outside of Europe (data not shown). The top investor in Europe is the *Executive Agency for Small and Medium enterprises*.

[2] https://www.nature.com/subjects/regenerative-medicine

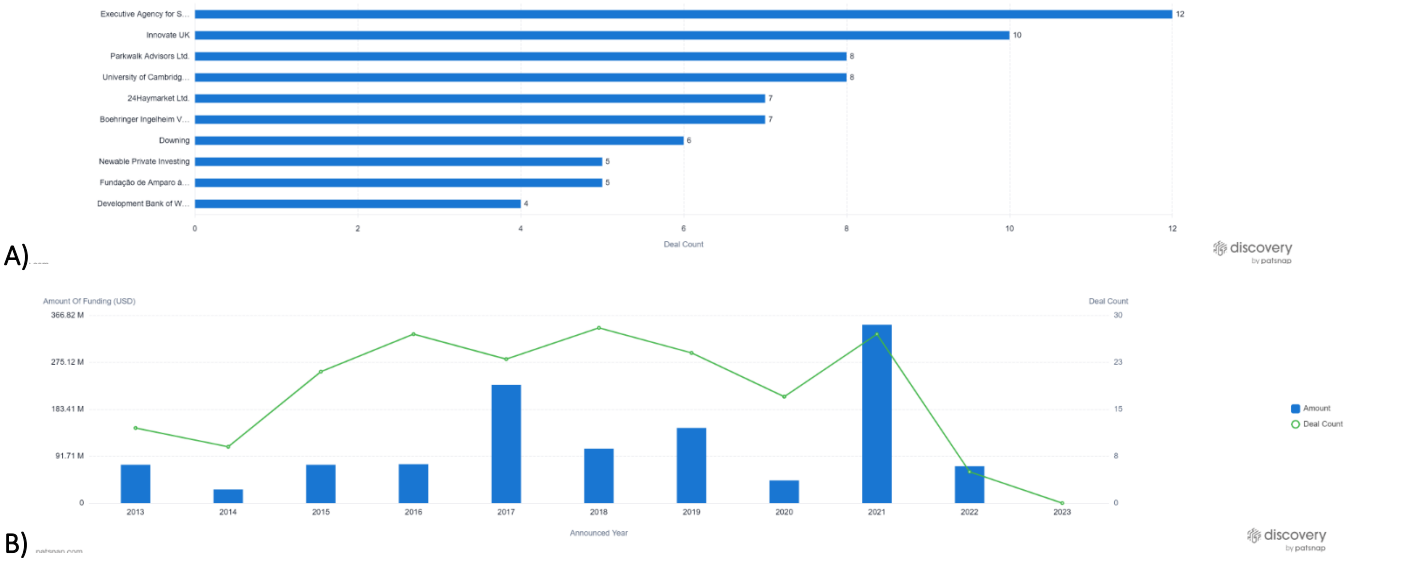

Figure 2. VC investment overview in Europe in the regenerative medicine field (PatSnap Discovery). A) Main investors in Europe. B) Amount of funding by year.

The Regenerative Medicine Market has been consistently expanding in the recent years and is predicted to reach an estimated global market size of $183 Billion by 2031[3]. The key drivers of this growth include high rates of clinical trials, accelerated pathways for product approvals, new technologies to support cell and gene therapy manufacturing, and the potential for cell therapies to revolutionize healthcare. Accelerated pathways for product approvals, specifically ATMPs (advanced therapy medicinal products) exist in the United States, Japan and South Korea, with relevant legislation having been implemented in 2017, 2014 and 2016 respectively. The European Union has implemented a similar program for product acceleration called "Adaptive Pathways and careful guidance for ATMPs". Additionally, pharmaceutical companies are increasingly interested in regenerative medicine, as a result of progress with immunotherapy treatments, such as CAR-T cell therapies, most notably *Kymriah* and *Yescarta*. More than 900 companies are active on the global regenerative medicine marketplace[4], trying to disrupt established healthcare processes with innovative products and services.

Report from the Second regenerative Medicine workshop – Prague, 12.10.2022

The idea of the *Second Regenerative medicine workshop* was based on the observation of an urgent clinical need to improve the regenerative options in healthcare and the importance to support their development. The event organized by AMIRES, took place on October 12, 2022, at the Technology Centre Prague in the Czech Republic. Dr. Mariana Pacheco Blanco – Programme Manager for Health and Biotechnology in AMIRES – welcomed participants both on site and online. Different EU-funded projects and companies were invited to present, with the aim of facilitating an active exchange of outcomes and experiences in the development of technologies, products, and solutions in the regenerative medicine field. Thereby, the workshop also successfully set the stage to start new partnerships, and new research projects.

EU-funded projects: the start of new solutions

The first session saw a series of presentations of EU-funded projects in the regenerative medicine field which are briefly outlined below:

[3] https://www.globenewswire.com/news-release/2023/04/12/2645244/0/en/Regenerative-Medicine-Market-Investments-Share-and-Revenue-Analysis-Latest-InsightAce-Report.html

[4] https://www.researchandmarkets.com/reports/4787326/global-market-for-regenerative-medicine-rm-2019

Laser Bioprinting for regenerative applications and organ on chips: EU Project TUMOR-LN-OC[5]

The first talk was presented by Prof. Ioanna Zergioti from the National Technical University of Athens in Greece. TUMOR-LN-OC project focuses on monitoring the interaction between a tumour and the lymph node of the same patient through an organ-on chip solution. The Consortium of this project will develop an integrated microfluidic platform based around a chip with two chambers, containing tumour and immune cells, and various channels which will enable the communication between them. Any cell migration will be monitored real-time via a complex automatic image analysis and signal processing system. The final solution will be used to develop drug testing strategies as well as for metastasis detection and personalised medicine. The platform consists of 6 technological modules to be developed: The microfluidic chip and peripherals, Mid-IR Photothermal spectroscopy sensors, imaging sensors, machine learning and deep learning algorithms, molecular analysis for biomarker detection and drug testing on patient cells and tissues. One of the main challenges is to mimic the function of the variety of cell lines which are needed to be printed as part of the organ. The laser bioprinting of lymph node and tumour cell lines in this project is under initial evaluation, and Prof. Zergioti showed encouraging preliminary results, which will be key in the Regenerative medicine field.

For more information on the project, visit https://tumor-ln-oc.eu/

EV-based therapeutics for cardiac repair and regeneration: Where are we now: EU Project MARVEL[6]

Prof. Lucio Barile from Istituto Cardiocentro in Ticino, Switzerland provided insights on the outputs and progress of the MARVEL project, which aims to use Extracellular vesicles (EV) for cardiac repair and regeneration applications.

Prof. Barile presented how MARVEL outputs could be an alternative to the therapeutics on acute ischemic syndromes. He shared how the cardiomyocytes, the cells that form our heart muscle, have been shown to uptake extracellular vesicles. In this presentation interesting results on the explant derived cells which have been studied. Most importantly, these advancements have been following Good Manufacturing Procedures (GMP) for cell banking and EV production. This is under preclinical studies and with the intention to advance for clinical evaluation.

For more information on the project, visit https://marvel-fet.eu/

Bringing new alternatives to chronic liver patients: EU Project ORGANTRANS[7]

The third project funded by the European Commission under the H2020 programme was presented, was ORGANTRANS by senior R&D engineer Diane Ledroit from the Swiss Center for Electronics and Microtechnology (CSEM) in Neuchatel, Switzerland. She presented the work that has been done within the ORGANTRANS consortium in bringing new potential alternatives to chronic liver patients, based on stem cells, advanced biomaterials, bioprinting, sorting, perfusion, vascularization and biovalidation, through *in vitro* and *in vivo* tests. The consortium has developed a platform, which follows a workflow from the cell production to the maturation of the construct, and that is now being *tested in vitro* and *in vivo* for function. All processes developed had established Standard Operating Procedures (SOPs), which will be key for the standardisation of these building blocks that are crucial for regenerative medicine.

For more information on the project, visit https://organtrans.eu/

Innovative companies, innovative solutions

In the second part of the event, representatives of three companies presented their view of the regenerative medicine field and the innovative solutions they are offering.

Regenerative Medicine research projects: which approach would be most suitable?

This presentation was given by engineer Konstantin Sipos from Rescoll, a French company focused on Research and Development (R&D), validations and tests under ISO 17025, manufacturing under ISO 13485, providing the costumers to work with high technology readiness levels (TRL).

Eng. Sipos shared his experience of how people tend to avoid changes, and that moving from improvement to innovation in R&D is challenging. This is also reflected in regulation. This can be related to the concept of MAYA – Most Advanced, Yet Acceptable - which was proposed by the famous industrial designer Raymond Loewy. This concept underlines that innovators should keep a certain amount of familiarity in their developments in order to ensure faster

[5] This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 953234, project Tumor-LN-oC.

[6] This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement № 951768, project MARVEL.

[7] This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 874586, project ORGANTRANS.

market uptake and user acceptance. If the step to innovation is too big, many will hesitate to adopt the novel technology. But how to maintain the fine balance of innovation and acceptance? Eng. Sipos presented how this problem was approached in two examples of regenerative medicine at TRL 4 to 6:

- The first example is an electrospun cardiac valve, mimicking a natural valve in children. This idea (also funded by the EU) allowed to implement and combine different technologies ranging from electrospinning, vacuum plasma to new polymers. The valves were successfully implanted in 6 sheep. Despite promising results, including successful publications, there was no follow-up to this project, in a first-in-human-trial or similar. This might be due to mistakes made, such as the fact that no regulation and validation partners were included in the consortium, as well that the end of the project meant the end of the material availability. At one point, the industrial partner changed strategy and lost their interest. A very common situation in similar projects.
- The second example was a 3D printed/electrospun bone scaffold, which mimicked the bone and periosteum membrane. This project followed the MAYA approach on their novel surgical technique, and included partners dedicated to validation, which has completely changed the project and ensured a high likelihood of a follow-up. In addition, good chances of commercial success exist, since 2 Key Opinion Leaders (KOLs) are supporting the project.

As a conclusion of the presentation, Eng. Sipos suggested to follow the MAYA principle: big changes are a big risk and clinicians do not like radical changes. In addition, he strongly recommended to always include partners responsible for validation, regulatory and quality when working towards TRL4-6.

3D printed personalized implantology and tissue substitutes

The second speaker was Dr. Marek Schnitzer from the company Biomedical Engineering and Technical University of Košice (TUKE), Slovakia who presented their joint work on the manufacturing of personalized implants using diverse materials. Some of the developed implants are currently part of clinical case studies, such as a cranial implant, maxillo-facial implant, mandibular implant, thoracal implant and many others. Overall, Dr. Schnitzer and his team have designed, manufactured, verified and applied over 350 implants in different countries. In order to start designing a patient specific implant, a first scan of patient data is needed, and the overall design can take 3-4 weeks. Once the design is frozen, two weeks are needed for manufacturing. The team of Biomedical Engineering and TUKE envision the next generation of healthcare as personalised hospitals where implants, vaccines, medicines would be developed patient-specifically in-house. In terms of liability of the implants, the medical doctor rather than the manufacturer is liable. However, the company is responsible for the process, and would need to present evidence from the quality perspective in the case that something happens.

Scaffold biomaterials: from ideation to clinical use

Dr. Amélie Béduer, CEO and founder of Volumina in Switzerland, presented the success story of the company. Volumina started as a spin-off of EPFL (Swiss Federal Institute of Technology, Lausanne), with the main interest from plastic surgeons for reconstructing breasts of women after breast cancer. A tumour can leave the breast disfigured, resulting in a strong market need for suitable solutions. Up to 50% of currently used silicone implants have to be reimplanted due to complications, suggesting the urgent need for new and better materials. In response to this, Volumina developed ADIPEARL™ – an injectable biomaterial supporting the breast to repair after trauma. After the material is injected by the surgeon, it takes 30 minutes to shape the breast. In a few months, only healthy tissue remains. ADIPEARL™ is classified as a Medical Device, which uses raw material known to be safe. This product is ISO 13485 certified and validated according to Good Manufacturing Practices (GMP). Until now, large animal studies have been completed, and the first in-human trial is on-going, with the participation of 12 patients. Dr. Béduer shared the company's objective to reach FDA approval by 2028, as well as CE marking for further expansion. She also emphasized the importance of keeping in mind the needs of the patient and the market in the development of medical solutions, based on the observation that sometimes scientists overcomplicate the solution, forgetting the initial needs and interest of the patient.

Economic and social impact of new therapies, medical device and emerging technologies - method HTA

The final speaker of the session was Dr. Lukas Peter from Betthera, Czech Republic, who presented the importance of Health Technology Assessments (HTA) and consideration of regulatory aspects during the development of regenerative medicine solutions. Betthera provides services in both these two topics. In Dr. Peter's experience, quality and regulatory processes are addressed in most cases only after prototyping. However, they should be considered already during the

design of solutions and by the manufacturer early on. HTA looks into medical, economic, social and ethical implications of new technologies. From the economic point of view, it will provide answers on the monetary savings that the developed technology brings. The main goal of an HTA is to provide evidence for decision making and policy. Other objectives are to 1) Uniform methodological guidance, 2) Standardise procedures, and 3) Strictly specify conditions and procedures, among many others. The HTA Framework follows EU HTA Regulation 2021/2282 on health technology assessment and amending Directive 2011/24/EU, which was adopted by the European Union on 15 December 2021 and entered into force on 11 January 2022. HTAs are part of health economics, which uses databases to evaluate inputs using economical models. For example, one of the inputs for cost-benefit analysis is the evaluation of positive and negative aspects i.e. adverse events of similar devices. In the UK, regulation on medical devices is close to MDR (Medical Device Regulation) but it has minor differences. Dr. Peter recommends that an HTA should ideally be launched before any development – a practice that is not followed by many. While most companies consider regulatory aspects, few take the time and resources to conduct an HTA. Responding to a question from the audience on how to bring a healthy patient back to the hospital for the follow-ups needed for regulators, Dr. Peter mentioned that currently this is often done via mobile applications.

Round table: challenges & hurdles of practical deployment of the new technologies in regenerative medicine

The intention of this session was to get insights from the speakers, who acted as panellists, on topics related to standardisation, exploitation of results, health economics and regulatory aspects. This session was not streamed online in order to have a better interaction between the people physically attending the meeting. Main conclusions and opinions shared are described below.

Standardisation in the field of 3D bioprinting, biomaterials, cells sources

What are the needs and bottlenecks that you have identified as part of the standardisation of different technologies used in regenerative medicine, such as 3D printing, biomaterials, cells?

- Dr. Schnitzer from TUKE and Biomedical Engineering responded that one of the challenges is the software standardisation. If a company or organisation produces personalised implants, a certification of the materials is needed. At the same time, it is an opportunity for new software to get certified. For small companies, it is impossible to pay software licences on € 100 000 a year, so they need to go with new approaches or ideas. The other challenge is whether to print cellular or acellular, because printing acellular implants, even resolvable/active ones, is very different than cellular, that is highest level of regulation. The results need to be comparable in order to standardise. He also added that as a researcher and developer you need to try several times to compare results. Without comparison, standardisation is impossible.
- Eng. Sipos, from Rescoll, indicated that the issue is how to standardise something that has been done just once i.e. how to standardise new and still evolving technologies and processes. Standardisation should make things easier to justify to the authorities, but it is difficult for personalized implants or complex new innovations.

Which procedures or methods do you implement in your organisation/project for standardisation? In which initiatives do you take part to contribute to standardisation (e.g. workshops organised by notified bodies or European Commission)

- Eng. Ledroit from CSEM mentioned that CSEM as a research and technology organisation works on different projects and tries to integrate several standards. There is some labware for instance, that can help to standardise. CSEM is also trying to automate some procedures, which contributes to the standardisation. For instance, there are some standard operating procedures (SOPs) for cell cultures in place. More discussions with regulatory bodies would be very helpful.

How do you suggest improving the increase of standardisation at your organisation/project?

- Eng. Ledroit from CSEM commented that it is difficult to have standardisation for innovations. Homogenised protocols would help, which could be used for different groups. Workshops and discussions with regulatory bodies and experts are crucial.
- Dr. Béduer from Volumina indicated that the first step is to decide what is needed to be standardised, and then to think of the acceptance criteria, e.g. of acceptable impurities of cell culture or quality of biomaterials. The end properties should be clear, otherwise, it will not be possible to define what needs to be standardised.
- Eng. Ledroit intervened that in many projects, partners are unable to define the acceptance criteria. In the beginning, everyone wants to keep it open, even if it is established that the criteria can change during the process.

It is difficult to consider everything from the beginning during the development process and problems are usually discovered along the way in such projects.

<u>Dissemination, exploitation, and commercialization: balance of exploitation of results and IP protection vs communication and dissemination (mainly for the EU funded projects)</u>

For the EU-funded projects, how do you manage the balance between the requirement of communication/dissemination and the interests of the partners in protection of the results? At which point in the project were you able (or do you hope to be able) to effectively discuss and align on IP interests?

- Dr. Daniel Quesada, as representative of EU project MARVEL commented that if you are able to patent your technology, once patented, you can publish freely. In other cases, it might not be possible to patent the technology, but it is a trade secret, often resulting in a more complex strategy. Usually, the system development is not explained in the scientific publications, instead only the results and observations from clinical studies etc. If the system is patented, there is no conflict of interest.
- Eng. Ledroit from CSEM highlighted that for every collaboration, at some point CSEM has a discussion on IP and works with the legal department to carry out an IP search to check for blocking patents in case there is interest in protection. The initial IP agreement should be concluded in the beginning of the project, but re-discussed once it is more developed.
- Eng. Sipos from Rescoll intervened that generally in his experience, it was possible to find a compromise between publication and patenting. In his company, they decided that if the technology is too easy to copy, they do not patent it. Once you patent, it is easy to copy and as a small company, they are in a difficult position to dispute it. Small companies have no capacity to go against the legal department of bigger companies. Moreover, patenting is expensive and has to be worth the investment from a business perspective. Big companies can easily spare the money, but for smaller companies, it is more difficult. In the case of Rescoll, they prefer to keep trade secrets, do exploitation themselves if possible.
- Dr. Schnitzer from Biomedical Engineering mentioned that the university can step in with the patenting. Each researcher can collaborate with the university who will pay for the patent, then it can be brought outside and transferred to the company. For them, access to transfer offices matter, but this differs between countries and universities. In the case of copying, you can legally claim costs for it. PCT (Parent cooperation treaty) for them now amounts to ca. 27 000 € for lawyers, applications in different markets etc.
- Dr. Pacheco added that the patenting and ownership can be different between countries and universities. Transfer offices in the research organisations are crucial.
- Dr. Schnitzer intercepted that you could establish the shares of ownership in a legal agreement with the university. Always patent first where your competition is, then look at where you intend to market. For example, patenting in China is complicated.
- Dr. Quesada added that in Spain, it is usually universities who come to the company presenting new technologies and ask to pay for the patent.
- Eng. Sipos commented that there is a cultural problem in France: fundamental research and innovating is easy, transforming it into a business is the difficult part. Until now, this was not understood. Many universities are asking for royalties. Airbus example – the design and production of A380 went relatively smoothly, but then many other elements of the chain did not fit anymore (hangars, airport slots etc). Once low TRL work is done, you might have to redo everything about the business to accommodate for the product at higher TRL.

<u>Health economics: health technology assessments, cost-benefit analysis</u>

Have you considered HTA analysis in your projects/organisation? If no, why not?

- Volumina was not asked for it by the authorities, but decided to proactively conduct an HTA, for early cost-effectiveness analysis and integrated it into the device. They also considered the code for reimbursement during the pricing analysis and engaged with health agencies. This was a good decision since investors are often asking about the reimbursement and pricing analysis, in addition to the business model.
- Eng. Ledroit mentioned that HTA is not well-established and risk analysis is used more often. CSEM does not sell or commercialise the results of their projects, potentially they are involved in spin-off creation.

Question for Betthera: lately, the importance of HTAs and cost-benefit analyses has been increasing, the authorities are adding it as a requirement, for instance, in the European funding calls. Are there new challenges and opportunities for Betthera in light of this trend? Has your demand increased?

- Dr. Peter confirms that there are many opportunities. In one case, a company approached them because the competitor started selling the product, so this company needed to show to the investors that their technology is still profitable. As MDR is working, many companies ask if Betthera can also help with HTA.

Stakeholder engagement, clinicians and patient organisations

Who are the end-users of your technology? To which degree and how have you or do you plan to engage with them? How do you engage with clinicians and patient organisations?

- Dr. Schnitzer indicated that at all operations in which their implants have been needed, a biomedical engineer of the team is present who is also in contact with the patient. It is difficult to do the follow ups, and a mobile app with Patient Reported Outcome Measures (PROMs) is not enough. It is a big problem to get healthy patients back in the hospital. However, according to the MDR, the producers need 10 years of follow up as input for regulatory requirements starting from 2024. Dr. Schnitzer team mainly give a chance to other companies to sell and distribute materials they developed, and they would like to cooperate with device producers to add their materials to their machines. They are close to a network with clinicians in Kosice.
- Dr. Béduer mentioned that cooperating with patients is complicated if the product is not yet on the market. However, Volumina is in contact with the patients and asks about their needs. In breast cancer, many active patient organisations exist, who have participated in workshops and discussions. At the same time, the company is careful not to provide false hope. Volumina is still in the development phase, and not yet sure if their product will even make it to the market. Nevertheless, patients want to be treated immediately. The innovators have to balance being empathic to understand what patients need but also keep distance, not to overpromise.
- Eng. Sipos pointed out that RESCOLL does not have contact with the patients. However, the company is in touch with clinicians during product development to ensure end-user needs and requirements are met.
- Dr. Quesada noted that most clinicians are attached to their own methods, and it is difficult to convince them, even if the new products promise better, faster results. He has been involved in survey with patients, which is a way a new method can be compared to state of the art.
- Dr. Pacheco added that in the Organtrans project, a patient organisation was warning partners not to overpromise when publishing or posting in social media, not to get the hopes too high for current patients. This is because patients read everything. The new technologies will take years to reach them, or worse, will never make it to the market. That is why is important to be mindful in the communication with patients.
- Eng. Sipos indicated in his experience, that COVID pandemic significantly changed the regulatory landscape, everything was accelerated. Authorities and end users are suddenly much more receptive of new solutions which fulfil an urgent need.
- Dr. Béduer intervened that the COVID emergency provided clear evidence of the cost-benefit balance of vaccines and other diagnostic tools. The benefit was very high and the need very urgent.

Are patients sometimes hesitant? How do you convince them?

- Dr. Schnitzer commented that they need to convince mainly the clinicians of the innovative technologies and procedures. However, in many cases, surgeons are quite hesitant change their practices.
- Dr. Béduer mentioned that as manufacturer, they are not allowed to convince the patient, or to persuade the doctor for the patient.

Regulatory and legal aspects

How do you manage the regulatory barriers related to the market entry of innovative solutions?

- Dr. Béduer responded that they raise funds. Money is a regulatory barrier, and it is crucial to have sufficient funds. Research is not the most expensive part, but rather transfer and entry to the market. Consulting meetings with the regulators to review draft procedures, recommendations, is not very specific in Volumina experience. At the pre-submission meetings in the USA, specific points are discussed, and more precise advice is received.

- Eng. Sipos added that nowadays, more funding and engagement with a notified body is needed to pass regulatory hurdles. Even better to enter into a dialogue with two or more notified bodies, if possible. He thinks that the regulation is going far from patient safety, it is about administrative procedures.
- Dr. Peter responded that at the end of the day, anything (any procedure) can affect patient safety.
- Dr. Schnitzer stated that the question which remains is what kind of notified body is available in each country. The approaches and prices can differ significantly, depending on the country. In Slovakia, the situation is not ideal, for example, better notified bodies with more experience are found in Poland. It is quite complex; 147 documents are associated with MDR.
- Dr. Pacheco added that some calls for Horizon Europe programme, proposers already need to have contact with regulatory, such as EMA and FDA. Applicants should show that they have experience on how to enter the market.

Have you received scientific advice from EMA or other regulatory authorities?

- Dr. Béduer responded that in Europe, notified bodies will not consult or advise you. However, there are meetings where you can provide your documentation and they can give hints. In the US, there are pre-submission meetings where they can give you advice.

What are the main aspects to consider from your experience to enable a smooth regulatory approval?

- Dr. Quesada mentioned that is important to start with ISO certification early on. Even if the idea is to licence out, bigger companies will still ask for ISO certificates. Therefore, is important to start by getting ISOs in the beginning.
- Dr. Peter commented that the right mindset is crucial: if you feel that regulatory aspects can help you, it starts being helpful. If you start with regulatory in the beginning, start thinking what is necessary, what you should be prepared for based on the usability of the product. If you start developing something without this exercise, you develop the prototype fast, but you will spend way more time on the other steps.
- Dr. Schnitzer added that for them it was useful to use ISO/FDA-certified partners, who audited them and helped increase their knowledge. This adaption is now an advantage.
- Eng. Sipos indicated that when they develop a scaffold for someone else, in parallel to production, they validate the product. The consumer should tell you how they want to validate the procedure. At Rescoll, they develop and certify simultaneously.

Wrap up and closure

Following key takeaways from this discussion were underlined by the panellists:

- Keep close to the patient (design, needs).
- Keep it simple.
- Regulations cannot be changed, innovators need to comply and start thinking about regulatory strategy early.
- Engage with clinicians, they are the ambassadors of the technology to solution.
- Think about HTA, it will support your development.