Title

Translational Research Symposium – Collaborative efforts as driving forces of healthcare innovation

Authors

João Q. Coentro[+] (1, 2), Andrea De Pieri[+] (1, 2, 3), Diana Gaspar[+] (1, 2), Dimitrios Tsiapalis[+] (1, 2), Dimitrios I. Zeugolis (1, 2), Yves Bayon* (4)

Affiliations

(1) Regenerative, Modular & Developmental Engineering Laboratory (REMODEL), National University of Galway Ireland (NUI Galway), Galway, Ireland

(2) Science Foundation Ireland (SFI) Centre for Research in Medical Devices (CÚRAM), National University of Galway Ireland (NUI Galway), Galway, Ireland

(3) Proxy Biomedical, Spiddal, Galway, Ireland

(4) Medtronic, Sofradim Production, Trevoux, France

+João Q. Coentro, Andrea De Pieri, Diana Gaspar and Dimitrios Tsiapalis share equally first authorship.

* Corresponding author: Yves Bayon, Medtronic, Sofradim Productions, Trevoux, France. Telephone +33 4 74 08 90 00; Email: yves.bayon@medtronic.com

Abstract

The 5th Translational Research Symposium was organised at the annual meeting of the European Society for Biomaterials 2018, Maastricht, the Netherlands, with emphasis on the future of emerging and smart technologies for healthcare in Europe. Invited speakers from academia and industry highlighted the vision and expectations of healthcare in Europe beyond 2020 and the perspectives of innovation stakeholders, such as small and medium enterprises, large companies and Universities. The aim of the present article is to summarise and explain the main statements made during the symposium, with particular attention on the need to identify unmet clinical needs and their efficient translation into healthcare solutions through active collaborations between all the participants involved in the value chain.

Introduction

Traditionally, the medical device industry has been driven by technological innovation to address clinical needs. As pressure on healthcare systems increases, there are foundational changes in the care delivery model, and as a result, the industry value chain is up for a drastic overhaul. During the 5th Translational Research Symposium (TRS), organised at the annual meeting of the European Society for Biomaterials (ESB) 2018 in Maastricht (the Netherlands), speakers from industry and research institutes discussed and described the future of healthcare in Europe. Moreover, importance was given on the need to identify unmet clinical needs and improve collaborations between industry and academic institutions for the development of new solutions.

The Esther vision – Towards a novel healthcare system

The combination of an ageing population and pressure on health budgets is pushing European countries to find ways to reduce the growing burdens of healthcare systems. For this reason, a paradigm shift is currently taking place in healthcare from symptomatic treatment of (acute) diseases towards the so called Predictive, Preventive, Personalized and Participatory (P4) medicine. P4 Medicine will offer new opportunities for patients and the healthcare systems in Europe [1]. In this changing environment, the overall aim of stakeholders should be improving collaboration and closer feedback loops between basic research, applied research, entrepreneurial innovation & MedTech regulations, with strengthened roles of patient communities, to support the changing healthcare systems.

To effectively address these issues, the MedTech industry has reached a consensus among multinational companies (MNCs) and small and medium enterprises (SMEs) to join forces with European public authorities and other healthcare stakeholders in an Industry Driven Initiative on Emerging and Strategic Technologies for Healthcare (ESTHER). This task force was very inclusive of the HealthTech / MedTech value chain stakeholders, with the representation of MNCs, SMEs, trade associations, technology providers, clinicians, regions and clusters. Although the borders

between Pharma and HealthTech / MedTech are becoming looser with anticipated benefits from cross-sectorial partnerships, ESTHER was built-up as the counterpart of the Pharma industry initiative [Innovative Medicines Initiative (IMI) - A health institutional public private partnerships (iPPP) program], to reflect the uniqueness of HealthTech / MedTech innovation challenges and priorities (e.g. product development cycles, business models). ESTHER proposed a strategy roadmap, inspired by growing challenges (e.g. increasing cost of healthcare, ageing population associated with a rise in chronic diseases and comorbidity prevalence, the threat of antimicrobial resistance, uneven access to healthcare in Europe), to deliver optimal healthcare services to all European citizens in an equitable way [2]. The combination of emerging medical technologies associated to digitization should be a major game changer in healthcare innovation. The convergence of Key Enabling Technologies (KETs), namely nanotechnologies, advanced materials, micro / nano electronics, photonics, biotechnologies and advanced manufacturing associated with big data and digital technologies should offer new possibilities. For example, it should allow more precise understanding of the progress of chronic diseases with more effective prevention and detection. This should also facilitate the integrated healthcare approach with more personalised and cost-effective treatment of disease conditions. Therefore, to enable this healthcare transformation, Research and Innovation Programmes should improve public-private co-operations to:

- Advance patient-centric, integrated and holistic healthcare solutions;
- Develop and integrate the full potential of digital health into care models through connecting devices, managing data from gathering to analysis and correlation, and adapting artificial intelligence (AI), new protocols and innovative digital technologies;
- Speed up the development of KETs, as well as molecular technologies and next generation sequencing (NGS), which build the basis for many innovative medical devices and *in vitro* diagnostic tests.

Over the years, numerous products have been developed, including nanocomponents for hard and soft tissue engineering, pancreatic constructs for pancreatic islet transplantation, bioactive dermal

triggers for dermis tissue engineering, bioactive bone and cartilage constructs for osteochondral regeneration and myocardial and liver triggers for myocardium and liver engineering, respectively. There was also an apparent blossoming of various technological areas, such as material design and synthesis, engineering new methods of assembling, cell engineering and bioreactors. Moreover, it was observed a growth in the development of KETs of nanostructured and bio-competent components, bio-active analogues and scale-up and Good Manufacturing Practice (GMP) of synthetic methods. Despite the recent technological advances in the field of tissue engineering, the ESB community has identified the pressing need of translating advanced biomaterials solutions into meaningful outcomes, such as functional biomaterials, advanced therapy medical products (ATMPs) and theranostics. This need is also strengthened by the predictions of using more sophisticated biomaterials to support tissue regeneration by 2025 [3].

Most of the current commercially available implants are intended to repair defective tissues. However, these medical devices may be associated with complications, such as adverse immune-reactions [4], inappropriate degradability in clinical settings [5] or failure of the device. Therefore, the ESB's perspective is the development of disruptive innovative biomaterials, with emphasis in tissue integration and regeneration. Smart biomaterials can be designed to be structurally simple and affordable, yet functionally complex enough to trigger biological processes to promote the body's inherent capacity of healing and self-repair. To this end, surface properties of biomaterials such as topography, rigidity, roughness and chemistry play a critical role in cell responses such as attachment, migration, proliferation and differentiation [6, 7]. Another type of approach involves the use of synthetic biomaterials that fully integrate molecular cues and recapitulate certain structural aspects of the native tissue or function of the native extracellular matrix (ECM). These biomimetic / bioactive biomaterials that mimic the advantageous features of the natural ECM should facilitate cell recruiting, adhesion, proliferation, differentiation and neotissue formation [8]. An example of this is the design of bottom-up self-assembled approaches that will accelerate the production and deposition of cell and tissue-specific ECM, controlling thereof the phenotype of permanently differentiated cells phenotype

or directing stem cell lineage commitment [9-12]. Such strategies will enable the formation of bioengineered tissue equivalents with high levels of biomimicry that can be used as substrates for tissue engineering applications. Biomaterials with multi-cargo capacity that can act as controlled delivery vehicles of multiple bioactive molecules will also play a relevant role in the development of more biologically relevant, scalable and safe implantable devices [13]. However, the scope of ESB goes beyond just designing functional implantable devices, with one of their goals being to also recreate three-dimensional systems as *in vitro* pathophysiology models. Thus, different biomaterials such as hydrogels, electro-spun fibres, sponges and decellularised tissue grafts are gaining popularity to imitate the malignant tissue microenvironment (e.g. cancer) for drug development and screening [14]. Theranostics is a field of medicine focusing on diseases by combining specific treatments and precise diagnostic tests. The theranostics model aspires to develop a single agent that will enable diagnosis, molecular delivery and monitoring of the treatment [15]. Theranostic materials hold a great potential to facilitate enhanced cargo's therapeutic efficacy and reduced off-target toxicity [16]. Imaging agents allow monitoring of the release of the drug, the active and passive targeting and the progression of the treatment [17]. Nonetheless, implementation of advanced biomaterials into clinical application includes certain difficulties, such as the missing expertise, the lack of a well-defined regulatory framework regarding the ISO guidelines for medical devices and the clear allocation of responsibilities between academia and industry. To overcome these limitations, ESB has proposed a model of technopreneurship, inspired by the multidisciplinary process of drug discovery. This process involves the identification of the need to develop a treatment or a product, the preliminary biological validation, the target characterisation, the lead optimisation, preclinical validation and then the continued development and the large-scale production. Thus, different stakeholders, including academia, industry, hospitals, governmental agencies / offices and health technology assessment (HTA) organisations with specific expertise on the various steps of the process should closely collaborate to

- identify the clinical need,

- develop a treatment or advanced biomaterials, and
- get market approval of the medical products and, possibly, their reimbursement.

Taking a step back – Refocusing innovation on clinical needs

An important matter discussed during the 5th ESB TRS was the need to shift the focus back to unmet clinical needs, as there is a great disconnect between innovative biomaterials and measurable patient benefits. Often, research and development providers try to look for applications of newly developed technologies, instead of starting from the identification of well-defined clinical needs. This results in a very low success rate for translational research, highlighting the need for further collaborative interdisciplinary work that prioritises clinical outcomes with patient-centric approaches.

SMEs account for approximately 95 % of the MedTech companies in Europe [18]. Since large companies usually target acquisition of smaller enterprises, along with their intellectual property (IP) and products, it is becoming apparent that SMEs are in fact the drivers of innovation in the field. However, due to the *biomaterials paradox*, where it can be hard to attract large industry investment if a new technology is not novel enough or if it is too novel, it can be hard for SMEs to be commercially successful, further increasing the difficulty in bridging the gap to the clinics. This is further aggravated when SMEs fail to translate promising research due to lack of commercial development experience (e.g. with regulatory, production logistics and sales management [19]), as is evidenced by a reluctance in adopting new, unproven biomedical products that fail to prove measurable clinical benefits [20]. This has been observed, for example, in the orthopaedic industry, where innovation has declined over the last 30 years, with many companies just deciding to acquire smaller companies rather than investing in new product development projects, due to their high risks and costs [21].

This clear disconnect between new technologies and actual significant improvement for patient benefits highlights the need to first identify a clear unmet clinical need. One representative case of this type of approach can be found in the development of orthopaedic screws for improved imaging of spine tumours. One of the most used and effective methods to treat spine tumours is the combination of radiotherapy and surgery [22]. However, conventional pedicle titanium screws can lead to the creation of imaging artefacts, due to radiation scattering, which can in turn limit the dose

of radiation used and difficult the imaging of the irradiated area, reducing treatment efficacy. The early determination of this problem as an unmet clinical need was the driving force behind the development of enhanced screws that can prevent this. For instance, the augmentation of the implant-bone interface through a coating system, namely polyethyl–ether–ether–ketone, has been shown to reduce radiation scattering and artefact creation, leading to improved imaging and therapeutic effect [23]. This has been successfully applied in the treatment of spine tumours, with the improved imaging resulting in the early detection of 6 tumour recurrences [24].

It is also worth noting that focussing on specific needs leads to realistic goals and expectations. Such is the case for the development of treatments for diabetes mellitus, given that this is a manageable condition and emphasis is placed on improving current treatments. It is estimated that 422 million patients worldwide suffer from this condition, with an estimated incidence of up to 10 % being diagnosed with type I [25]. This is mostly characterised by the autoimmune destruction of insulin producing beta cells in pancreas, independently of life style factors, resulting in varying glucose levels for the patient [26, 25]. Current treatment approaches try to mimic the sensory and secretory function of pancreatic islet cells, which can be a very unreliable method of treatment, resulting in variable levels of glucose, with recurrent low blood levels, that are counteracted by regular insulin administrations [27]. There is a clear need for patient-friendly treatment and, ideally, a cure [28]. Therefore, new developments should focus on realistic treatment goals with more stable glycaemic controls over time and limited side effects. Promising solutions include closed loop insulin delivery systems [29] and beta-cell replacement therapy [30]. While the former has been shown to improve glycaemic control and reduce time spent in hypoglycaemia, it may still suffer from delays in glucose measurement and insulin action, thus giving here margins of improvement for even better control of the glycaemic levels. Despite this, it is expected that these devices can serve as a treatment option for the short-term application in the clinic. Beta cell transplantation has been successfully used in the clinics, greatly improving glycaemic control [31], however its generalised application can be hindered by donor organ shortage and the need for immunosuppressant drugs, which have associated side-

effects [32], as well as uncertainty regarding the long term (e.g. several years) persistence of clinical benefits with such an approach [33]. This could be overcome by the use of stem cell-derived beta cells and the use of immune-evasive delivery vehicles, which show great promise as a long-term solution [34]. However, their large scale implementation in the clinics is still far from becoming a reality for a number of factors, beyond just technical challenges, including, high average selling cost and long path to regulatory approval [35].

Cardiovascular diseases account for approximately 47 % of deaths in Europe and an associated cost of €200 billion per year to the European economy, thus making them a pressing concern for healthcare research [36]. Making the most of a multidisciplinary team including industry, clinic and academic research partners, the NanoAthero consortium, funded by the European Union FP7, is focused on the development of nanomedicine applications for the treatment of atherosclerosis. Fucoidan can act as a ligand of p-selectin, which is expressed in activated platelets and acts on leukocyte recruitment, therefore being present in structures such as blood clots [35]. Further, fucoidan, a brown algae sulphated L-fucose-rich polysaccharide [37] has been shown to have a diverse range of potential applications, including immune modulation [38, 39], cancer inhibition [40], pathogen inhibition [41] exhibiting proangiogenic effects [42] and even anti-thrombotic effects [43]. This led to the idea that nanoparticles functionalized with a contrast agent and fucoidan could be used for the detection and live imaging of a thrombus through single-photon emission computed tomography (SPECT) imaging [44]. This idea was confirmed through successive testing, with involvement from all the partners of the consortium, starting from the synthesis of the nanoparticles *in vitro*, followed by *in vitro* safety and proof of concept assays, which were then confirmed in *ex vivo* and *in vivo* studies and finally in a phase I clinical trial with GMP-grade fucoidan nanoparticles.

During the development of new therapies, a vast amount of preclinical and clinical information is produced, with part of it being publicly available in several databases, allowing for the meta-analysis of different therapeutic agents and their efficacy when translated to the clinic [45, 46]. Such is the case with nanotherapeutics designed for the delivery of anti-tumour drugs, which despite showing a

great potential, have failed to translate successfully in most cases to clinic (e.g. Opaxio™, PCNU16614™ and PNU166945™) [47, 48]. Many of these systems have fallen short of showing an enhanced anti-cancer effectiveness when compared to the administration of the correspondent free drugs [49]. This can severely compromise the credibility for this type of research, due to the lack of *in vitro* to *in vivo* correlations, highlighting the need for more reliable pathophysiological models. Exaggerated claims regarding the efficacy of new treatments in a preclinical stage, can be questioned by the different stakeholders involved and hinder the clinical assessment of new therapies.

There is a need for the development of more integrated systems that can be used for the elaboration of systematic efficiency meta-analysis studies, with a focus on transparent information disclosure that can lead to evidence-based therapeutic innovation [50, 51]. Along these lines, improvement on some factors will be crucial for this methodology to succeed. Some examples include: improving *in vitro-in vivo* validations by developing more individualised models with patient's cells instead of cell lines and choosing *in vivo* models representative of the disease, focus on better understanding the different biodistributions of materials in animal models versus humans; carefully designing materials so that drugs and their delivery systems better suit the specific disease sites; developing suitable biomarkers that can accurately measure the efficacy of a novel drug; and finally, to design more patient-centric clinical trials, which try to involve all the different stakeholders on the life cycle of a product and reduce the speculation around preclinical results, which can generate unrealistic expectations for this type of therapies [52, 53].

Enter ECRIN - Driving innovation by collaboration

Interdisciplinarity and collaboration between partners with different types of expertise are essential for successfully being able to bridge the gap between academia and clinic in the current MedTech landscape. As such, new methods of pioneering innovation are necessary to continue to strive in a dynamic and highly competitive MedTech sector. International and inter-sectorial collaborations are also of paramount importance for successful clinical translation of novel therapeutic approaches [54].

The European Clinical Research Infrastructure Network (ECRIN) is an example of a non-profit organisation, which allows to connect scientific partners and networks across Europe to facilitate multinational clinical research. ECRIN is funded directly by governments of member countries (Czech Republic, France, Germany, Hungary, Ireland, Italy, Norway, Portugal and Spain). ECRIN provides several services to support clinical trials from beginning to end, including trial design and methodology, investigation sites and patient recruitment, funding applications, regulatory affairs, assessment of project implementation plan, trial coordination and data management. Access to such support services allows the entities involved to ensure consistent implementation of standard operation procedures, therefore leading to collection and analysis of more reliable and reproducible data, whilst overcoming limitations of human and financial local resources [55, 56]. Particularly for the clinical translation of medical devices there are specific barriers, including randomisation, choice of control group, timing of assessment, learning curve of implantation procedure, outcome evaluation, lack of scientific advice and regulations, that ECRIN aims at overcoming [57, 58]. Further, another recurrent issue in medical device testing is a reporting bias from industry funded trials, which tend to favour experimental clinical intervention even when non-significant data is obtained [57]. Although industrial involvement is key to drive technological advances, multi-sectorial involvement, particularly of non-profit entities such as ECRIN, becomes of the outmost importance to ensure clinical research and innovation are based on scientific grounds and fully transparent.

Evolution of the innovation models – Examples of research partnerships

One example of success in translational medicine following this philosophy is that of Medtronic – Sofradim Production (Trevoux, France), which focuses on medical device development. On their opinion, open innovation may be, on a case by case approach, a valuable option to collaborate with partners having complementary expertise, particularly for potentially disruptive projects at an exploratory stage. Some fruitful examples of this type of partnership are the Tendon Therapy Train project and the Penta Aenas EU Serene IoT project. For these projects, academic institutes, clinics

and companies brought together their expertise to explore new biomaterial formulations for tendon tissue repair, and the integration and analysis of patient's data in the clinical environment though interconnected medical devices, respectively.

Another successful example of this kind of integrative collaboration brought together academic (National University of Ireland Galway), industry (Neuravi, Galway, Ireland) and clinical (Mayo Clinic, Rochester, U.S.A) partners with the joint goal to better understand and characterise blood clot composition in acute ischemic stroke in order to identify novel biomarkers that could feed into the improvement of thrombectomy device development [59]. This illustrates the advantages of creating a project comprising different key stakeholders, as their varied expertise and specific needs come into play and result into a much more focused product development.

One other successful partnership includes that of Viscus Biologics LLC (Ohio, USA) with the National University of Ireland Galway in the assessment of decellularized porcine peritoneum as a tendon protective sheet in tendon tissue engineering [60]. Ingrained in their vision statement, the objective to collaborate with key opinion leaders, end users and institutions in order to guide the design of new solutions has led Viscus to collaborate with an academic partner. Thus their end goal of validating and characterizing the potential applications for their products by an independent partner has resulted in an unbiased assessment of their product, which in turn leads to safer and more effective product development.

In general, it seems that over the last decade, many companies have started to shift their focus from internal discovery to external engagement, opening their minds to the potential benefits of such collaborations, which has also been embraced by many scholars and consequently, governments, that have started to re-align their policy-making frameworks to focus more on open-innovation projects [61]. Regarding academic and industry interaction, these can be distinguished into two types, formal and informal interactions, with consulting, contract and collaborative research being included in the former and academic engagement, counselling and networking with practitioners in the latter. As these different models involve different types of commitment and revenue generation, capable

support structures are essential to guiding both academic and industry partners in their relationships, on how to better optimise them, so that both partners can benefit the most from that partnership [62]. When taking this into account, in an increasingly competitive environment, such as the medical device sector, multi-disciplinary collaborations are the key for success. To survive in such an environment, SMEs need to create new business models (such as syndicates of interconnected SMEs or even partnerships with larger companies at early stages of commercial development) and create disruptive technologies focused on unmet clinical needs and/or generating clear added value from patient quality of life and cost-effectiveness perspectives. These types of syndicates and collaborations between different companies allows them to complement each other's specialities and expertise. This results in a much more effective product development altogether, that can benefit each of the partners more than if they were acting on their own. The same strategy can be followed by collaborating with large established companies. They can provide unique insights based on their vast experience of commercial translation at a large market scale, such as:

- with key experts in their domains such as R&D&I, Clinical & Medical, Marketing, Regulatory Affairs, having tackled issues for several major projects,
- from their access to dense networks of key opinion leaders (KOL) for the evaluation of products in terms of fulfilment of clinical needs and usability, from the early stage of development, and
- extensive market access experience.

Beyond of this experience that could benefit the youngest SMEs, additional support may be financial and facilitating the distribution of final products. These examples illustrate the necessity for companies to diversify their business models and create inventive partnerships to gain effectiveness and competitiveness in a global market such as well thought-out and balanced open innovation approaches [54].

Conclusions and future perspectives

Clinical translation of novel therapeutics is still to this day hindered by an extremely low commercial success rate, with high associated costs and risks during their development. In the past, technical innovation has been the driving force for the development of new clinical treatments. However, there is currently a great disconnect between the development of innovative biomaterials and measurable patient benefits. This is aggravated by rising pressures on the global healthcare systems due to an increasingly ageing population, health budget constraints and a gradual shift from acute to chronic care, which altogether impose the need for a paradigm change in clinical development. As such, it is imperative to refocus the development of medical devices on well-defined unmet clinical needs, while prioritising the patients' clinical outcomes and wellbeing. With this paradigm shift in course, it is important that the interests of all the health stakeholders are aligned to maximise the chances of commercial success. With this in mind, initiatives such as ESTHER, which bring together industry partners, public research institutions, public authorities and other healthcare stakeholders are invaluable in providing guidance and establishing guidelines for other institutions and partners to follow. To achieve these goals, several approaches were discussed during the TRS symposium at ESB 2018, with the take-home message being that as the development of medical products becomes more specialized and complex, it is crucial that innovation stems from interdisciplinary and collaborative ventures, involving partners with different expertise. It is expected that this will increase the commercial viability and success rate of new products, ultimately helping bridge the gap between academia and clinic. It was also advocated that a model based on open innovation might be the ideal solution in some specific cases, specifically when dealing with highly exploratory and disrupting technologies, which would need to be supported by public-private partnerships and public funding. Other disruptive business strategies that can allow SMEs to remain competitive and continue to drive innovation in the field include the creation of syndicates of interconnected SMEs or partnerships with larger companies at early stages of commercial development, to complement their know-how, resulting in a more effective product development. In the coming years, clinical translation will be more focused on clearly defined unmet clinical needs, with integrated medical data analysis feeding

directly into the development process. Meanwhile, disruptive interdisciplinary collaborations between different stakeholders will become the main drivers of innovation in the field, resulting in a more efficient and successful product development, which will ultimately improve the patients' access to adequate healthcare and their quality of life.

Author Declaration

JQC, ADP, DG, DT and DIZ have no conflicting interests. YB is an employee of Medtronic – Sofradim Production.

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