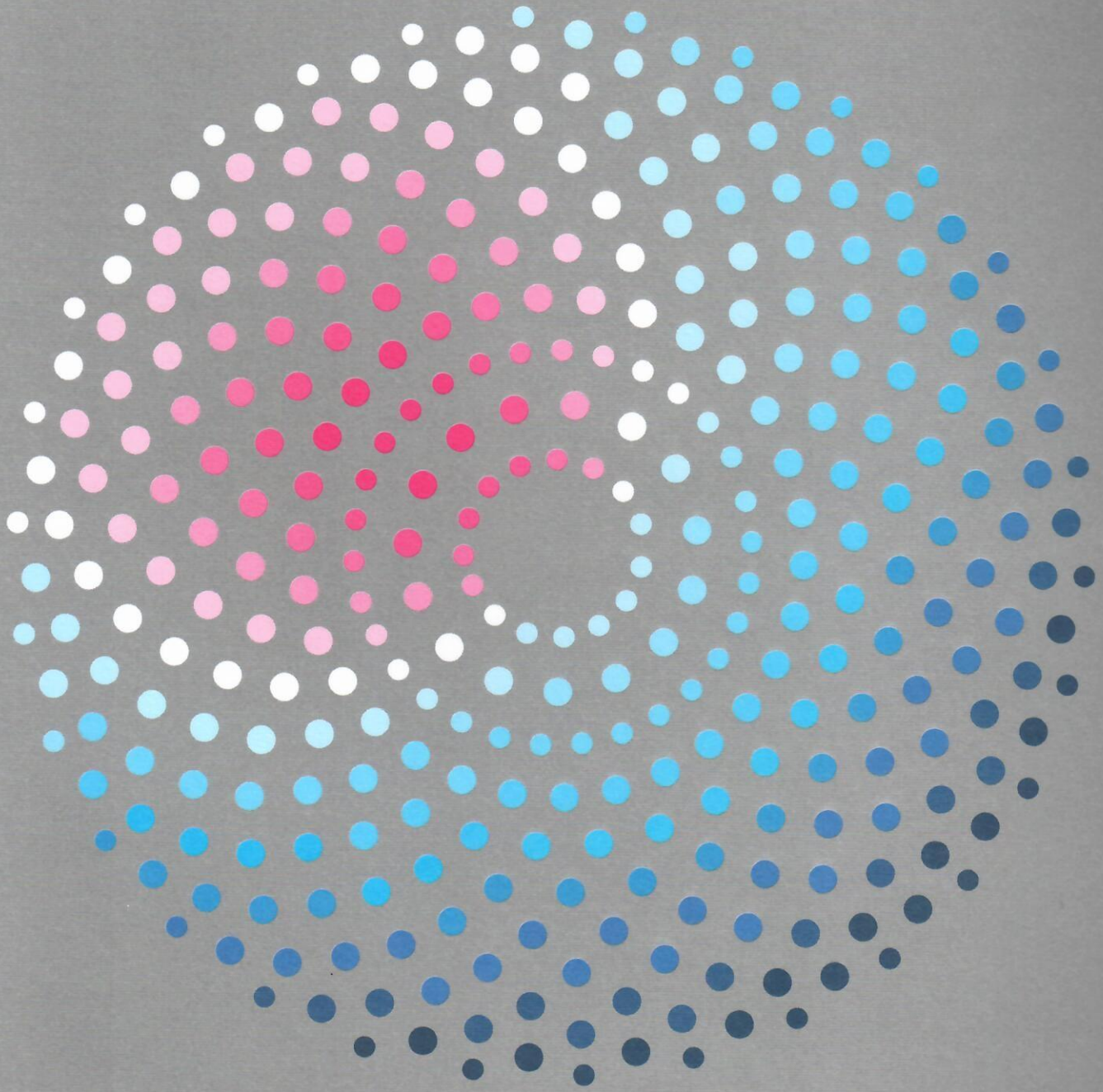
A REPORT ON THE BIOMATERIALS RESEARCH TRANSLATION IN EUROPE



European Society for Biomaterials

40 years 1976-2016

OPINION LEADERS' PAPERS

The Editor's Introduction

Biomaterials : *quo vadis*

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On the initiative of the ESB President, Prof. Matteo Santin, with the unanimous agreement of the Council of the ESB, Prof. Maria Dulce Nombre Vallet Regi and I approached several senior members of the Biomaterials Community to solicit their "Opinion" on the future directions of Biomaterials Research.

We are greatful to all those colleagues for their contributions, which follow.

These short papers reveal to the younger generation of Biomaterials Scientists the evolving approaches to dealing with such a complex, highly interdisciplinary scientific subject with the final aim of offering useful therapeutic tools and devices to the 'clinical arsenal'.

As it may be discerned through these Opinion Papers, great advances have already taken place.

And, despite the title of the book that my good friend the late Prof. Jozef Helsen and I published in 2010 " BIOMATERIALS, a Tantalus Experience " , we would like to encourage once again the scientific community to reflect on the following:

'Myths are created by the powerful to intimidate the public even when they are charming. But myths are also useful in driving our thoughts beyond the current horizons of knowledge.'

Stepping gently on the shoulders of the pioneers of this exciting field, new advances are at the horizon to contribute to a healthier life in a better society, with peace reigning everywhere.

Finally, let me say that "words" are useful when are followed by the right "actions".

The biomaterials debate

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A 'leading opinion' should be an authoritative, informed but opinionated, presentation of the status of a subject; it may in part be reminiscent and in part prognostication, but should always be written by someone who has made a contribution to that which is being reminisced about and who also has a stake in that which is prognosticated. Intellectually-informed, but not idly-constructed, controversial statements should add to the value of, and interest in, such a leading opinion. So, what can be said of the status of biomaterials science, a subject which may sound dry and unappealing to the disinterested layman, but which impacts the lives of millions of people, mostly in the rich developed world but increasingly in the poorer emerging and developing world.

There can be no doubt that biomaterials (note that I use the simple noun here and not the compound noun, biomaterials science) have revolutionized areas of medical therapies, transforming or extending the lives of very many patients. This is self-evident from the current-day situation where the sight of millions of people is dependent on the polymers of intraocular lenses, continued heart function in equal numbers is predicated on implanted pacemakers, defibrillators, heart valves and coronary stents, where haemodialysis extends the life of those suffering end stage renal failure, joint replacements allow millions to walk again with freedom from pain, and so on. The reminiscent part of this opinion starts with my early professional life experiences of meeting and talking with some of the pioneers of these clinical technologies, including John Charnley, Willem Kolff, Chris Barnard and Denton Cooley. The overwhelming memories of such meetings were of ambitious, totally driven individuals who, through intuition, conviction and perseverance, visualized and implemented radically new therapies and products. The risks that they took were considerable, and such 'experimental surgery' would not be allowed now; it is quite possible that today's armamentarium of medical devices and procedures would not exist without the benefits of these human experiments. However, although the selection of materials for these products was an important consideration, it was not the most significant, and many pioneers quite simply got the material selection wrong, largely because of a lack of appreciation of the critical balance between functionality and biocompatibility.

The situation has changed somewhat by today, but we have to ask ourselves, how and why. The reason why I stated earlier that it was biomaterials and not biomaterials science that have revolutionized medical therapies, is that biomaterials science still does not properly recognize the criticality of this balance. The problematic use of metal-on-metal hip replacements revealed a poor understanding of the difference between tissue responses to micron-sized polymer wear debris and nano-sized cobalt-chromium wear particles. The reason why polypropylene meshes fail to give 100% satisfaction in urogynaecology applications is related to the poor understanding of the contributions of the biomechanics, sub-clinical infection and the inflammation – fibrosis balance in the female pelvic area. This lack of understanding is now getting in the way of progress in the newer areas of biomaterials applications, including scaffolds (or templates) in tissue engineering and systemically injected nanoparticulate products for diagnostic and therapeutic purposes in the area of nanomedicine.

To put this into perspective, and to pave the way for the prognostication part, it has become increasingly obvious, at least to me, that success with biomaterials-based medical devices is generally achieved when the material is maximally inert, from chemical

and biological perspectives. With so much discussion about 'smart' materials, it is worth considering that the smartest materials are the most inert materials, since they may passively avoid the defenses of the human body. Indeed, the evidence suggests that, through following this maxim, with most types of implantable device, performance is controlled first by the quality of the surgery, second by the characteristics of the patient, and only third by the nature of the biomaterial. As I have argued recently (Williams DF Biocompatibility pathways: Biomaterials-induced sterile inflammation, mechanotransduction and principles of biocompatibility control, ACS Biomaterials Science and Engineering 2017,3(1),2-35), the ability to achieve better performance, especially in newer technologies such as tissue engineering and contrast agents, is dependent on a better understanding of the mechanisms of biocompatibility pathways, and the use of this knowledge to control the pathways and the eventual outcome within the host. It is time for the science of biomaterials to catch up with their contribution to health care.

Biomaterials new frontiers: from synthesis to engineering

Biocues-tethered biomaterials and their future applications

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State-of-the-art of the biomaterial science: basic knowledge and R&D

Implantable materials have made an enormous impact on the treatment of injury and disease of the human body throughout time, particularly after the initiation of aseptic surgical techniques in the late 1800's. Simple materials like glass and clothing materials have functioned surprisingly well to replace a damaged human body part as a non-living prosthetic and have increased the quality of life for many patients. As our understanding of developmental biology, disease, and healthy tissue and organ structure and function has improved, the concept of attempting to regenerate damaged tissues with biomaterials rather than simply replacing them emerged. Biomaterials can impact cell function like an extracellular matrix through similar cell-extracellular matrix mechanisms. Cues for proliferation or differentiation can be provided directly by the biomaterials surface chemistry, 2-D features, topography and pore size. As the material degrades, different signals may be presented to the cells from the degradation products of the biomaterial. Degradation products of biomaterials may provide undesirable cell signals; for example, inflammation due to particulate debris may lead to a complete loss of the newly regenerated tissue.

Translation into clinics/market: successes and limitations

Translation into the clinics/market has been relatively easy for devices made of biomaterials. Widely used biomaterial devices that positively impact human health include metallic and polymeric hip and knee implants, heart valves, stents and contact lenses. Important quality measures include measurements of physical and chemical structure and biocompatibility testing and degradation. Carefully documented and successfully completed in vitro and in vivo animal safety testing is required at the time of application to gain Food and Drug Administration (FDA) approval to begin a human clinical trial. In the last 20 years biomaterials use has been extended from a relatively inert device to an active delivery vehicle for biomolecules that guide cell behavior. This blending of aspects of pharmaceutics and engineering within a single product has made FDA regulatory approval of biomaterials combination products more complicated. Biomaterials use as scaffolds for cell therapy also have further complicated translation efforts. Standardized testing and characterization methods that can verify the postulated activity of biomaterials in drug delivery and tissue engineering/cell therapy products is being developed through the International Standards Organization (ISO) and the American Society of Testing and Materials International (ASTM). Since the FDA will accept test results obtained using these standards as part of the package submitted to gain FDA approval, standards may help accelerate the FDA approval process for combination products. Experts from academia and industry and medicine are always being sought out to participate in ASTM (www.astm.org) standards writing.

A vision for the future

The biomaterial surface plays a critical role in determining

tissue–biomaterial interactions and this concept has governed the development of many new surface modification techniques that continue to increase efficacy of biomaterials. Surface modification thus remains an important area for research in biomaterials and includes surface modification of diagnostic implants seeking to detect variations in the health status of a person. Biomaterial surfaces that support organ-on-a-chip technology by providing tissue specific cues that mimic extracellular matrix guidance of the development and maintenance of various tissues are also needed. The use of nanomaterials to deliver biomolecules systemically in a targeted fashion based on the presentation of cell specific ligands to cells requiring the therapeutic will be a continued area of growth within the biomaterials industry. Biomimetic design of biomaterial scaffolds with the ability to spatially and temporally control delivery of multiple growth factors is another futuristic product design feature. Tissue regeneration can be optimized by sequential presentation of biological cues to cells, rather than co-delivery, in order to most efficiently guide cells along a differentiation or de-differentiation pathway. Despite extensive research at top hospitals and universities and corporations around the world, there are still many unanswered questions regarding the biological response to biomaterials and the optimal role of biomaterials in tissue regeneration. New discoveries in biological research; such as human embryonic stem cells and CRISPR/Cas9 technology for genome editing, will continue to motivate biomaterials research and new product inventions of the future.

Bioceramics and the worlds of meso, micro and nanoscale

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Background

Nowadays, the prefix bio before the term materials has given rise to the incursion of biology in fields as important as engineering, food and health. Biomaterials are classified within the field of biomedical engineering and combine knowledge from the worlds of science, engineering, biology and medicine. The evolution of medicine has gone from intuition to evidence and is now evolving towards prediction, using computer data in clinical records, which aims to reach a personalized medicine; hence it requires knowledge of mathematics. The evolution of biomaterials in the last 70 years has also been remarkable. The shift from using inert materials to replace living tissue, towards the design of bioactive, biodegradable materials aimed at repairing said tissues, has led to a third generation of biomaterials where the emphasis is in tissue and organ regeneration. This evolution, in a relatively short time lapse, has changed many concepts. The qualitative shift from replace to repair is already surpassed by the idea of regeneration. First generation biomaterials were not specifically designed to interact with the biology world; third generation biomaterials, on the other hand, are designed taking into account their subsequent contact with living tissues and that surface properties of said materials, such as topography, surface charge and all aspects of surface chemistry, play a pivotal role in obtaining a positive outcome when these materials are

implanted among living tissue. This entails a proper functionalization of the free surfaces of these biomaterials, to facilitate cell adhesion, proliferation and differentiation in optimal conditions

Bioceramics

Since the 1950s up to the early 21st century, ceramics have evolved significantly. By mid-20th century, inert ceramics began to be used as replacement of damaged parts of the human skeleton. Only a few ceramics, not specifically designed for biomedical applications –such as alumina and zirconium-, were used. Nowadays, in the 21st century, those bioceramics in clinical use are all specifically designed to repair and regenerate the human skeleton, and several commercial products are in supply for traumatology and maxillofacial surgeons, providing different types of bioceramics. We may consider all these commercially available products as 'traditional' bioceramics, i.e. can be used with all applicable regulations and homologations for this kind of prostheses, fulfilling real and specific needs in the clinical field. Other materials, the so called 'new bioceramics', are instead at the frontier of knowledge; specifically designed for a given function, they will have real applications in the near future and are still a promise.

Evolution in Bioceramics

Third generation bioceramics are used to build scaffolds which support cells performing the regeneration process. Ideally, from the perspective of tissue engineering, said scaffolds should provide mechanical support and biocompatibility, without any induced negative tissue response and with temporary mechanical load bearing capability. In this sense, its degradation rate should be as close as possible to the tissue regeneration rate, interconnected porosity with an optimum pore size distribution, promoting cell and tissue colonization, metabolite transit while offering a high surface area for cell anchoring. There have been great advances in these requirements; four dimensional (4D) printing, for instance, is an emerging technology in tissue and organ engineering which is based in multi-material reprogramming, capable of changing form, function and/or properties trying to adapt to the environment. In the specific issue of tissue and organ regeneration applications, printing materials must be biocompatible and able to perform 4D dynamic processes in a physiological environment. There is still a long road to go, with great requirements of scientific and technological workloads, but 4D printing can clearly be a powerful tool in the future to carry out biomedical studies of functional synthetic organs and tissues.

The nano- prefix in biomaterials

The emergence of nanoscience and nanotechnology as areas of enormous interest in research is experiencing a dramatic development.
Advances in the preparation of nano-systems with applications in the field of medicine have given rise to new challenges in the design of smart materials capable of responding to new clinical requirements, and various types of ceramic nanoparticles play an important role in this context.
A common concern in medicine is to be able to administer therapeutic agents to the patient through a physiologically more acceptable route. In many cases, the dosages are excessively high, but are prescribed to ensure that the minimum required dose reaches the area where it is needed. But most of the dose administered to the patient, or should we say nearly all of it, acts throughout the whole body, affecting regions where it should not be acting. Therefore, large doses are required in many cases because the drug is released along the way, not specifically, and in areas where it is not necessary. This problem is exacerbated in oncology treatments, where the risk-benefit ratio associated with chemotherapy often makes it difficult to take a wise decision, as a consequence of the cytotoxicity of the drugs to be used. It is generally accepted that the absorption of the drug by the body is favored by its smaller size and by the overlay or packaging material used. A local and smart drug release would be

the answer to these issues. The main advantage of many nano- or microparticles, such as silica mesoporous particles, is their potential multifunctionality. Among the different functions that can be simultaneously achieved we may highlight the following: Load and subsequent release of different drugs, anchoring of biomolecules such as proteins, vectoring agents or nucleic acids to the external surface of the particle and towards therapeutic targets, anchoring of fluorescent molecules or active complexes for magnetic resonance imaging (MRI) in order to perform optical monitoring, inclusion of magnetic nanoparticles, coating with different materials such as certain polymers or metals such as gold.

The Road to the Future

The future development in biomaterials, both in the form of prostheses or replacement parts and as nanoparticles, will require all of these size scales: PICO, NANO, MICRO and MACRO, while molecular and cell biology will provide solutions to clinical problems. Biomaterials porosity should be analyzed at all size scales, in order to understand them and offer new solutions to specific issues. New and future technologies will provide new solutions, and the use of cell-free organs as scaffolds could, with time, be the answer to many problems. The development of biomaterials in 70 years has been astonishing, and it is clear that it will not stop in the near future. Thanks to the advances in molecular and cell biology, these last three decades have been devoted to intensive efforts in regenerative medicine to promote autonomous regeneration of a damaged organ in the body, something already observed in certain species –such as the salamander- but never in humans. Certainly, we are on the right path.

Biocomposites as driving model for future therapy strategy

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Anatomic structures consist of a composite of hard and soft tissues that differ drastically in composition, structure, and properties, and yet integrate and function in synchrony. Because of their ability to mimic the extracellular matrix structure, composite biomaterials have been developed to solve clinical cases in which non-healing conditions prevent tissue repair. Nature-inspired material science can be considered as the last frontier in biomaterials research: indeed, the design of complex structural architectures from sub-micronic to nanometric dimensional scale allows geometrically and topologically mimicking the native state of extracellular matrix and its complex supramolecular assemblies. Composites, Nanofibrous & gel scaffolds could be used to mimic the fibrillar structure of ECM, and provide essential cues for cellular organization, survival and function.

Composite materials with polymeric matrix emerged as strong candidate to substitute metals and ceramics for many applications and lately transferred to the biomedical application. Polymer composites found their applications in load bearing applications (such as hip joint, plates, cages) and as scaffold for tissue engineering and structures for advanced therapy medicine.

Tremendous advances has been made in the composite materials and technologies to design complex structures. Many synthetic and natural polymers, biodegradable and not, have been introduced. Biomaterials, in form of matrix and

reinforcement (fibre and particles) were synthesized to control specific material properties (i.e. hydrophilic/ hydrophobic domains, mechanical, degradation, etc.) and to modulate the biosignals through chemical and surface modification with biomolecules (i.e. peptides, amino acids, etc.), to mimic the environment of living tissue.

Thus, the biocomposites may be considered at the centre of any successful regenerative medicine strategy and provides many essential features and cues to direct the cells toward a functional outcome.

Modern medicine is based on the implementation of a personalised approach together a less invasive surgery for the restoration of human tissues and organs lost to diseases and trauma, this is forced also by the health care system as the related costs are increasing due to the aging population, for the decrease of birth rate and increase of the life expectancy that is frequently not matched by maintenance of health and quality of life.

More advanced techniques are now available which can clearly produce macromolecular structures of nanometres size with a finely controlled atomic composition and architecture. Polymer chemistry combined with novel processing methodologies such as bioprinting, electrospinning, direct patterning and self-assembly have been used to manufacture nano-composites which can lead to design novel advanced bio-inspired materials able to mimic the different types of extracellular matrices. Nanocomposites are continuously under intense investigation in regenerative medicine to change the physical or chemical properties of biomaterials and guide the activation of specific cellular signalling. This is a unique approach for designing a multi-scale, multi-functional and cell-instructive materials.The design of bio-inspired materials, able to guide therapeutically tissue regeneration and repair remain a challenging goal for the future. Moreover, some phenomena have still to be investigated, the capacity to design and understand the multiscale systems is not sufficient, more effort should be done to analyze the interfaces among the "scale". "Smart sensing" can be a methodology that leverage quantum techniques for use in characterizing subcellular behavior. This includes novel methods in the discovery of ground-breaking basic science that can range investigations at the quantum, atomic and molecular scales within the biological landscape. This should aim to better achieve a clearer understanding of chemical biology and biological physics and subsequently to develop the next generation biocomposites, providing appropriate solutions aid in solving the problems of treating chronic disorders in an aging population by tailoring systems for specific patients and disease states.

References

From bench science to clinics: the tortuous journey of translational research

The biomaterials drift from the clinic (and back to the clinic)

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The field of biomaterials as we know it today started in the clinic. Willem Kolff, M.D., in the late 1930's, using sausage casing, a washing machine and some tin cans, demonstrated that a patient with end stage kidney failure could be revived. John Charnley, M.D., in the late 1940's and early 1950's restored ambulation to patients with failed hips using "modern" materials such as stainless steel and ultrahigh molecular weight polyethylene. Harold Ridley, M.D., also in the late 1940's and early 1950's, addressed cataracts, the most common cause of blindness, with an intraocular lens of poly(methyl methacrylate). About 1950, Arthur B. Voorhees, Jr., M.D., developed the first vascular graft from parachute cloth. Other devices with clinical origin from that time period included the artificial heart, the hydrocephalus shunt, dental endosseous implants and finger joint implants (arthoplasty). All these devices were developed by physicians to meet clinical needs, with the focus on directly impacting patients.

In the 1960s, the words "biomaterial" and "biocompatibility" first appeared in the literature and we saw the launch of a nascent community of scientists and engineers working with physicians on clinical issues. By the 1970s that community spearheaded the formation of the Society For Biomaterials, the European Society for Biomaterials and the The Controlled Release Society. These groups were driven more by scientists and engineers than by physicians (note: clinicians were active in the earliest days of these groups, but leadership soon shifted to engineers and scientists). Basic research on themes relevant to biomaterials was launched in the same time period when these research societies evolved. Subjects such as blood compatibility, protein adsorption, cell interactions, osteogenesis, complement activation, bacterial infection and surface analysis began to dominate our scientific forums.

In parallel with the emphasis shift toward science and engineering occurring in the biomaterials field, the molecular biology revolution happened. Biology transformed from a descriptive science to an intellectual partner with chemistry and physics. The importance of DNA and nucleotides was appreciated. Cytokines and cell surface receptors were discovered. Biology was suddenly mechanistic and amenable to being engineered for specific applications. Biomaterials researchers were quick to embrace these ideas and, to this day, biomaterials meetings are dominated by themes addressing basic science relevant to biomaterials issues. These modern biomaterials research themes, for example, tissue engineering, will lead to stunning advances in the future. But, how far in the future? Given our slow-moving regulatory agencies, challenges in manufacturing and risk aversion in commercialization, these ideas may become important 20 or 30 years in the future.

My opinion is that we need to revive some of the "traditional themes" in biomaterials to make progress in the clinic on a time scale responsive to physician and patient needs. At the University of Washington we have launched a Center for Dialysis Innovation (CDI) to have clinical impact in 5 years in one of the earliest of the biomaterials themes, kidney dialysis.
Why do we need progress in kidney dialysis? Consider this. Kidney hemodialysis originated in Seattle in 1960 where the first successful

chronic dialysis took place leading to the world's first dialysis center. Before chronic dialysis people with end-stage renal disease (ESRD) had no options to live beyond about 3 weeks. Chronic dialysis made it possible to sustain the lives of such patients. Now we have some 2,000,000 people worldwide on chronic dialysis. But there are significant concerns. The average lifetime of a patient starting dialysis is 4-5 years due to complications of dialysis. Patients do not feel good while being sustained on dialysis therapy with complications including nausea, itching, fatigue, etc. Dialysis is expensive costing the $100B or more per year worldwide in direct expenses. Finally, due to the expensive and complex nature of dialysis therapy, there are as many as 7.1 million people with ESRD who die each year due to lack of access to this therapy. Little progress has been made in hemodialysis therapy since the 1960's due to an entrenched economic model that does not reward innovation. Many of the complications are associated with "old" biomaterials issues including blood compatibility, biofouling, infection, healing and blood access (thrombosis, blood vessel restenosis).

This opinion paper advocates for an enhanced emphasis on today's patients and for a sharpened focus on clinically-relevant medical devices. We must examine 70 years of biomaterials development and delve into the portfolio of excellent ideas to address immediate clinical issues connected with the human condition and economic stresses on our healthcare systems. The biomaterials of the future must be developed – many of these will trace their roots to tissue engineering and nanotechnology. But, there must also be increased emphasis on what we can do, in the short term, to bring biomaterials research back to the clinic and back to improving the lives of patients.

The biomaterial science: a clinician-scientist's perspective

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From its inception biomaterial science has been interdisciplinary, as the devices designed and manufactured by material scientists and engineers have to be applied to the patient by clinicians. However, the past three-and-a-half decades have witnessed the birth and development of the fields of Tissue Engineering (TE) and Regenerative Medicine (RegMed), which have expanded this interdisciplinarity in a remarkable fashion. How this has evolved within the individual subjects contributing to biomaterials would breach the limits of the present short essay, so that I will confine my remarks to a few selected areas which reflect the perspective of a clincian-scientist, whose research activity has nevertheless been at the basic science end of the spectrum.

In essence, the biomaterial field can be divided into two major areas of scientific endeavour, namely, the materials and the life sciences. The former encompasses all those branches of science necessary to design, develop and produce biomaterials for the clinic, and thus contains numerous disciplines of engineering, but also chemistry and physics. The life sciences are no less multifaceted than the material sciences, and cover a spectrum from numerous basic sciences such as developmental biology, immunology and the various branches of cell and molecular biology via almost all clinical specialities, both conservative and surgical, through to medical ethics. These individual specialities are listed in order to underline the all-embracing nature of modern biomaterial science. Moreover, there are very good

reasons for this rapid and extensive development.

At the risk of making serious omissions, I would mention three elements of the materials sciences which I regard as particularly promising for medical applications.

First, hydrogels will undoubtedly be of immense help in targeted therapy. According to modern concepts and technologies these can be synthesized with responsive, instructive and resorbable characteristics, having the ability to release biologically active molecules under microenvironmental control, for example, released cellular enzymes.

Second, nanotechnology, and in particular, nanoparticles, carry the hope of being able to help diagnose, treat and monitor disease, the „theranostic" concept. Third, rapid prototyping offers the technology to use patient-specific imaging data (e.g. CT, MRT) to build anatomically correct structures for replacement or regeneration which could be used with or without the patient's own (autologous) cells.
In the life sciences the advent and rapid growth of stem cell biology in all its facets have taken regenerative medicine from wishful thinking to reality.

Naturally, there are many regenerative niches in the human body which are still only understood in a very rudimentary way, and include the brain and heart, both organs with a great clinical demand for effective healing. However, progress in live cell imaging has provided a functional tool to investigate niches in the living organism. Models in vitro need to continue their development towards more complex in vivo-like systems and include the exciting field of co-cultures. A further challenge for life scientists is to be found in the need to establish disease models, both in vitro and in vivo. For the former, induced pluripotent stem cells (iPS cells) will undoubtedly be one of the platforms for progress, whilst in the latter successful establishment of disease models in suitable experimental animals will make in vivo experimentation more akin to the real human disease situation. Currently, most models in vivo still use healthy animals.

Finally, if we are to take biomaterial science into the translational phase we need much more integration of clinicians ab initio into the biomaterial research programmes, as the meaningful pathway begins with the clinician describing what the clinical problem is.

The expertise of the material scientist will then hopefully bring a translatable solution.

Understanding the state of translational research in biomaterials in Europe: A stakeholder perspective

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The research conducted in October 2016-January 2017 illuminates some interesting and challenging issues for translational research in biomaterials.

The outstanding finding is the low involvement of patient groups reported as 2.10% across all the projects reported by stakeholders. The highest involvement being cited in cell based therapies and here the response was only 7.10%. Given that 83% stakeholder respondents indicated that public funding supported their research be that directly (50%) or indirectly through European Research Fellowship Grants (17%), charities (3%) or private / public partnerships (11%) it is a surprisingly low level of engagement with patients and the public who are either the beneficiaries of the proposed research or who are funding the research albeit indirectly, through taxation.

As the questionnaire of the present study was mainly director to team leaders across Europe, the 201 respondents can be considered fairly representative of the biomaterials communities that include an approximate number of 20 major research groups in most countries with the exception of few where the community is relatively small. However, there is sufficient numbers to indicate a trend of low participation by public and patients when we see they are reporting against 478 projects undertaken across Europe.

This is more surprising when it is clear that it is not only bench scientists who are responding to the survey. This report is about translational work and included projects listed as 'clinical trials' in the following categories: biomaterials for regenerative medicine, tissue engineering, implants, medical devices, drug delivery, cell based therapy, diagnostics and 'other' non-defined projects. All these project categories suggest the 'subject' of the clinical trial would be a patient. The implication is therefore that patient and public involvement in the design, delivery and dissemination of outcomes is missing in 97.9% of the research reported to this survey.

Scientists engaged in applied research have become more familiar with patient and public involvement / engagement (PPI/E) in the design and delivery of research (Dobbs and Whitaker,2016), notably in the UK where the main funder (the National Health Institute for Research, NIHR) has required there to be involvement throughout the research. Indeed, funding is contingent on demonstrating genuine involvement (Involve, 2015). Therefore, a policy push has been effective in driving change in the UK albeit limited to applied scientific research. However, there remains a lack of hard evidence to determine the benefits that patient and public involvement brings to applied research despite drives to capture these data. This is because of variation in the way in which PPI is defined and how the various levels of engagement and involvement are reported (Staniszewska, Adebajo , Barber, Beresford, Brady, Brett, et al. 2011). Fundamental questions remain as to whether PPI can be accurately measured (Staniszewska, Adebajo , Barber, Beresford , Brady , Brett , et al. (2011). So a legitimate challenge is why should scientists be engaged if the PPI/E community and the social scientists who research participation are at odds with one another? Here we nudge at an epistemological and ontological debate with regard 'evidence and legitimacy' that can of itself be circuitous and serve only to furnish the vocabulary of critique

rather than a willingness to engage with the public and patients for whom the biomaterials science is intended.

There are good examples where patients and the public have been involved in priority research setting exercises with the James Lind Alliance, an agency that facilitates points of contact for researchers and PPI representatives, as one example. PPI engagement in priority setting is not without controversy as achieving consensus is complex and challenging especially where the legitimacy of the participants who are representing patient groups and for what purpose can be challenged (Hunter, Kieslich, Littlejohns, Staniszewska, Tumilty, Weale, Williams, 2016). However, there is strong, unrefuted evidence that front end PPI engagement facilitates the accessibility of research materials and helps to shape recruitment strategies (Brett, Staniszewska, Mockford Herron-Marx, Hughes, Tysal, Suleman, 2014 a).

The evidence is weak and largely anecdotal when it comes to bench scientists working with PPI. However, the importance of working with the people for whom the research is intended to drive the bench scientists' enthusiasm and sustain their motivation when the laboratory work is found to be challenging has been highlighted. Patient and public involvement also enables scientists to reflect on their public engagement, find better ways in which to communicate lay accounts of their work and consider the broader moral and ethical issues inherent in their research (Brett, Staniszewska, Mockford, Herron-Marx , Hughes, Tysal, Suleman, 2014 b).

Basic scientists may be more reluctant to engage in these activities because they perceive their work to be too specialist or too complex to be understood by anyone outside their disciplinary community (Dobbs and Warwick, 2016). They might hold that patient and public involvement is not considered relevant to their science, that consultation might introduce confounding variables to their work and risk the introduction of bias that could only serve as a distraction rather than a benefit to their productivity. Simply, biomaterials scientists might not like what they hear when they consult the public but avoidance is only deferring the inevitable.

Non engagement in the short term can be rationalised as having a lack of money and time to authentically engage in PPI (Brett, Staniszewska, Mockford, Herron-Marx, Hughes, Tysal, Suleman, 2014 b).In the longer term no such reasoning will be considered viable. Projects have to be designed with PPI/E in mind and include robust costings to ensure this can be done effectively throughout the research project. To do this requires a change in attitude and a fresh approach to challenge the status quo. Good science demands good communication and contemporary practice requires dissemination using alternative media beyond the academic journal. Traditional researcher training may not have equipped the scientist with such skills. Socialisation of generations of scientists through technical supervision might have contributed to entrenched positions to avoid patient and public involvement.

In the past, dedication to a research career in biomaterials science to the exclusion of any other 'distraction', including wider researcher development might have served individual scientists and their direct disciplinary community well. Indeed, the Ingenio survey (2016), cites writing scientific articles, preparing research proposals, and laboratory work as the primary job tasks of the respondents. This suggests a knowing of biomaterials solely from the perspective of biomaterial science. Such an approach serves to retain a mystique that maintains the exclusivity of its elite membership, but, is this a viable option in contemporary society? Is this a sustainable position when inter disciplinarity to advance science is promulgated by funders and policy makers (add the industrial partners stuff reference from Monday)?

The results from this survey of 201 European biomaterials scientists implies that time is ripe for change. There will be a requirement to change as more funders require evidence of patient

and public involvement in the design and delivery of research, lay representation of the science and lay accounts of the pathway to impact the research will track. The biomaterials community will have to engage with people outside their direct scientific network as the public demands to know more about the research that is being undertaken to improve their wellbeing and health funded by the public purse. That pressure will intensify as the moral and social issues that surround the potential outcomes of the research become apparent. it is time to awaken to ways in which such political influence can empower the scientists and involve communities in our basic science. This does require a different way of thinking – but who better to help facilitate that than the patients and public for whom the research is both for and about? One model of doing this is presented below.

A new model of patient and public involvement in research known as the beneficiaries model is being developed. This approach places patients, the public alongside clinicians (nurses, allied health professionals and medical staff) and scientists together so they can learn from one another to facilitate involvement in research and public engagement. The novelty is in engaging and involving all three partners from setting research priorities to research design and application (Stewart, 2016). The literature reports PPI occurring as a bipartite relationship between a clinician and PPI or the researcher and PPI (Brett J, Staniszewska S, Mockford et al, 2014b) not with an ambition to engage all three parties from start to finish.

This work has to emerge out of research collaboration with multi-disciplinary colleagues working in the biomaterial research. Such a method should establish a forum that solicits financial, political and human debate about the place of innovative treatments in our society and in turn on the global community. This should include discussion about what is considered morally acceptable, feasible and ethical alongside engaging the patients and their families about the acceptability of the science that is being proposed.

In the past beneficiaries of such an approach were considered to be the persons for whom the treatment was being developed. Here we propose that everyone is a beneficiary. The full extent and range of those benefits is the subject of further research.

This model of PPI has recently been generated through a knowledge exchange conference hosted by the University of Brighton which was attended by key stakeholders including clinicians, bench scientists and the public. The emergent values that were established at the conference are realized and sustained by continuing participation in our bid writing, reviewing, delivery of research, co-production of research and dissemination of research materials and public engagement activities. At each point there is a tripartite meeting of clinicians, researchers and the patient and public. The beneficiaries model further distinguishes itself because we have created different roles within our network of experts (patients, the public, clinicians and researchers) who can be called upon to work with teams of researchers from inception of research proposals to the dissemination of research and all stages in between, but also who actively participate in our wider public engagement activities. Interdisciplinary teams are established that cross social science, the arts and humanities as well as life health and physical sciences and incorporate a network of the public and patients who can participate in our diverse range of activities according to their area of interest. Their legitimacy determined by their commitment to participate, not solely because of a vested interest. An ever widening panel of interested parties ensure that we can reduce the burden that might otherwise fall to a few individuals.

This is not easy. Nurturing the enthusiasm beyond initial interest and seeing this through to completion of a project does require attention. Here it is recommended that this work package be facilitated by a named person, be that a colleague outside the biomedical science community or a scientist who is keen to foster this work. However, one important but unreported

resistance might be the personality of the scientist and how they were drawn to bench science in the first instance: a talent for maths, chemistry and or physics rather than social science, the arts or humanities. The language of science potentially limits discussion and the forging of professional relationships with a wider non-academic / outside specialism scientific community unless purposively facilitated. So having an 'outsider' to take the lead on PPI/E in the first instance and to build up the scientists repertoire of skills of effective involvement and engagement is not without challenge. Further, we describe 'working with' not 'devolving to' colleagues if the approach to PPI is to be long term and sustainable.

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The role of ICT in biomaterial research and development

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The history of Biomaterials shows that different civilizations have implanted materials in the human body. The advances in Medicine and Surgery allowed different countries with different political systems to build up their own healthcare systems, public, private or mixed, after the Second World War. Biomaterials became Science and Technology because the need to treat large numbers of patients in these welfare societies produced a large industrial demand of implants. The evolution from substitutive implants, for which the main requirement was their inertness and tolerance in the biological environment, to instructive biomaterials, able to play a key role in regenerative therapies, has taken place in the last thirty years. With the advent of what is called the 4th industrial revolution, the evolution of the incremental knowledge generated in Biomaterials Science and Technology seems assured. This does not necessarily mean that the industrial/clinical successes will increase. The low rate of industrial achievements coming from the European Commission funding in Biomaterials research projects is a good example. Probably, new views could come to favour new approaches.

The idea that Information will take humanity towards an Informational Society, as Industry took it to the Industrial Society, was published by Manuel Castells (1996). Industry changed totally society in terms of economy, work, social relations, family, etc. Castells' thesis is that something similar is going to happen with Information. In terms of higher education and research, Industry transformed universities. Previously non-existing high level professional degrees became strongly necessary and demanded: engineering, economics, psychology, etc. The need to generate not only knowledge but also diverse know-how changed the focus on education, and boosted as well the need for research to be transferred to industry and to the economic and social world.

Information and ICTs have started to transform our way of living and our society. The changes in the photography and music industries are now fully recognizable and there are clear signs that the automobile industry will come next. Big Data and more specifically the application of the theory of complexity may change our way to address scientific problems. The concept of Emergence in complexity means that the whole is more than the sum of the parts and this is what happens in biology and life. The reductionist approach applied in molecular biology research has greatly benefited the spectacular evolution of Biology. The theory of complexity brings holistic views that are substantiated in what is called systems biology. At present, Machine Learning or Artificial Intelligence is being applied with success in regenerative medicine research, such as obtaining a regeneration model for planarian, creating tadpoles with pigmentation non-existing in nature, analysing patterned differentiation of mesenchymal stem cells, or predicting stem cells knee arthritis outcomes. Artificial intelligence and machine learning are becoming an integrated part of life science research. There is increasing evidence that we are moving towards an algorithmic theory of biology.

The important issue is then to understand how such holistic approaches are going to change our scientific way of thinking. If scientific methodology does not need to be only reductionist, then regenerative medicine and more specifically, biomaterials for regenerative therapies could be designed according to the complexity existing in biological systems. Biomaterials researchers will be able to develop their work faster and in a more informed and accurate manner.

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