Review

Engineering and commercialization of human-device interfaces, from bone to brain* ,**

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Abstract

Cutting edge developments in engineering of tissues, implants and devices allow for guidance and control of specific physiological structure-function relationships. Yet the engineering of functionally appropriate human-device interfaces represents an intractable challenge in the field. This leading opinion review outlines a set of current approaches as well as hurdles to design of interfaces that modulate transfer of information, i.e. forces, electrical potentials, chemical gradients and haptotactic paths, between endogenous and engineered body parts or tissues. The compendium is designed to bridge across currently separated disciplines by highlighting specific commonalities between seemingly disparate systems, e.g. musculoskeletal and nervous systems. We focus on specific examples from our own laboratories, demonstrating that the seemingly disparate musculoskeletal and nervous systems share common paradigms which can be harnessed to inspire innovative interface design solutions. Functional barrier interfaces that control molecular and biophysical traffic between tissue compartments of joints are addressed in an example of the knee. Furthermore, we describe the engineering of gradients for interfaces between endogenous and engineered tissues as well as between electrodes that physically and electrochemically couple the nervous and musculoskeletal systems. Finally, to promote translation of newly developed technologies into products, protocols, and treatments that benefit the patients who need them most, regulatory and technical challenges and opportunities are addressed on hand from an example of an implant cum delivery device that can be used to heal soft and hard tissues, from brain to bone.

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1. Introduction

Analogous to the survival of trees within the ecosystem of the Amazon rainforest, cellular survival in the complex ecosystem of the human tissues, organs, and organismal systems depends not only on patent transport pathways but also on the efficient transport of chemical, electrical, and biophysical information across interfaces bounding tissue compartments. Cutting edge rapid throughput imaging technologies, in combination with geonavigational approaches to analyzing massive imaging data sets from human tissues, are enabling an epidemiological approach to understanding human health in context of organ and tissues’ cellular inhabitants’ health (Fig. 1) [1–4]. Equally critical, the maintenance of functional barrier properties at tissue compartment interfaces allows for control of the respective systems’ steady state and dynamic equilibrium properties, where breaches at boundaries (interfaces) risk destabilizing those properties [2]. Coupled computational modeling and multimodal imaging approaches are enabling unprecedented understanding of
information transfer between and across different tissue compartments making up the complex biosystem of the human body [4,6,7]. While a number of studies have described the importance of the blood supply and vascularization for engineering tissues and next generation implants, engineering of interfaces represents a less explored yet equally important facet for success of human-device interfaces over time, providing the impetus for this review.

So much about the basic physiology of our own ecosystem remains unknown and needs to be addressed in order to engineer interfaces using top-down and bottom-up approaches. Indeed this is a grand challenge for development of next generation implants that integrate seamlessly between the device and the human ecosystem, between the organs and tissues comprising our bodies, and between these tissues and their cellular inhabitants. For example, every nonarticular surface of our bone is bounded by a soft tissue interface called the periosteum. Much like the blood-brain-barrier, the periosteum exhibits functional barrier properties and serves as a gatekeeper for transfer of information via all nonarticular outer surfaces of bone. Furthermore, the periosteum exhibits a remarkable capacity to respond to external stimuli to modulate its molecular permeability [8] as well as its mechanical properties [9]; during and after trauma, the third leading cause of mortality worldwide [10,11]. Stimuli-adaptive and responsive properties are defined as smart properties [8,11–14]. Periosteum’s smart permeability properties emerge from spatiotemporal dynamics of molecular scale cell adhesion protein complexes called tight junctions [11,12]. Its smart mechanical properties emerge from spatial distribution and multiscale architectures of structural proteins including collagen and elastin making up the soft tissue sleeve and connecting it to bone, tendon and muscle [15,16]. Such smart properties provide inspiration for emulation when engineering functional tissue interfaces.

In that sense, engineering at the interface, and ultimately, the engineering of functional interfaces, itself serves as a portal to innovation. The challenge is to address multiscale mecano-, chemo- and electrophysiology from the organ to the molecular length scale and back again. Cutting edge developments in engineering of tissues, implants and devices allow for guidance and length scale and back again. Cutting edge developments in engineering of tissues, implants and devices allow for guidance and length scale and back again. Cutting edge developments in engineering of tissues, implants and devices allow for guidance and length scale and back again.

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Fig. 1. Geonavigational approaches to understanding human physiology in context of inhabitant cell population health. Similar to the Amazon, the complex biosystem of the human body comprises diverse ecosystems such as bone and brain. Living ecosystem inhabitants, from trees to human cells, adhere similarly to the laws of physics and present similar challenges when one considers engineering their replacement and/or interface with medical devices, implants and materials. A,B. Like individual trees (B3), osteocytes (A3) are non-motile cells that depend on patent transport pathways for their basic metabolic needs and molecular communication. (A2). Notably, the relative length scale ratio of osteocyte:femur (A3:A1) is similar to that of a single tree:whole Amazon basin (B3:B2), circa 1:1 \times 10^6. Used with permission [2]. C. Connectivity of tissues’ cellular inhabitants provides an important measure of cellular communication efficiency and tissue patency, e.g. in bone (osteocytes) and brain (neurons). New rapid throughput imaging modalities such as multibeam electron microscopy allow for organ to tissue to cellular length scale assessment of cell and tissue health, in bone (C1, from a hip replacement patient, obtained with Institutional Review Board approval of the Cleveland Clinic, Dr. Ulf Knothe) and brain (C2, from the mouse brain with IACUC approval of Harvard University, Professor Jeff Lichtman) Used with permission. In combination with geospatial navigation methods such as Google Maps API, it is now possible to navigate and interact with these high resolution maps of human tissue to study epidemiology of cell populations within individual patients (an example is available to explore at the link provided in mechbio.org) [4]. These enable R&D teams to ‘see the forest for the trees’ while also seeing the ‘trees for the forest’.
cells inhabiting the tissue but perhaps more importantly provides a conduit for the immune system traffic.

Ultimately, these insights, enabled through rapid developments in imaging and modeling technologies, will lead to better design and prescription of medical devices as well as physiotherapy protocols to optimize human-device integration and performance, ultimately enhancing human health. For, once the natural system is understood, “mechanically active” device designs can be tested and optimized in silico to harness physiological forces to facilitate transport of molecules and cells as well as those biophysical and biochemical signals that modulate system equilibrium [13,23]. Similarly, physical therapy protocols can be developed to enhance transport and/or healing of mechanically active devices [2,24]. As such, this approach exhibits numerous potential clinical applications in arenas including surgery (device design and surgical technique), physical therapy (rehabilitation and preventative protocols), and pharmaceuticals (better understanding the transport properties between interfaces will allow for the development, design and delivery of drugs that are either preventative or restorative). In sum, an integrative approach to mechanical modeling and device design has the opportunity to improve clinical interventions, and ultimately patient outcomes.

3. Gradients to link disparate tissues

Interestingly, just as functional barrier properties are key for certain physiological functions, the lack of clear boundaries is just as important for other functions. For example, abrupt changes in mechanical stiffness result in stress concentrations, which are the ‘weakest link’ of the system under dynamic loads. Nature “overcomes this weakest link” by using gradients in mechanical properties, avoiding stress concentrations, from a mechanical perspective, and providing a myriad of physico-chemical signals to cells, the living inhabitants of tissues on the other hand.

Indeed, nature is replete with gradients, defined as the variation in any quantity from one location to another, e.g., temperature, pressure, mechanical properties, material composition, concentrations of cytokines, etc. Following the theme of nature’s engineering paradigms applied to the engineering of tissues [2,7,17,25–27], gradients are crucial to de novo tissue generation in embryogenesis as well as to tissue regeneration in wound healing [7,17,26,28]. As such, gradient engineering provides a novel approach to engineer tissue interfaces [29–37] that better mimic natural interfaces, e.g., bone – cartilage, muscle – tendon, and—bone interfaces, which themselves exhibit gradual transitions in cellular, extracellular matrix and mechanical structures and functions from one tissue to the next (Figs. 3,4) [16–18,33,34]. Numerous recent studies employ a range of gradients in their tissue engineering design approach, including gradients in peptides or receptor ligands, growth factor release or immobilization, and even surface roughness [35–43].

Among the numerous methods to incorporate gradients into tissue engineering, the use of microspheres provides a unique capacity to control material properties at 3D microscale resolution in clinically relevant biomaterials [44–49]. For example, microspheres can be combined into mechanically robust, macroporous biomaterials capable of releasing opposing gradients of signals [50] and/or creating gradients in material composition and thus mechanical stiffness [50]. Microspheres can be sintered together using heat, dense phase CO2, or mild solvents, avoiding the need for a separate carrier material such as a hydrogel [51–53]. Microsphere-based approaches provide a distinct advantage, enabling encapsulation of ‘raw materials’ for tissue regeneration; these materials can serve as both building blocks and signaling molecules [54,55]. In proof-of-concept studies, microsphere-based scaffolds with
gradients in material composition and/or growth factor release have been shown to be effective in regenerating osteochondral defects in rabbit knees [56,57] and mandibular condyles [58]. However, future studies in large animal models and clinical trials will be crucial for refining the technology in terms of suitable degradation profiles and material composition.

With the current explosion of 3D printing [25,36,41,59] and rapid manufacturing methods including electrospinning [60–63] and computer controlled weaving [23,64], the number of ways to engineer and build gradients increases every day. A key to the translation of such approaches will be the feasibility of implementation in a clinical context, such as the surgical operating room, while addressing standard commercialization considerations such as regulatory approval, competitive pricing, insurance reimbursement, hospital profit, and ease of manufacturing and distribution (cf. Translation and Bridge to the Future for more detail). By taking business as well as clinical considerations into account when implementing engineering approaches, next generation device and implant designers will be able to leverage gradients’ innate power to make a lasting impact on the regeneration of functional tissue interfaces.

4. Engineering mechanically functional interfaces in the brain: overcoming strain gradients

Matching of mechanical stiffness is a recurrent challenge in the seemingly disparate biosystems of the musculoskeletal and nervous systems, e.g. at interfaces including hip prostheses anchored in bone and electrodes inserted into the brain (Fig. 3). Stress shielding around orthopaedic implants has been implicated in their failure over time due to maladaptation of apposing tissue which is offloaded by the stiffer implant. In contrast, use of stiff implants in the brain causes damage during insertion and maladaptation over time.

The engineering of mechanically functional interfaces with the brain is a multifaceted problem not unlike engineering interfaces in the musculoskeletal system, where transfer of electrical information plays a dominant role yet overcoming strain gradients presents a currently unsolved challenge. Several classes of neural interfaces have been developed to transmit information to and from the nervous system. In the brain, electrical signals recorded from neurons by intracortical microelectrodes have been used to better understand the function of the brain in health [65–67] and disease,
as well as by human patients to communicate with computers and to control robotic limbs [68–72]. Other clinical applications are being explored, with expectations remaining high.

A current hurdle to the field is the inconsistency in signal quality and the length of time that useful signals can be recorded [73,74]. Inconsistencies in recording capabilities have been tied to the stability of the materials used to create the electrodes [75]. However, the consensus view of the scientific community is that the inflammatory response to the microelectrode contributes, at least in part, to recording reliability [73,76,77].

Traditional microelectrodes have been composed of extremely stiff materials such as metals or silicon. The high stiffness has facilitated microelectrode implantation into the cortical tissue [78]. However, a number of groups have hypothesized that increased stiffness may adversely impact neuronal tissue through a variety of mechanisms [79–87].

Finite element models predict micromotion of the brain relative to a stiff microelectrode induces strain fields on the surrounding tissue, with highest strain found closest to the surface of the brain [82,88,89]. Such strain profiles are validated by the non-uniform, depth-related gradient tissue response to the microelectrodes [90]. Similarly, comparing the inflammatory response of identical devices that are either tethered to the skull, or untethered and free-floating within the cortical tissue, shows that tethering induces a more robust inflammatory response, leading to a more significant loss to local neuronal cell populations [91]. As truly wireless systems are yet to be fully developed, current microelectrodes are typically tethered to the skull to enable connection with external hardware for signal transmission.

One feasible approach, the utilization of lower modulus polymers to create intracortical microelectrodes with decreased strain profiles, creates a new set of challenges. For example, to avoid buckling during insertion, the forces that the implant must overcome during insertion (insertion force) must be lower than the critical loading force for a given electrode design. Otherwise, the implant will either fail to insert, implant at an unwanted trajectory, and/or break [81,92]. Several groups have investigated making the implants larger to enable implantations. Such methods range from increasing the cross-sectional area of the implants [93], to applying a 5–10 μm thick silicon layer to the polymer to prevent buckling during insertion. However, increasing device size or adding a non-compliant backing reduces device compliance and increases strain induced on the surrounding tissue. In addition, increasing device size exacerbates the initial iatrogenic injury (refer to [94] for a recent comprehensive review on this topic).

Alternatively, in situ softening materials have been investigated as substrates for intracortical microelectrodes [39,79,84,89.95–97] to facilitate ease of insertion into the brain tissue while softening significantly upon implantation to more closely match the mechanical properties of the brain. The first realization of such materials for intracortical microelectrodes was based on the design and architecture of the sea cucumber (Fig. 4) [96]. The sea cucumber is a sessile sand sifter that crawls along the ocean floor. When threatened by a predator, the animal can rapidly and reversibly crosslink collagen fibers within its skin to become stiffer and unpalatable [39,97–99]. The defense mechanism was
mimicked in which the general design consisted of a soft polymer matrix that is reinforced with rigid nanofibers to create polymer nanocomposites [96]. The sea cucumber-inspired nanocomposites are based on a poly(vinyl acetate) (PVAc) matrix reinforced with rigid cellulose nanocrystals (CNCs) [100]. When dry, these nanocomposites are in a rigid state ($E^r = 5.1$ GPa), due to the glassy matrix and the rigid percolating network of the CNCs. Upon implantation into the brain, the nanocomposite undergoes a phase transition and softens ($E^f = 12$ MPa) as water plasticizes the matrix and disassembles the CNC network.

Unlike neat polymer controls, or earlier polymer based microelectrode designs, dry implants comprising the sea cucumber inspired nanocomposite can readily be inserted through the pia mater into the cerebral cortex of a rat without the need for assistive devices [92]. Further, ex vivo studies confirm rapid softening of the initially stiff microscale nanocomposites upon insertion into the rodent brain [92,97]. A comprehensive evaluation of the neuroinflammatory response to PVAc/CNC nanocomposite implants through a 16 week implantation period demonstrated nearly complete attenuation of inflammatory cell activation, and the absence of any appreciable neuron loss surrounding PVAc/CNC nanocomposites compared to chemically-matched PVAc-coated MI-style microelectrodes at chronic time points [89]. However, at earlier time points, the chemically matched stiffer controls and the compliant nanocomposite based devices show few physiological differences. The nanocomposite based device can also be used as a vehicle for short-term anti-inflammatory release, to synergistically target complementary neuroinflammatory mechanisms [101] and device stiffness/compliance may be tunable to optimize electrode recording quality of functional microelectrodes [84,85].

Interestingly, recent studies confirm that the sea cucumber inspired compliant microelectrodes reduce micromotion and tissue strain within 30 min of implantation [86]. Yet, a temporal mismatch persists between the bulk tissue and micromotion induced strain on brain tissue by microelectrodes, and the acute inflammatory response. Therefore, these results suggest that the bulk tissue effects of device stiffness may play a more dominant role at more chronic time points due to alterations in the maturation of the glial scar [89]. For example, chemotactically-driven pathways may dominate early time points following device implantation.

Mechanosensitive pathways exert a temporally correlative effect in this process [101]. Strain-specific inflammatory pathways are up-regulated early after implantation of stiff, non-dynamic implants. Yet, months after implantation, the effect of mechano-sensitive pathways is abrogated, presumably due to scar maturation. Alternatively, in vitro and in vivo evidence indicates that substrate stiffness may influence neuronal and glial cell types through a variety of mechanisms [77,102,103].

An array of variables resulting from both biotic as well as abiotic factors likely result in poor recording quality and microelectrode failure. However, the complexity and interconnectivity of such failure modes makes improving microelectrode performance a challenging problem. While a number of failure modes have been identified, a more in-depth mechanistic understanding is still needed. Despite the challenges and questions that remain, the exciting possibilities are encouraging. Stimulating advances in the fields of material science, neural engineering and bioengineering should be fostered to create dynamic multi-disciplinary teams, in order to accumulate the skills and knowledge to design, test, and integrate the next-generation intracortical microelectrodes, capable of long-term clinical deployment for neuro-rehabilitative applications, and beyond.

5. Translation and bridge to the future

Finally, to promote translation of newfound knowledge and newly developed technologies into products, protocols, and treatments that benefit the patients who need them most, regulatory and technical challenges are addressed. Given the multifaceted approaches necessary to engineer human-device interfaces, it is essential to understand the product development and regulatory challenges associated with these “combination” devices, “comprising two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity” (FDA definition) [104]. These challenges are placed in context using an example of an engineered interface implant cum drug delivery device inspired by the smart properties of the periosteum (Fig. 5).

The engineering of interfaces using top-down and bottom-up engineering approaches poses a grand challenge for the success of next generation implants that integrate seamlessly between the device and the human ecosystem (and/or its organs and tissues). For example, much like the blood-brain-barrier, the periosteum exhibits functional barrier properties and serves as a gatekeeper for transduced information across all nonarticular outer surfaces of bone. Furthermore, periosteum’s smart properties, including the capacity to modulate its molecular permeability [8], as well as its mechanical properties [9], and mechanical stiffness in response to impact loading associated with trauma, emerge from its molecular level architecture (organization in space and time). Periosteum’s ‘smart’ permeability properties emerge from spatiotemporal dynamics of tight junctions that link cells into tissue sheets with stimuli-responsive (e.g. mechanical, chemical, electrical) permeability [8,11,12]. Similarly, shape shifts in its structural proteins intrinsic to the tissue’s mechanical state imbue periosteum with ‘smart’ mechanical properties. These ‘smart’ mechanical properties emerge from both the spatial distribution as well as the multiscale architectures of structural proteins including collagen and elastin [11,12]. The resulting capacity of periosteum’s circa 500 micron soft tissue sheath to confer an inexplicable boost in bone’s fracture strength under traumatic loads has inspired a new class of mechanoactive materials and implants cum delivery devices. While providing inspiration for emulation when engineering and commercializing human-device interfaces, the creation of materials and systems with such smart properties is not a trivial endeavor and requires the integration and use of different technologies to break through current hurdles.

As an example looking forward in the RDC pathway, an implant cum drug delivery device inspired by the smart properties of the periosteum was developed and tested preclinically by a surgeon - biomedical engineer team (both authors on this manuscript), with recent issue of a patent, bringing it from the preclinical (yellow) to the clinical space (blue), and hence just entering ‘the valley’ (Fig. 5). While the time from patent filing (7 March 2011) to patent issue (17 March 2015) comprised almost exactly four years, the development process took much longer (Fig. 5:1,2). First a novel one stage bone transport procedure was developed to harness the regenerative capacity of the biological tissue periosteum [106]. This was followed by a series of preclinical studies (2004–2008) using periosteum in situ to bridge critical sized defects in an ovine femur model [107] and in limited human patients [108]. Thereafter, in the bioengineering labs, a periosteum substitute was developed and tested (2008–2010), in an analogous preclinical ovine model (Fig. 5:3). The biomaterial designed to substitute for the biological tissue replicated key features of the periosteum, including vectorial delivery of biologics (including cells and biological factors such as growth factors) and pharmaceuticals; vectorial refers to the control
of the direction and concentration of factors released by the implant cum delivery device [109]. While this product might be considered a delivery device alone, its mode of action includes use for delivery of pharmaceuticals as well as biologics, placing the device squarely within the combination product category [104,110].

An understanding of the regulatory challenges is key to commercialization of this product. Furthermore, decisions must be made whether to license the technology and/or to spin off a company to commercialize the product. Licensing the technology ideally speeds its commercialization by experts in the commercial space; licensing has a further advantage of separating the commercial and R&D teams, which may help to avoid conflicts of interest. Starting a company provides unique opportunities for stewardship and advocacy, given the scientific and clinical guidance of the inventor team; conflicts of interest inherent to start ups or spin offs must not only be disclosed but also a management plan for these conflicts of interest should be put into place. Such transparency leverages the power of R&D in university labs to create and commercialize new technologies. This has the potential to stimulate economies and create jobs for university graduates, while strengthening bridges between university and industry sectors and increasing industry relevance of a university education.

The path from IP protection to FDA approval and product launch can take just as long as the developmental pathway. By example, looking backward in the pathway from the perspective of a number of related and successfully commercialized products, FDA approval of new product developments can span well beyond two decades (Table 1).

In this case, where the first four products would not be considered combination devices, the fifth product and its predecessor were among the first combination products approved by the FDA. Of note, specific lots of the BioMend® product were recalled in 2013 due to “deviations” in the manufacturing process that resulted in unacceptably high levels of pyrogens in the product; pyrogens are fever inducing substances typically produced by bacteria, molds, viruses and yeast [117].

6. Conclusions

Using examples from the disparate musculoskeletal and nervous systems to exhibit common paradigms between tissues, this review addresses the currently intractable challenge of engineering
functionally appropriate human-device interfaces. The field is at a watershed, where transdisciplinary approaches will yield tremendous opportunities for the design of interfaces that modulate the transfer of physiologically relevant information between endogenous and engineered body parts or tissues. While research grant agencies have traditionally encouraged science and its translation to focus on single tissues and molecules, new approaches suggest that single tissue centric or single signaling pathway specific approaches may limit opportunities for successful translation. For, as reviewed here, it is the interfaces between tissues and between endogenous and exogenous tissue replacements and/or devices that present the weakest link to success. In this way, these interfaces also have the greatest potential to be game changers and enablers if successfully addressed!

How then does one go about understanding interfaces between tissues in a more comprehensive and insightful manner? As with other breakthroughs in the field, technology is leading the way forward. Seamless multiscale imaging technologies are enabling R&D teams to tie events at different time and length scales in unprecedented ways [3,15,18]. In addition to opening our eyes to the nanoscopic through mesoscopic worlds of cells and the tissues and organs they inhabit, cutting edge multiscale imaging technologies are also enabling the development and validation of seamless multiscale virtual models that will enable efficient predictive studies. Together, paired imaging and virtual modeling methods will create a portal to new technologies and innovative approaches to engineer and translate emergent behavior, where emergence refers to properties or patterns arising from the putting together of simpler elements which themselves do not exhibit the properties or pattern [3,4,12].

Furthermore, new rapid manufacturing methods enable not only the production of complex medical grade products but also products that will be more affordable and reimbursable than the current state of the art. These will have a profound effect on the workforce and economies, as the need for workers skilled in technology and science will increase; combined with the shift to more automated production methods, economies with higher education levels may benefit from new opportunities in the manufacturing sector. The increasing integration of "biologics," including donor and patients’ own tissues, cells and factors, in medical devices will increase the need for quality control in manufacturing as well as the need for development of novel protocols and technologies to enable not only sterile production but also storage and transport modalities.

Finally, just as interfaces are gatekeepers for communication across boundaries between tissues and organs, R&D, Tech Transfer and Commercialization teams need to create interfaces that facilitate communication across diverse boundaries, e.g. disciplinary, cultural and fiscal, to enable rapid translation and commercialization of novel products. Inclusion of translational and commercialization expertise already at the very early conceptualization of ideas by R&D teams will not only speed the rate of translation but may also determine whether a product successfully traverses the valley of death on the path to commercialization. Similarly, envisioning of reimbursement codes at very early stages of commercialization may appear overly calculated at early stages of innovation; however, the imperative for such considerations are regularly underscored in the current market environment.

For, at the intersection of tissue engineering and next generation implants, the engineering and translation of tissue - implant interfaces is not only challenging but also crucial to ensure the efficient transfer of e.g. mechanical, chemical, and electrical information between tissues and their replacements. Across tissue types, from bone to brain, there are remarkable similarities in the need for efficient information flow between neighboring dynamic systems; the bridge or port that allows for optimisation of flow may relate to efficient navigation of cells or to mitigation of stress concentrations as well as stress shielding. By engineering spatial gradients in material properties and interactions as well as through harnessing of natural human movements and functions over time, delivery of molecular and cellular agents can be fine-tuned to facilitate healing and maximize performance. The current grand challenge to the field is to combine fundamental approaches from different disciplines to develop and translate paradigms more closely mimicking nature’s robust and elegant engineering paradigms. Finally, cognizance of and proactive strategic approaches to intellectual property and clinical trial management are critical early factors in successful later translation of engineered interfaces, which themselves are de facto combination products. The future is great for engineering tissue-implant interfaces; bridging across currently separated disciplines while embracing rapid manufacturing technologies and commercialization approaches conducive to combination product development paves a translational path that will greatly enhance patient care and quality of life.

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