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Biomaterials and biotechnology: From the discovery of the first angiogenesis inhibitors to the development of controlled drug delivery systems and the foundation of tissue engineering

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Abstract: This paper describes the discovery of the first inhibitors of angiogenesis; the discoveries that led to the development of the first biocompatible controlled release systems for macromolecules, and findings that helped to create the field of tissue engineering. In addition, new paradigms for creating biomaterials, early work on nanotechnology in medicine and intelligent drug delivery systems are discussed. © 2013 Wiley Periodicals, Inc. J Biomed Mater Res Part A: 101A: 2449–2455, 2013.

Key Words: drug delivery, biomaterial, tissue, engineering

INTRODUCTION

In this paper, I describe the studies that led to the Founders Award of 2013. These include the discovery of angiogenesis inhibitors, the development of controlled release systems for macromolecules as well as smart delivery systems, the creation of new biomaterials and helping to create the field of tissue engineering.

The discovery of angiogenesis inhibitors

Starting in the mid-nineteenth century, scientists including Rudolf Virchow, noted that tumor growth is frequently accompanied by increased vascularity. Major conceptual advances took place in the 1930s and 1940s, when it was hypothesized that the ability to induce new vessel growth through release of vasoproliferative factors confers a growth advantage on tumor cells.[1]

Similar observations implicating blood-vessel growth in intraocular disorders leading to blindness were made. In 1948, Michaelson proposed, on the basis of embryologic and clinicopathological studies, that a diffusible factor could be responsible not only for the development of the normal retinal vasculature but also for pathological neovascularization in proliferative diabetic retinopathy and other disorders.[2] A major advance came in 1971 when Judah Folkman proposed that antiangiogenesis could be a strategy to treat cancer and possibly other disorders.[3,4]

As has often been the case in the development of new medicines, discoveries were hampered because no bioassay existed to address their study. As a postdoc with the late Judah Folkman, he and I proposed using controlled release polymers that could slowly release angiogenic factors (which were large molecules) in the normally avascular rabbit cornea. Up until that time, no one had ever slowly released a macromolecule from a biocompatible polymer system and many considered this an impossible feat.[5] However, we discovered that certain polymers, when dissolved in organic solvents, could be mixed with molecules and used for controlled release of molecules of virtually any molecular weight (see next section for further discussion).[6] Among other studies we conducted, we took polymer pellets containing tumor angiogenesis factor and implanted them into 20 rabbit corneas.

In every case vessels sprouted from the corneal edge and grew towards the polymer (Fig. 1). No edema or white

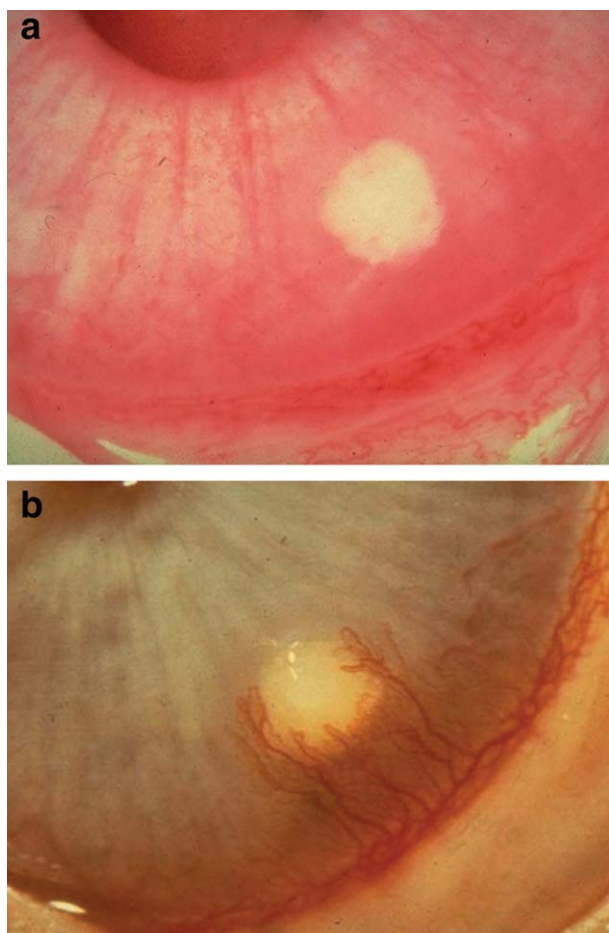**Correspondence to**: R. Langer; e-mail: rlanger@mit.edu

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FIGURE 1. (a) Control–Day 20; (b) Experiment–Day 20.

without inhibitory activity were tested. By contrast, when inhibitor was present, vessels were sparse, grew slowly, and failed to grow in a zone surrounding the polymer [Fig. 2(c)]. By the 4th week many vessels were regressing. This study[7] established that angiogenesis inhibitors did, in fact, exist, and helped to lay the ground work for the isolation of future inhibitors.
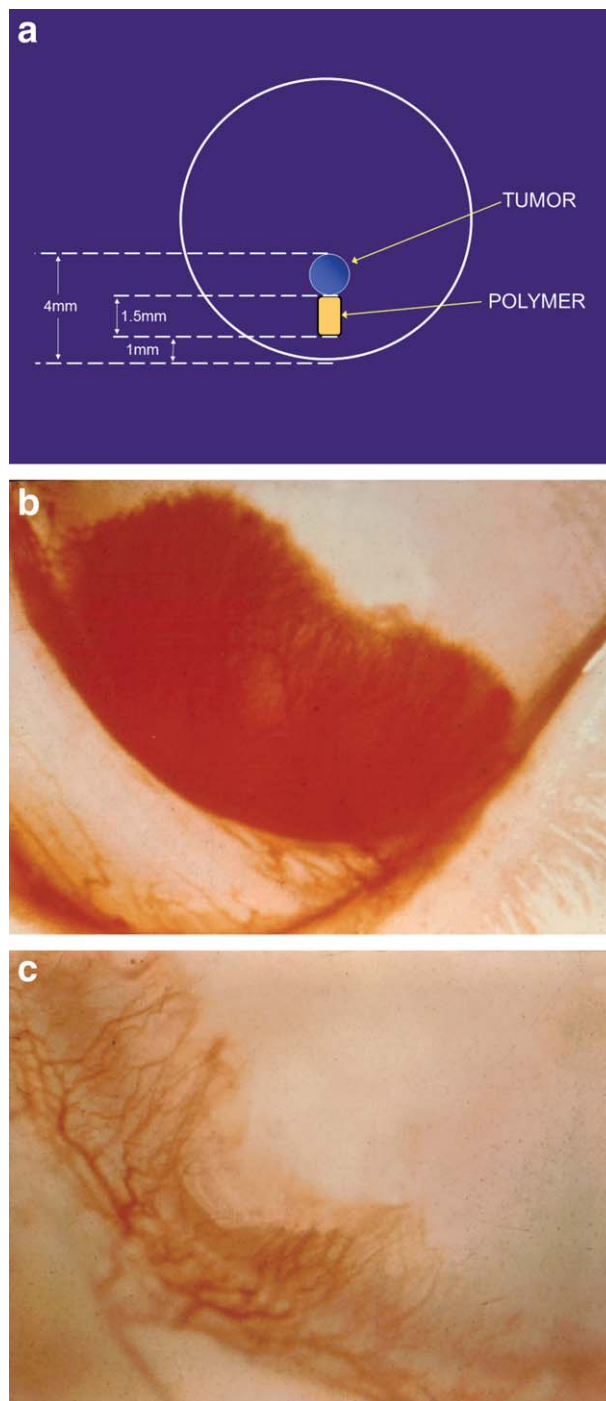
FIGURE 2. (a) Schematic of rabbit cornea test, (b) Control cornea–Day 17, (c) Treated cornea–Day 17.

cells were detected. After 40 days, several of the polymer pellets were removed and vessels disappeared within 21 days. When the same polymer pellets were washed in Ringer's solution and transplanted to new corneas, vascular responses were again observed. This assay has been used in the isolation and testing of essentially all angiogenesis stimulators and inhibitors.

In 1976, we reported the isolation of the first substance to inhibit the vascularization of tumors. Using the rabbit cornea as a bioassay for tumor induced vascularization, we assessed the inhibitory effect of different purified fractions of cartilage. Pellets of polymer and pieces of tumor (V2 carcinoma) were placed into corneal pockets [Fig. 2(a)]. The tumors grew as thin plaques, inducing vessels to sprout from the edge of the cornea 4–6 days after implantation. Vessel length and tumor diameter were measured every few days.

When polymer pellets were empty, vessels appeared as a dense carpet sweeping over the polymer toward the tumor [Fig. 2(b)]. When vessels penetrated the tumor, it grew rapidly into a large protruding mass occupying nearly the entire cornea. Very similar results were obtained when polymer pellets containing substances

CONTROLLED RELEASE POLYMER PELLETS ENABLE BIOASSAYS FOR NEARLY ALL ANGIOGENESIS STIMULATORS AND ANGIOGENESIS INHIBITORS

The above controlled release polymer systems have proven fundamental to the isolation and study *in vivo* of nearly all angiogenesis stimulators and inhibitors.[8–14] These are just a few early examples of the thousands of studies that have used these polymer systems to isolate and test angiogenesis factors. Without this polymer assay, the isolation of these inhibitors would likely not have been possible. For example, as Judah Folkman noted in his abstract for the 2006 Symposium Celebrating Thirty Years of Robert Langer's Science, "Early research in tumor angiogenesis was propelled by the pioneering work of Robert Langer who discovered how proteins and other macromolecules could undergo sustained release from polymers that could be implanted into the avascular cornea of animals and into other tissues. This advance provided a general platform for the subsequent discovery and purification of angiogenesis regulatory molecules. It is difficult to imagine how such proteins could have been isolated and their angiogenic activity identified without Langer's contribution." Similarly, as Cramer has written,[15] "The first proof that numerous angiogenic proteins stimulate new vessel formation arose from an elegant feat of chemical engineering by Robert Langer, who devised a polymer bead. The bead, when placed in the avascular cornea, slowly and continuously released these proteins to stimulate the formation of new vessels." The National Academy of Sciences 1999 Beyond Discovery Report "Polymers and People,"[16] notes that "Robert Langer and Judah Folkman used this approach to isolate the first angiogenesis inhibitor."

These bioassays[6] for angiogenesis stimulators and inhibitors and other informational molecules that have been essential to the isolation of nearly all angiogenesis inhibitors such as inhibitors of epidermal growth factor,[17] fibroblast growth factor (FGF),[18] vascular endothelial growth factor (VEGF).[19]

Numerous angiogenesis inhibitors have now been approved by regulatory authorities and are in clinical use. A partial list is provided in Table I.

Controlled release of macromolecules

As aforementioned, I began my career working with the late Judah Folkman, attempting to isolate the first inhibitor of angiogenesis. To do so, it was critical to develop a bioassay for angiogenesis inhibitors, nearly all of which were macromolecules. We conceived of using a rabbit eye assay, but it was critical in doing so to have a controlled release system that would not cause inflammation, and that could slowly and continuously release macromolecules (e.g., peptides, proteins, and nucleic acids). When I started my investigations, it was widely believed that only low molecular weight compounds—but certainly not peptides or proteins—could be slowly released.[20] However, we discovered that certain biocompatible polymers could enable the slow delivery of molecules over 300 molecular weight.[6]

I began studying this problem by utilizing hydrophobic polymers, like ethylene-vinyl acetate or lactic-glycolic acid copolymers[6,21] dissolving them in certain solvents (like methylene chloride), and mixing them with bio molecules (often at low temperatures). Then, depending on the fabrication procedure, these polymers could be made into microparticles, nanoparticles, or other physical forms. These particles could continuously release bio molecules for over 100 days. By controlling implant geometry, molecules could slowly be released at a constant rate.[22]

This discovery was initially ridiculed by the scientific community and I was turned down on my first 9 grant applications and almost lost my professorship.[23] However, over time this finding enabled the practical use of many peptides, charged low molecular weight pharmaceuticals and proteins. Since, such molecules have extremely short half-lives in the body (minutes in some cases), a controlled release system must often be used.

To determine how biomolecules could be continuously released from these seemingly impenetrable polymers, Rajan Bawa in our lab employed a cryomicrotome to cut thin sections through polymer matrices. This helped to elucidate the polymer microstructure. When no biomolecule was placed in the polymer matrix, no pores were found, and molecules of 300 Daltons or greater were unable to diffuse from one side of a thin (5 μm) polymer matrix section to the other. However, if a biomolecule was placed in a polymer matrix and sectioned, a phase separation was observed. When these systems were released for a year and then thin sections were cut, pores were left behind in place of the biomolecules that were originally there. The pores were created by this phase separation. In observing these pore structures by scanning electron microscopy, we found that the pores were large enough for molecules, even of several million daltons molecular weight, to pass through. However, the pore connections were tightly constricted and the pores themselves were very tortuous, slowing the net rate of molecular movement out of the matrix. Using approaches such as controlling polymer molecular weight or composition[24] and biomolecule particle size and concentration,[25] the pore structures could be predicted and even tailor-made to achieve different release rates.

Impact on biology and medicine. The above research has also had a significant impact on developmental biology, starting with Silberstein and Daniels paper in Developmental Biology[26] where they used our ethylene acetate based implants to study the development of mammary and salivary glands. Many other investigators have used these implants to release different substances to study developmental processes. Park and Hollenberg provide an early review of this research and its impact[27] and numerous investigators have used these implants to study such areas as eye specific segregation,[28,29] development of neural maps,[30] development of visual cortex,[31] spinal cord development,[32] and many other developmental processes.

The controlled release principles established have been important to the development of numerous clinically used therapeutics. As former Nature editor, Phil Ball, has written in his book[5] describing this field "It was widely believed at

Bulk Erosion

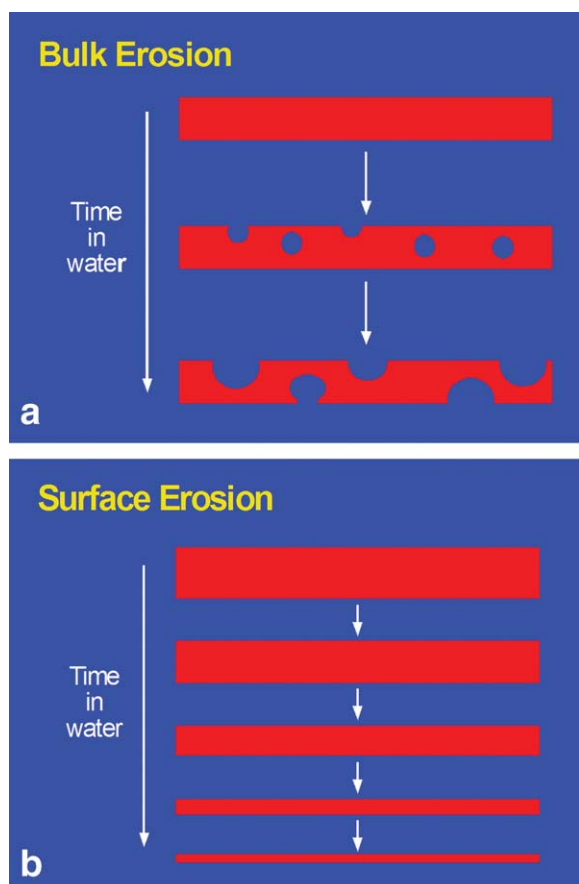Time in water

a

Surface Erosion

Time in water

b

FIGURE 3. (a, b) Idealized diagram of polymer matrices displaying surface erosion.

first that polymer delivery systems would not be equal to this task. . .. But in 1976, Langer and colleagues found that certain polymers, generally ones that were highly hydrophobic (water-repellent) such as copolymers of ethylene and vinyl acetate, could be mixed with powdered proteins and formed into microspheres that would release the proteins at a steady, slow rate, persisting sometimes for up to one hundred days. There seemed to be no limit to the size of the large molecules that could be released controllably in this way, nor to their nature: proteins, nucleic acids, and polysaccharides (sugar polymers) could all be used. In 1989, a controlled release system of this sort—microspheres made from a safe biocompatible copolymer of lactic and glycolic acid—was approved by the Food and Drug Administration (FDA) for use with a large-molecule peptide drug that combats prostate cancer. This was the first polymeric controlled-release system for peptide based drug to find medical approval and it now provides the mostly widely used treatment for advance prostate cancer."

Similar microspheres containing bioactive molecules have led to new treatments for schizophrenia, alcoholism, and narcotic addiction, as well as Type 2 diabetes. These microspheres have been used by many millions of patients.

Biomaterials: A paradigm shift

We and others also noted that most people used "off the shelf" polymers to address a biological or medical problem, even though the polymer was not designed for that purpose.[33]

We asked what are the important qualities desired from the polymer from the viewpoint of engineering, chemistry, and biology and then synthesized new polymers for the exact application. For example, in controlled release we and others proposed utilizing polymers that display surface erosion, a property, which could protect unstable molecules from water-induced aggregation, as well as prevent large amounts of drug from being released at once (Fig. 3).

To address this issue, we reasoned that the polymer should hydrolytically (as opposed to enzymatically) degrade because enzyme levels vary from person to person and over time due to the changing environment surrounding a polymer implant. To achieve hydrolytically induced surface erosion, we concluded that hydrophobic monomers connected by water-labile linkages were necessary and predicted the bond structures (anhydrides) to achieve this. We then selected nontoxic monomers and synthesized polyanhydrides from them.[34] As discussed subsequently, these polymers have made possible a new approach for localized long acting chemotherapy for brain cancer and helped open the door to localized polymer based chemotherapies.

Controlled release materials have made possible a new approach for localized long-acting chemotherapy for brain cancer. We synthesized a polyanhydride, combined it with a chemotherapeutic drug, and constructed it into a wafer, which is placed directly over the tumor region during surgery. This approach delivers extremely high sustained levels of chemotherapy directly to the tumor with virtually no systemic side effects. This fundamental advance in polyanhydride chemistry and its translation to a therapeutic has extended the life of numerous patients, from a few weeks to many years in some cases.[35–37] In 1996, the Food and Drug Administration (FDA) approved this delivery system, the first time in over 20 years that the FDA approved a new treatment for brain cancer and the first time the FDA ever approved a system that directly delivered chemotherapy to a tumor. The principle of localized drug delivery pioneered by us is now being used successfully in many areas such as polymer-drug coated cardiovascular stents. See, for example, the NIH 2004 Overview of Research Activities, which states that "Langer's work has made possible the drug-eluting stent which became available to patients with heart disease in 2003." Such stents have been used in over 10 million patients.

Another area where we have done a great deal of work is the high throughput synthesis of biomaterials like polymers and lipids. This work, led by David Lynn and Daniel Anderson, has led to new ways of delivering DNA, siRNA and other substances.[38–43]

Extensions to nanomedicine

The original controlled-release materials we developed were small particles, in many cases these were microspheres. Nanoparticles are critical for delivering significant payloads of any drug into cells, particularly newer potential drugs like siRNA.

TABLE I. Angiogenesis Inhibitors Approved for Clinical Use

Date Approved	Drug	Place	Disease
May 2003	Velcade (Bortezomib)	US (FDA)	Multiple myeloma
December 2003	Thalidomide	Australia	Multiple myeloma
February 2004	Avastin (Bevacizumab)	US (FDA)	Colorectal cancer
February 2004	Erbitux	US (FDA)	Colorectal cancer
November 2004	Tarceva (Erlotinib)	US FDA	Lung cancer
December 2004	Avastin	Switzerland	Colorectal cancer
December 2004	Macugen (pegaptanib)	US (FDA)	Macular degeneration
January 2005	Avastin	EU (27 countries)	Colorectal cancer
September 2005	Endostatin (Endostar)	China (SFDA)	Lung cancer
November 2005	Tarceva (Erlotinib)	US FDA	Pancreatic cancer
December 2005	Nexavar (Sorafenib)	US (FDA)	Kidney cancer
December 2005	Revlimid	US (FDA)	Myelodysplastic syndrome
January 2006	Sutent (Sunitinib)	US (FDA)	Gastric (GIST), kidney cancer
March 2006	Erbitux	US (FDA)	Head and neck cancer
May 2006	Thalidomide	US (FDA)	Multiple myeloma
June 2006	Lucentis (Ranibizumab)	US (FDA)	Macular degeneration
June 2006	Revlimid	US (FDA)	Multiple myeloma
August 2006	Lucentis	Switzerland	Macular degeneration
September 2006	Lucentis	India	Macular degeneration
October 2006	Avastin	US (FDA)	Lung cancer
December 2006	Velcade	US (FDA)	Mantle cell lymphoma
January 2007	Lucentis	EU (27 countries)	Macular degeneration
February 2007	Sutent	US (FDA)	Kidney cancer
March 2007	Avastin	EU, Iceland, Norway	Metastatic breast
April 2007	Avastin	Japan	Colorectal cancer
May 2007	Torisel (CCI-779)	US (FDA)	Kidney cancer
November 2007	Nexavar (Sorafenib)	US (FDA)	Hepatocellular carcinoma
December 2007	Avastin	US (FDA)	Kidney cancer
February 2008	Avastin	US (FDA)	Breast cancer
March 2009	Afinitor (Everolimus)	US (FDA)	Kidney cancer
May 2009	Avastin	US (FDA)	Glioblastoma
June 2009	Palladia (veterinary use)	US (FDA)	Canine cutaneous mast cell cancer
July 2009	Avastin	US (FDA)	Kidney cancer
October 2009	Votrient (Pazopanib)	US (FDA)	Kidney cancer
November 2010	Afinitor	US (FDA)	Giant cell astrocytoma
April 2011	Zactima (Vandetanib)	US (FDA)	Medullary thyroid cancer
May 2011	Sutent	US (FDA)	Pancreatic neuroendocrine tumors
May 2011	Afinitor	US (FDA)	Pancreatic neuroendocrine tumors
November 2011	Eylea (Aflibercept)	US (FDA)	Macular degeneration
January 2012	Axitinib (AG-013736)	US (FDA)	Kidney cancer
July 2012	Afinitor	US (FDA)	Breast cancer
September 2012	Eylea (Aflibercept)	US (FDA)	Central retinal vein occlusion
January 2013	Avastin	US (FDA)	Metastatic colorectal cancer

But, polymeric nanoparticles injected into the body were destroyed almost immediately by macrophages, and they were unstable because they aggregated. This made their use essentially nonexistent. In a 1994 Science paper,[44] we addressed these problems. We found that nanoparticles composed of a block copolymer of polyethylene glycol (PEG) and any other material such as poly lactic acid, and an added drug, could circulate for hours *in vivo*, be stable on the shelf for years, and not aggregate. These principles are being widely used by many scientists and companies to practice "nanomedicine."[45]

Smart delivery systems
We also made other materials or transport-based contributions to the area of intelligent controlled release. For example, we developed the first "smart" polymers that could be regulated by external physical forces and used for controlled release. We found that when small magnetic beads were placed within an elastic polymer containing a particular drug to be released, the resulting system could be magnetically triggered to release more drug when needed.[46] Other smart materials we developed include systems that can be ultrasonically,[47] enzymatically activated,[48] or even intelligent chemical microchips.[49,50]

TABLE II. Polymers used in Medical Devices

Medical Use	Initial Use	Polymer
Artificial heart	Ladies girdles	Polyether urethane
Dialysis tubing	Sausage casing	Cellulose acetate
Vascular graft	Clothing	Dacron
Breast implants	Lubricant	Silicone
	Mattress stuffing	Polyurethane

Tissue engineering

In a series of experiments in the 1980s, I (along with surgeon Jay Vacanti) discovered that liver, intestinal and other tissues and organs could be produced by combining mammalian cells on three-dimensional scaffolds of biodegradable, biocompatible polymer materials in cell culture. This discovery has been credited by the National Academy of Sciences as "leading to the field of tissue engineering."[16] See also Niklason et al., 1999[51] and Pearson, 2009.[52] When these devices were implanted into animals, new vessel formation was signaled and permanent functional new tissue was created, which could function as a living tissue replacement. This discovery was accompanied by the biologic finding that three-dimensional scaffold configurations, which mimicked nature's fractal branching patterns were the essential feature for survival and repopulation of structures large enough to generate useful living tissue (prior to this discovery, scientists were largely trying to achieve cell growth using two-dimensional systems as opposed to the three-dimensional systems we created). This discovery also solved the problem of mass transfer of oxygen and nutrients into large masses of cells by matching the surface area needed for diffusion to the volume of the device. There are approximately one billion living cells per gram of tissue and all need oxygen and nutrition which are supplied by diffusion from capillaries. In nonvascularized systems, this diffusional exchange occurs at the surface, but the surface area only increases as the square of the radius as a mass of tissue enlarges, but the volume increases as the cube of the radius. By creating branching fibrous scaffolds, we were able to greatly increase the survival of large masses of cells by greatly increasing the surface area for exchange. The cells could then go on to form vascularized living tissue after implantation.[53]

We built upon this initial discovery in a number of ways. For example, the concept of flow bioreactors to improve mass transfer as well as provide mechanical signals to the developing tissues (leading to a completely novel way to create blood vessels) was described in Niklason et al., 1999.[51] In addition, the use of stem cells in spinal cord repair[54] as well as the first example of controlling the differentiation of human embryonic stem cells[55] into vascular endothelial cells was achieved. Coupled with these discoveries of the necessary biological principles of tissue formation, we developed new chemical approaches to produce scaffolding materials, which would specifically signal genetic cellular events including proliferation, provide attachment sequences for the cells, as well as augment angiogenesis, all in harmony to produce normal tissue.[56] We also created new biodegradable materials to further advance scaffolding technology for tissue engineering.[57] Other contributions include the first methods to create materials for controlling stem cell differentiation,[58] methods of using stem cells to create muscle,[59] methods of using materials to create heart tissue,[60] and synthesizing the first surfaces for growing stem or iPS cells in a completely xeno-free, serum free environment.[61]

In Science article in 1993[62] (cited over 4,000 times), Vacanti and I helped describe the field of tissue engineering. Since 1986, we and our colleagues have demonstrated the formation of ~20 different tissues of the body in animal models as well as several tissues in humans. We engineered cartilage, heart valves, bone, liver, intestine, urological structures, tendons, and muscle. This work has helped lead to creation in humans of skin[63] now approved for burn victims and patients with diabetic skin ulcers (e.g., marketed by Shire), blood vessels,[64,65] urinary bladder,[66] and cartilage. Already over a million patients have received tissue engineered human skin (for burns or diabetic skin ulcers) based on Vacanti and our discoveries (e.g., Dermagraft, uses the exact polymer we originally used, polylactic glycolic acid, in this case with neonatal fibroblasts).

SUMMARY

These studies cover some of the biomaterials based contributions that I have been involved in. The terrific students and postdoctoral fellows who have worked with me, many of whom are world leaders in biomaterials themselves, are the ones truly responsible for these contributions.

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