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The emerging role of nanotechnology in cell and organ transplantation

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Abstract

Transplantation is often the only choice many patients have when suffering from end stage organ failure. Although the quality of life improves after transplantation, challenges such as organ shortages, necessary immunosuppression with associated complications and chronic graft rejection limits its wide clinical application. Nanotechnology has emerged in the past two decades as a field with the potential to satisfy clinical needs in the area of targeted and sustained drug delivery, non-invasive imaging, and tissue engineering. In this paper, we provide an overview of popular nanotechnologies and a summary of the current and potential uses of nanotechnology in cell and organ transplantation.

Grand challenges in transplantation

Over the past two decades, through improved surgical procedures and the use of powerful immunosuppressive drugs, cell and organ (i.e., kidney, heart, liver, pancreas) transplantations have become the standard of care for millions of patients with end stage organ failure [1–4]. Unfortunately, organ shortages, graft failure, and life-long administration of immunosuppressants continue to pose as critical obstacles limiting successful transplantation. In the case of kidney transplants, there were only about 17,000 kidneys

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available while approximately 99,000 patients were on the waiting list in 2014, in the U.S. alone [5]. In addition, an estimated 20% of the patients on the transplant list are those needing a replacement organ due to chronic rejection, even when undergoing broad immunosuppression [1, 2]. While immunosuppressant therapy has proven paramount to transplantation success, strenuous requirements or life-long systemic use, often lead to poor patient compliance causing eventual morbidity and mortality [6, 7].

In an attempt to overcome these existing barriers, promising alternatives are in development to improve transplant techniques. Nanotechnology has contributed immensely to the world of tissue engineering and has demonstrated encouraging results in drug delivery that would benefit the world of transplant therapy [8, 9]. By improving established manufacturing techniques and chemical modifications, many tunable nanotechnologies have been successfully applied in two areas of medicine: i) the localized, sustained, and controlled delivery of drugs and bioactive factors; ii) the imaging of clinically relevant biomarkers and functional parameters for diagnosis and treatment. In this review, we will provide a brief summary of the current achievements of nanotechnology in the field of drug delivery and will discuss some of the recent applications of this technology in organ transplantation (Table 1).

Significance and overview of nanotechnology

Nanotechnology has been defined as the science of developing and studying materials and devices that function within the nanometer scale [10]. As such, materials must be synthesized from pre-existing nanoscale building blocks exhibiting unique chemical and physical characteristics proper of the nanoscale. More recently, nanomedicine has emerged as a field which utilizes concepts from nanotechnology and medicine to prevent, diagnose, and treat diseases. As a result, a variety of nanoparticles and nanodevices have been created using a variety of materials including iron, carbon, gold, silica, and silicon [11]. Nanoparticles have been designed to serve multiple functions: drug delivery [12], receptor mediated targeting [13], environmentally-triggered release [14], thermal ablation [15], molecular imaging [16], and magnetism [17]. On the other hand, nano-fluidic systems and nano-membranes have been developed for the selective filtration of fluids [18], diagnoses [19], and sustained delivery of drugs [20].

One of the primary goals of nanomedicine, especially in the case of nanoparticles, is to increase the accumulation of a therapeutic or imaging agent at a target site, while minimizing toxicity to healthy tissue. In the context of cancer treatment, investigations into nanoparticles found significant therapeutic benefits through the utilization of the enhanced permeability and retention effect (i.e. accumulation of nanoparticles ranged 10-100 nm in tumor tissue) [21]. For example, liposomes, one of the simplest forms of nanoparticles approved by the Food and Drug Administration, loaded with doxorubicin, a chemotherapeutic used to treat various cancers including leukemia, were shown to significantly increase accumulation at tumor sites compared to free drug [22]. In their most basic form, liposomes are biocompatible spherical vesicles, with one or more lipid bilayer membranes, used to encapsulate a variety of hydrophobic and hydrophilic drugs [23]. In an effort to further increase their therapeutic potential, conjugations with polyethylene glycol,

ligands, antibodies, and proteins have been explored and demonstrated promising results [24]. Other lipid-based nanoparticles, such as micelles (lipid molecules spherically arranged in aqueous solutions), have also been explored for their potential use as drug carriers. Similar to liposomes, micelles have been exploited for their relative ease of production and ability to encapsulate poorly water-soluble drugs [25]. Regardless of the type of lipid-based nanoparticle, the ability to encapsulate biological agents (i.e., siRNA, enzymes) has garnered great interest.

Other groups have explored porous materials, to encapsulate and deliver nanoparticles, which provide space to attach additional targeting moieties, enabling greater tissue penetration [26]. For example, porous silicon has been widely investigated for its biodegradability and biocompatibility [27–29]. Features such as high surface area and tunable shape and size have led to porous silicon being used for a variety of biomedical applications (e.g. tissue engineering [30], biosensors [31], optics [32]). Recently, multistage nanovectors (i.e. disk-shaped porous silicon [33–35]) were developed to strategically overcome the body's biological barriers through unique size and shape tailoring (Figure 1). Researchers demonstrated that the degradation rates increase significantly as pore size increases [36]. Furthermore, modification of the pore size resulted in prolonged release of a fluorescent payload, and increased loading concentration as pore size increased. Additionally, Decuzzi and coworkers showed that particle geometry and size play a critical role in the biodistribution of particles in different organs after systemic injection. When mice were injected with plateloid-shaped multistage nanovectors, smaller particles (600×200 nm) accumulated at a higher rate in the liver and spleen compared to larger particles (1000×400 nm), while the reverse was observed in the tumor tissue [37]. Others loaded doxorubicin into polymeric micelles, then into multistage nanovectors, and showed that the toxicity to normal cells was significantly reduced while toxicity to breast cancer cells increased *in vivo* [12]. Furthermore, by conjugating a vascular endothelium growth factor receptor-2 antibody onto multistage nanovectors, particles displayed significant adhesion to inflamed vasculature compared to unconjugated particles [38]. Further functionalization of these nanovectors with cellular membrane proteins isolated from leukocytes [39, 40] gave particles the ability to avoid opsonization and macrophage uptake while increasing particle circulation and accumulation in a melanoma tumor mouse model, with no significant immunological impact [41].

As the gap between the availability of and the demand for organs used in transplantation increases, alternative methods need to be explored. Advances in nanomaterial synthesis and modification have played a significant role in tissue engineering and have led to promising results in regenerative medicine, leading to possible avenues for improvements in current transplant therapy [42]. In the following section, we discuss nanotechnology's current role in the treatment of organ transplantation through drug delivery and imaging techniques [10].

Nanotechnology as a tool in transplant therapy

1. Localized, sustained, and controlled delivery of drugs and bioactive agents

A number of (nanotechnology based) drug delivery strategies are currently being investigated to circumvent the limitations of conventional approaches and to increase the

potential of a drug. Targeted and controlled drug delivery carriers play fundamental roles in the individualization of drug-dependent therapies. While targeted delivery relates to the transportation of drugs to a desired location, controlled delivery relates to the release of the drug at a designated time, in an adequate concentration. Drug targeting and controlled administration are widely investigated, employing the novel tools offered by nanotechnology, resulting in a series of implantable and injectable nano-delivery systems [9, 43]. Substantial resources focus on the development of nanotechnologies to capitalize on their potential benefits in personalized treatments for a large number of clinical applications, including transplantation [44]. Recent studies showed that nanotechnology-based devices could deliver drugs within a specific therapeutic range while avoiding overdose and side effects typically associated with conventional treatments [45]. As a result, the adoption of nano-sized drug delivery technologies would improve the efficacy of treatments, reduce the necessary drug dosage, and minimize toxicity. Additionally, the employment of such devices would prevent issues related to patient compliance and significantly improve their quality of life [46]. The nano-channel drug delivery system is an example of an implantable device featuring precision-fabricated nano-channel membranes that achieve constant release over extended timeframes by simply tuning the channel size (2–200 nm) and density [45, 47–49].

In order to maximize the therapeutic indexes and minimize the side effects of therapeutic agents, a constant concentration of drug within the therapeutic range must be delivered to the plasma. This can be done by employing implantable drug delivery devices able to sustain the constant release of drug over long periods of time (i.e. weeks to years). The adoption of implantable delivery strategies allows for the controlled release of therapeutics in a systemic or localized fashion, dramatically reducing required dosages and associated toxicity (Figure 2) [50, 51].

A constant, single drug concentration in the plasma over an extended length of time is only achievable through zero-order release kinetics [52]. Zero-order release is achieved when the gradient of the drug molecule concentration, throughout a delivery device, stabilizes. Commonly, continuum-based diffusive processes are concentration dependent; the diffusion of molecules out of a delivery device decreases at decreasing concentrations in the reservoir. However, several technologies are now available to control molecule deployment and achieve a concentration-independent release. A zero-order release can be obtained with convective driving mechanisms such as osmotic pressure, mechanical pumping, and through electro-kinetic transport [53]. A constant drug release can also be achieved by tuning the properties of nanofluidic devices. It has been shown that, at the nanoscale, molecular constraints, surface effects, and charge interactions play major roles in molecule transport [54, 55]. Charge exclusion, concentration polarization, and streaming current phenomena have been observed at the nanoscale [56, 57]. Moreover, it was demonstrated that confined fluid at the nanoscale level present anisotropic properties [58]. Nanotechnologies allow for the exquisite control of nanostructure properties and nanoscale effects. This control cannot be obtained at the macroscale, where drug release follows a Fickian exponential profile and is strongly affected by the drug concentration [59]. Consequently, at the nanoscale level, a constant concentration–driven drug release can be achieved, allowing for the enhanced delivery of therapeutics in transplant therapies.

1.1 Liposomes, Nanochannel Membranes and other Nanocarriers—Over the years, immunosuppressive drugs have provided a significant increase in transplant patient survival. However, complications still arise because of the therapies' potency and pharmacokinetic variability. Therefore, it is critical to modify treatments based on each individual patient to avoid any adverse effects. Unfortunately, poor bioavailability and water solubility also make the administration of immunosuppressants complex. This, coupled with the requirement to combine multiple therapies following organ transplants, has led researchers to devise alternative solutions.

Nanotechnology has provided viable alternatives to combating issues related to increasing drug efficacy and solubility. For example, lipid-based formulations such as emulsions [60], liposomes [23], and polymeric micelles [12, 61] have demonstrated reliable alternatives to transport water-insoluble therapeutics. Following renal transplantation, a patient is typically required to take oral immunosuppressant drugs. However, previous literature reported that a high fat diet can display a pronounced effect on the adsorption of cyclosporine, a common immunosuppressant [62]. This led to the reformulation of cyclosporine into a micro emulsion (i.e. fine dispersion system), improving its pharmacokinetic variability [63]. This formulation was shown to be thermodynamically stable and resulted in a smaller droplet size (i.e. <150 nm). Other immunosuppressive drugs, such as tacrolimus [64] and rapamycin [65], have also demonstrated similar effective results when encapsulated within liposomes. For example, rapamycin demonstrated optimal results when encapsulated within micelles. As demonstrated by Forrest *et al.*, encapsulation within micelles bypasses the need for organic co-solvents or harsh surfactants to solubilize highly concentrated drug solutions [66]. In addition, the micelles were reported to be stable when in contact with serum albumin and exhibited a sustained release over the course of several days.

Although rapamycin has shown to be an effective immunosuppressant, its water insolubility has made it challenging to develop an oral or intravenous formulation. Rapamycin's solubility in water is 2.6 μg/mL, far below its desired therapeutic concentration of 1 mg/mL [67]. Although some formulations were able to overcome the solubility issue through co-solvent/water mixtures, its poor taste and specific storage conditions made it problematic for patients. The use of nanocrystals as a delivery platform for water-insoluble immunosuppressant drugs, overcame this obstacle by providing improved bioavailability [68]. The nanocrystals provided increased surface area while maintaining increased solubility and decreased thickness of the diffusion boundary layer.

Another area of recent interest is the role of nanoparticles in the disruption of signaling pathways in T cell activation and donor antibody functions. This could demonstrate great potential to treat immunological complications during transplantation [69]. Recent studies have also shown that inflammatory and immune responses are regulated by the small GTPase RhoA pathway via its downstream effector, the Rho-associated protein kinase (ROCK). The inhibition of the RhoA/ROCK pathway should interfere with immune cells and possibly limit or abrogate chronic rejection [70]. Studies in rodent models from various research groups show that chronic rejection of allo-transplants could be ameliorated by the administration of RhoA pathway inhibitors [71–73]. Recent studies showed that the application of nanotechnology in the sustained delivery of a ROCK inhibitor, Y-27632, to

the recipients of allografts, in a rat model, resulted in the drastic reduction of collagen deposition, the reduction of tissue fibrosis, and the marked improvement of vascularization in the transplanted heart (Figure 3) [49].

The central innovation of this sustained delivery technology, is the use of microfabricated nanochannel membranes which, like an hourglass, passively control the release of molecules. Nanochannel membranes bypass the issues of burst and trough release, associated with other delivery technologies and achieve constant drug release by imposing spatial and electrostatic confinement on molecular diffusion. In nanochannels, surface-to-molecule interactions passively control the drug delivery rate, rendering it constant, without the need for complex pumping mechanisms [47, 74]. Nanochannel membranes offer significant advantages as they achieve constant, sustained release and can be easily tuned in channel size (2 – 200nm) and density to achieve a clinically relevant, constant delivery of a broad spectrum of chemotherapeutics [75, 76]. The nanochannel technology has shown constant in vivo delivery of testosterone, leuprolide, interferon, lysozyme, genotropin and octreotide in dog, rat and mouse models for periods ranging from 1 to 6 months [43, 48]. Additionally, this technology demonstrated long-term (more than 6 months), sustained, and constant delivery of therapeutics in an *in vitro* model (Fig. 2C) [48]. The localized delivery of immunomodulator drugs in the vicinity of transplanted organs or tissues, using a nanochannel drug delivery device, protecting the transplant from immune rejection while eliminating adverse effects associated with systemic immunosuppression, would be the ideal choice in transplant therapy.

Nanocarriers have also proven to be a promising platform to achieve tolerogenic antigen presentation by delivering antigens of interest to specific cell types. Nanocarriers delivering a combination of antigens and immunomodulating agents, such as rapamycin, provide a unique technology platform with the potential to enhance outcomes for the induction of transplant tolerance [77]. Nanobodies, which are therapeutic fragments of antibodies with a single-domain of the antibody variable region, have been developed for cancer therapy with advantages in size, stability, and low immunogenic potential [78, 79]. This formulation can be applied in a similar way to stimulate inhibitory pathways and shut off immune cells to prevent allograft rejection.

1.2 Implantable Devices and Biocapsules—As opposed to constant drug administration, multiple therapies would benefit from the ability to tune drug release according to the circadian cycles. It is well known that the presence of biological rhythms, such as the circadian cycles, affects body metabolism in living organisms over 24 hour cycles and inflammatory markers follow definite circadian cycles. Organs, such as the kidney, liver, and gastrointestinal tract, are very critical to drug metabolism and are highly coupled with circadian rhythms. The pharmacodynamics and efficacy of treatments were demonstrated to relate to the time of administration during the circadian cycle [80]. Therefore, drug delivery strategies should consider the most ideal times for drug administration, in order to reduce toxicity and increase treatment efficacy.

Nanotechnology-based, tunable implant devices have the potential to adjust drug release based on the circadian rhythms of inflammatory markers. The synchronization of drug

delivery to bio-cycles using these devices represents an additional step toward individualized medicine. Consequently, some attempts have been made to achieve chrono-therapy with implantable drug delivery systems [57] based on degradable polymers and osmotic devices [81]. Here, researchers present a nanofluidic membrane technology capable of achieving active and tunable control of molecular transport through nanofluidic channels. By applying an electric field between two platinum electrodes positioned on either surface of a 5.7 nm nanochannel membrane, designed for zero-order drug delivery, temporal, reproducible tuning, and interruption of dendritic fullerene 1 (DF-1) transport, was obtained over multi-day release experiments [57]. This ability to actively control and tune delivery of drugs and particles from a subcutaneous implant device has broad applicability to various current and emerging therapeutics and clinical situations including organ and tissue transplantation. The tunable nanochannel drug delivery system (Fig. 4) presents a nanofluidic membrane technology capable of achieving active and tunable control of molecular transport through nanofluidic channels.

A promising approach for protecting cell transplantation from immune-rejection was proposed back in the 1980's. Microencapsulated islets implantation was used *in vivo* as bioartificial endocrine pancreas resulting in the correction of the diabetic state up to three weeks [82]. By enclosing cells within a physical barrier, the biocapsule allows the exchange of nutrients and metabolites while inhibiting the permeation of antibodies and the infiltration of immune cells. This type of technology would enable pancreatic islet cell transplantation, overcoming their immune-rejection without the need for immunosuppressive drugs and, in principle, restore normal glycaemia in diabetic patients, as demonstrated on numerous in vivo studies where experimental animals have recovered for more than 100 days [83–85].

Although progress has been made in the field of cell encapsulation, scientists still seek more favorable synthetic and naturals materials to help overcome previous obstacles such as chemical stability, functional performance, or the production of uniform capsules [86]. The use of photolithographic techniques in the fabrication of micro silicon membranes have helped to overcome some of these challenges by allowing precise control over the pore size and distribution in the range of 20 to 100 nm [87, 88]. *In vitro* studies showed that rat pancreatic islets cells could maintain their functionality and viability in the three-dimensional encapsulated environment and maintain their glucose-stimulated insulin secretion [89]. Moreover, the silicon-based biocapsule allowed the diffusion of essential nutrients while blocking the permeation of immune molecules. *In vivo* studies in mice showed biocompatibility of the biocapsule, the viability of the encapsulated cell lines without immunosuppressants, and the secretion of insulin in response to both basal and stimulatory conditions [90].

1.3 Nanoglands and Nanoparticles in Transplant—Nanotechnology-based encapsulation systems such as Nanogland (Figure 5) have successfully supported the engraftment of pancreatic islets in animal models [91]. These encapsulation systems protect the transplanted cells from immune attack and provide a physiological environment promoting cell survival and vascularization. The new generation of Nanogland is made with biocompatible, bioinert polymers (PLA/PCL). It is used to house pancreatic islets or islet-like insulin-producing cells in wells. Designed to maintain cell proximity while ensuring

sufficient separation to simulate the *in vivo* environment, the Nanogland, houses cells in a growths factor-rich matrix and presents surface modified microchannels that allow for rapid neovascularization of the graft. This is imperative to assure long-term transplant survival and viability.

Additionally, transplanted cells are protected from immune attack by local, constant, and sustained delivery of immunomodulator agents (e.g., CTLA4Ig). CTLA4Ig, delivered into the cell reservoir, slowly diffuses outside of the implant, generating a local concentration gradient, thereby protecting the transplanted tissue from immune attack. Constant and sustained CTLA4Ig delivery is achieved from an internal reservoir by means of a biocompatible, bioinert, and microfabricated silicon nanochannel membrane. The cell and drug reservoirs are separately fabricated by 3D-printing and assembled by polymeric welding [91, 92].

Nanotechnology has also been considered as a tool to address the poor viability and engraftment following pancreatic islet transplantation [93]. Specifically, these limitations led researchers to investigate peptide amphiphiles (PA) as a potential solution. PA, are peptide molecules that incorporate a hydrophobic domain on one end and a hydrophilic oligosequence on the other end. This promotes self-assembly into nanofibers, exposing the bioactive region on the outer surface to interact with the cell or protein of interest [94].

With this technology, Stendahl *et al.* explored the use of heparin-binding PA scaffolds for the delivery of angiogenic growth factors (i.e. vascular endothelial growth factor and fibroblast growth factor-2) to mitigate the adverse effects typically encountered with islet transplantation [95]. Remarkably, heparin-binding PA, combined with the angiogenic growth factors, displayed significantly superior vascularization in the omentum (interperitoneal fat mass). In addition, this led to higher cure percentages of diabetic mice and significantly decreased time to achieve normoglycemia.

As is the case for organ rejection, corneal rejection is also subject to a strict regimen of immunosuppressants typically administered systemically or through eye drops [96]. Currently, the two-year survival rate for those receiving an uncomplicated transplant is 90%, but this number can reach as low as 50% for those with neovascularization in the cornea or who have previously experienced graft failure [97, 98]. Although corticosteroids are typically administered to minimize graft rejection, administration can often be required as often as 1 h immediately following transplantation [99]. This strenuous requirement leads to unsatisfactory patient compliance and, eventually, increased rejection rates [100]. Efforts have been made to address this concern including the administration of corticosteroids via a subconjunctival injection immediately following surgery. Unfortunately, rapid clearance of small molecules (i.e. drugs) from the ocular tissue significantly impacts the extent of their therapeutic effects.

Nano- and microparticles have presented a viable strategy to overcome the rapid clearance of small molecules from the occular tissue and improve therapeutic drug levels. Specifically, polymer particles are being employed for the delivery of therapeutic agents to the eye by harnessing various routes of administration, such as intravenous, subconjunctival, and

topical administration [101]. For example, Pan, *et al.*, demonstrated that dexamethasone sodium phosphate-loaded nanoparticles provided sustained release *in vitro* and resulted in effective prevention of corneal graft rejection when injected subconjunctivally in a rat animal model [102]. Conversely, when injected with free drug, rejection occurred as soon as three weeks following transplantation, with all mice experiencing rejection at four weeks.

2. Imaging and functional parameters for diagnosis

Nanotechnology has made substantial progress in the world of medical imaging. Similar to their ability to deliver therapeutics, nanoparticles can be used to deliver contrast agents to assist in delineating anatomy and physiology for medical imaging. Examples include the use of iodine-encapsulated liposomes for x-ray computed tomography [103], gadolinium within mesoporous silica nanoparticles for magnetic resonance imaging (MRI) [104], and perfluorocarbons within polymer nanocapsules for ultrasound [105]. Nanoparticles have transformed the way we use complex contrast agents. Here we expand on one example, gadolinium, and its contrast enhancement for MRI. Magnevist is a clinically available, and widely used, agent for MRI comprised of gadolinium chelated with an aminopolycarboxylic acid-based agent. This formulation suffers from rapid clearance from the blood and limits their use for MR-based angiography [106]. A possible solution was to encapsulate gadolinium into PEGylated liposomes, which produced significant contrast enhancement of tissue vasculature enabling high spatial resolution [106]. Furthermore, excessive chelation of gadolinium and other contrast agents can substantially reduce their contrast enhancement. In this case, investigators used carbon nanostructures to enclose gadolinium ions within fullerene cages [107] or gadolinium ion clusters within nanotubes [108, 109] and achieved 10 and 40 times greater contrast enhancement, respectively. The loading of these agents within nanoporous silicon particles yielded a 6-fold contrast enhancement of the embedded payloads (Magnevist, gadofullerenes, gadonanotubes) attributed to their nanoscale confinement [110, 111].

In addition to the delivery of contrast agents, some nanoparticles can serve as imaging agents due to their unique nano-scaled features. For example, gold nanoparticles can serve as contrast agents for computed tomography [112], iron oxide nanoparticles for spin-spin relaxation (T2-weighed imaging, MRI) [113–115], quantum dots for near infrared (NIR) fluorescence-based imaging [116, 117], and carbon nanotubes for NIR and ultrasound imaging [118, 119]. In general, these imaging properties are size-dependent, so MRI contrast enhancement increases with increasing diameters of iron oxide nanoparticles. However, large nanoparticles tend to aggregate and are more readily recognized by the immune system, therefore, a certain balance must be reached depending on their intended application [120]. Quantum dots (2–15 nm) also show a size-dependent correlation; their fluorescence emission can be tuned from blue to red by increasing their size, representing a powerful alternative to traditional dyes, permitting broad excitation spectra, high quantum yield, and remarkable resistance to photobleaching [121]. Due to the high surface area of nanoparticles, they can also be decorated with various recognition moieties (e.g. antibodies, aptamers, peptides, etc.) to target and enhance the imaging of cancer [122], apoptosis [123], hypoxia [124], angiogenesis [125], atherosclerosis [126], and inflammation [127]. In addition, therapeutics and other diagnostics can be added to their surfaces to create particles

able to provide both therapy and imaging (i.e. theranostics), including radioactive probes for positron emission tomography imaging [128, 129]. However, when using metallic and semiconductor nanoparticles, one needs to be cautious of possible adverse immunological and toxicity effects.

Clinical approval of iron oxide nanoparticles to diagnose lymph node metastases and liver lesions with MRI was obtained in 1996 for Feridex (iron oxide nanoparticles decorated with dextran) [130]. Following this, other agents (e.g. Resovist, Combidex, Clariscan, and Gastromark) received approval or were in development for clinical use [131]. However, the production of these agents was discontinued due to safety concerns. High false-positive rates, and minimal market representation (penetration?), and thus, have been phased out of use [131, 132]. Several promising nanoparticle-based imaging applications are currently in clinical trials, or expected to be in the near future, including nanoparticles for MRI contrast that target an integrin commonly found on the surface of newly developed vessels, and applying carbon nanotubes as possible x-ray sources for a new type of computed tomography scanner [133]. Nanoparticles with metallic components can be used as biosensors, for imaging capability with CT (such as super-paramagnetic iron oxide) in the attempt to better visualize cancer masses [134].

With respect to the transplant field, nanoparticle approaches for imaging have predominately been used to monitor transplanted grafts [135, 136], track distribution (dispersion) of administered stem cells [137–139], gauge viability of implanted cells within scaffolds [140, 141] or within tissues [142, 143], and to evaluate drug release from scaffolds [144]. In summary, nanotechnology has the potential to provide powerful solutions to permit noninvasive imaging of organs and tissues before and after transplantation and as means to visualize the vasculature and enhance the resolution for superior medical imaging.

Summary and perspectives

Nanotechnology presents novel ways to approach the different barriers that organ and cell transplantations present today. The implementation of nanotechnology has demonstrated various successes including the recent use of nanocomposite polymer as scaffolding for the synthesis of a successfully implanted artificial trachea [145]. In addition, nanotechnology has been shown to play a significant role in ensuring successful transplants for patients with high risk of chronic rejection by providing targeted and controlled delivery of immunosuppressive drugs. The use of these platforms has also provided viable alternatives to combating issues related to drug solubility and increasing drug efficacies. Nanoformulated emulsions [60], liposomes [23], and polymeric micelles [12, 61] have been shown as reliable alternatives to transport water-insoluble therapeutics. In tissue engineering, nanomedicine has been employed to regenerate healthy tissue using a variety of composites, nanodelivery systems, implantable nanochannels, and nanoencapsulation platforms. New developments in nanomaterials such as the inclusion of bioactive properties, able to enhance cell growth and function, offer a promising future for today’s transplant therapies and could improve the prognosis of transplant patients.

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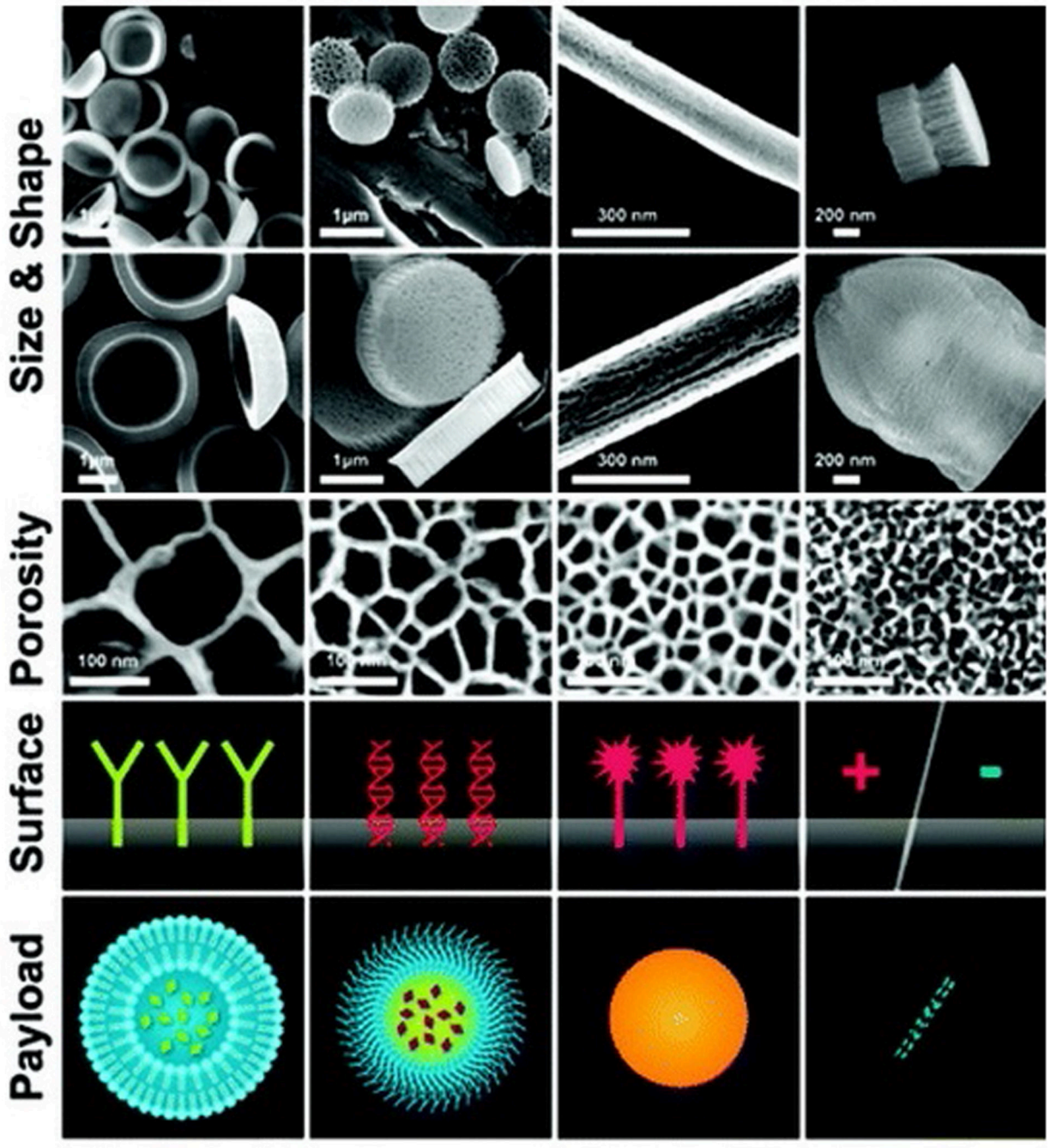

Figure 1.

Schematic of synthesis and functionalization of particles. Size, shape and porosity: Mesoporous silicon nanoparticles with various aspect ratios and various pore sizes (e.g. Discoid nanoparticle, semi-spheres, nanorods). Surface modifications of particles: Positive/ negative surface charges, peptides, antibodies. Payload nanoparticles: named second-stage carriers (SSNs) are nanoparticles within the approximate size range of 5-100 nm in diameter (e.g. liposomes, micelles, inorganic/metallic nanoparticles, and carbon structures).

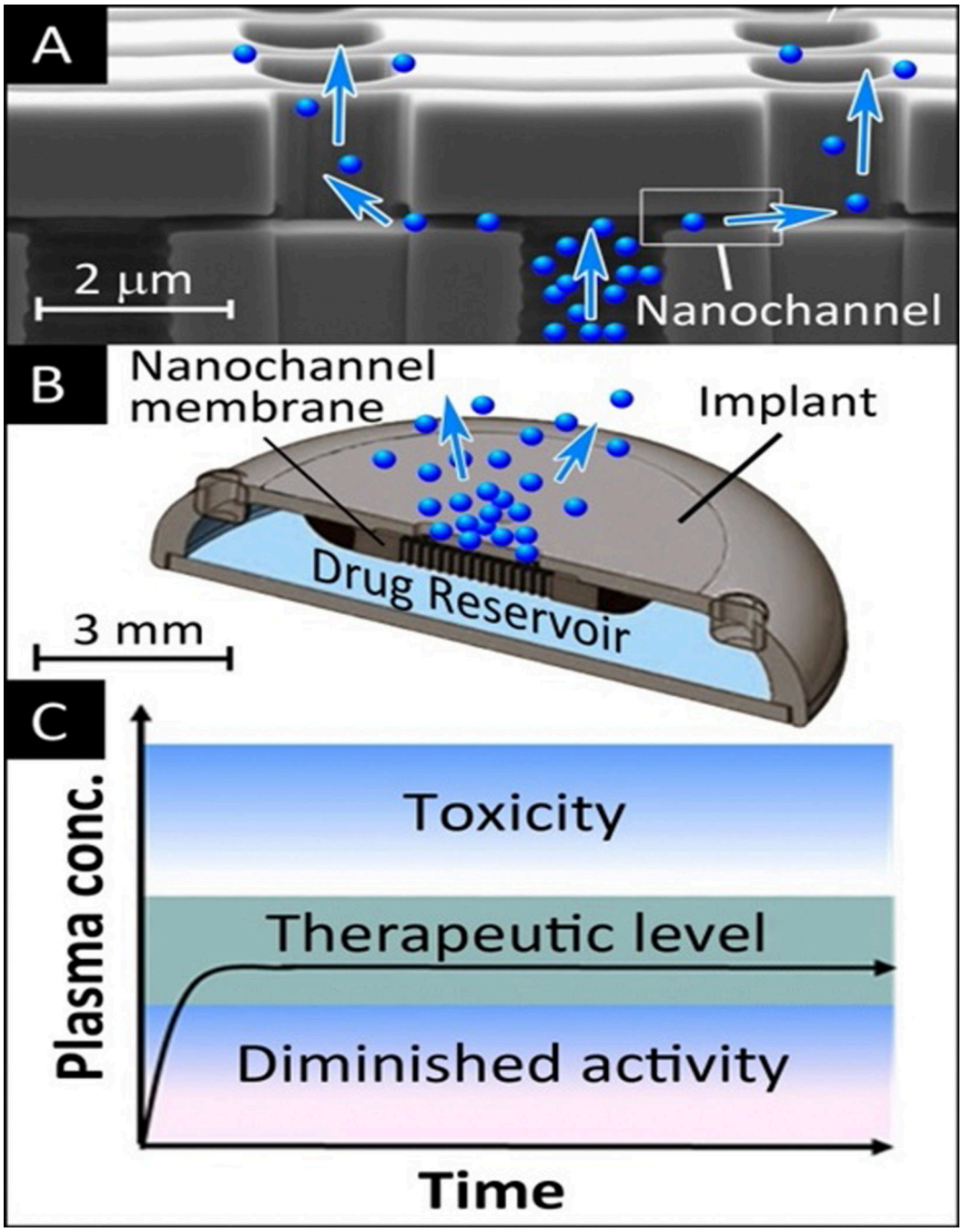

Figure 2.

Scanning electron microscopy image of the cross section of a silicon – silicon nitride nanochannel membrane designed for constant and sustained drug release (A); 3D rendering of the structure of a drug delivery implant incorporating a nanochannel membrane (B); zero-order sustained release can achieve and maintain plasma level of drugs within the therapeutic window for the duration of treatment (C). This has potential for improved efficacy and reduction of adverse side effects of treatment as compared to the conventional bolus administration of therapeutics.

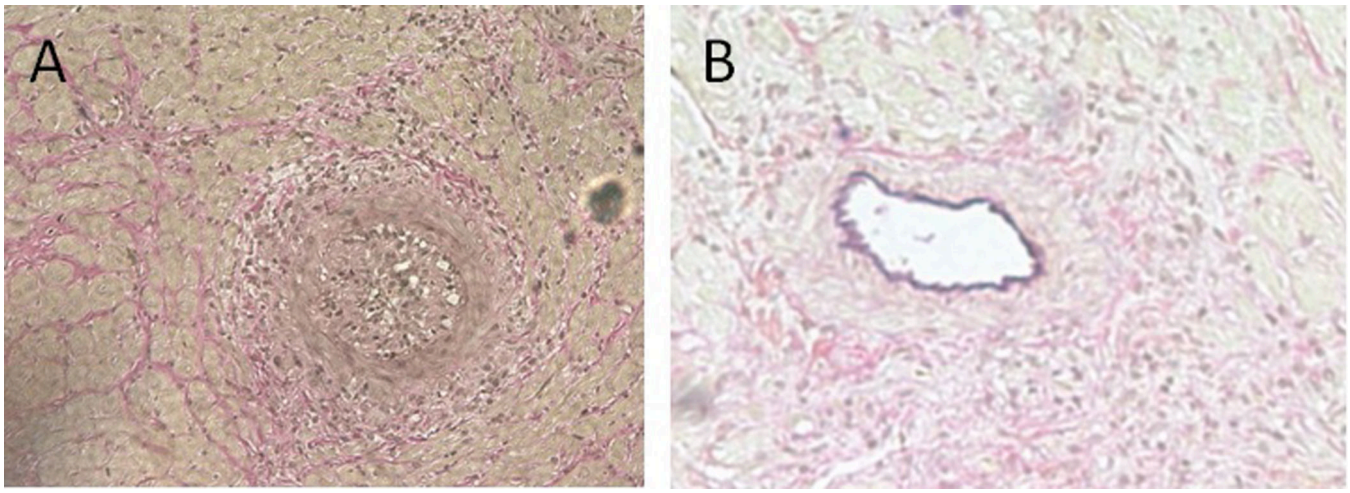

Figure 3.

Sections of transplanted rat hearts VVG stained. Chronically rejecting heart shows fully occluded vessel (A). Recipient treated with RhoA inhibitor delivered from nanochamber shows healthy unoccluded vessels (B).

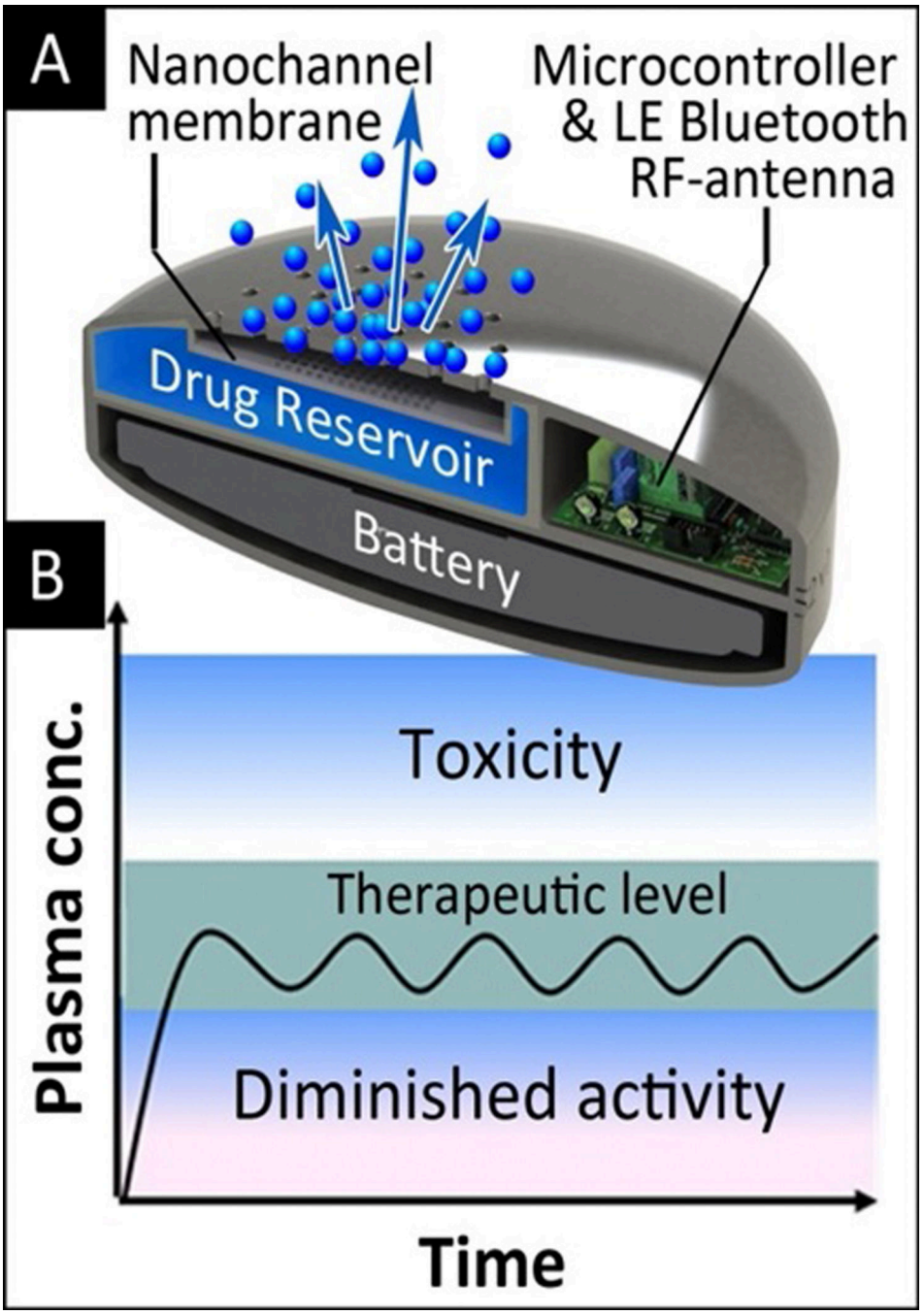

Figure 4.
3D rendering of a drug delivery implant for the remotely controlled administration of therapeutics (A). The implant comprises an electrode-coated nanochannel membrane for tuning a low-power applied electric field and tune drug release according to need. Drug administration can be synchronized to the biological clock to maximize the efficacy of treatment (B).

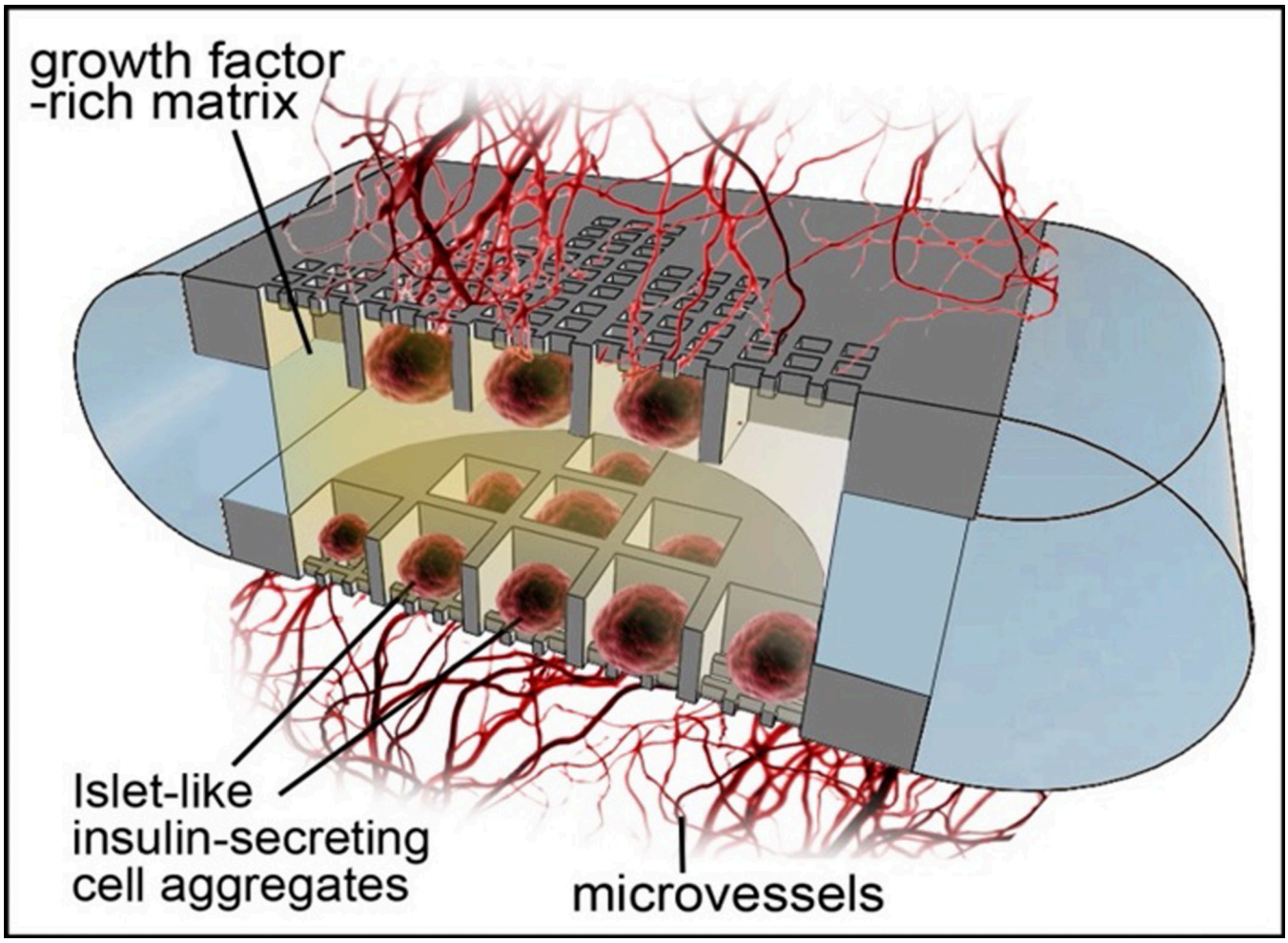

Figure 5.

3D rendering of a nanochannel encapsulation of insulin secreting cells. The encapsulation creates a protective environment to improve graft survival and to promote rapid vascularization post transplantation. The encapsulation may supply the graft with oxygen, nutrients, growth factor and immunosuppressive agents *in situ*, to promote long term viability and abrogate rejection.

Table 1

Application of Nanotechnology in Transplantation

Applications in Transplantation	Platforms	Description
Delivery of Immunosuppressants and other Drugs	Nanoparticles	Nanoparticles allow for a targeted, sustained and more controlled drug delivery dosage, reducing the side effects of indiscriminate prolonged used.
	Liposomes & Peptide Amphiphiles	The use of lipid-based delivery platforms and Peptide Amphiphiles help in the delivery of water-insoluble therapeutics, increasing drug efficacy.
Donor Specific Tolerance & Rejection	Nanochannel Membranes	Nanochannel membranes offer a constant, sustained release and can be tuned in channel size (2 – 200nm) and density to achieve a clinically relevant, constant delivery of drugs. It has shown constant in vivo delivery for periods ranging from 1 to 6 months.
	Nanobodies	Nanobodies (therapeutic fragments of antibodies) present advantages in size, stability, and low immunogenic potential and can be used to stimulate inhibitory pathways and shut off immune cells to prevent allograft rejection.
	Biocapsules & Nanoglands	The use of biocapsules and Nanogland platforms, allows the exchange of nutrients and metabolites while inhibiting the permeation of antibodies and the infiltration of immune cells. They are designed to maintain cell proximity while ensuring sufficient separation to simulate the *in vivo* environment.
Imaging, Diagnostics and other uses	Nanoparticles (e.g., gold, iron oxide, quantum dots)	Often used to deliver contrast agents to assist in delineating anatomy and physiology for medical imaging, the use of nanoparticles in diagnostic imaging has exhibited a six-fold contrast enhancement compared to the use of free contrast agents.