Advances in Biomaterials and Devices, and Their Financing

Welcome and Introductory Remarks
Dean Ronald Cass
Prof. Michael Baram

Dean Cass:

Hello, my name is Ronald Cass and I am Dean of the Boston University School of Law. We are delighted to have you here today. I understand we have a very exciting group of speakers and a very interesting topic that has been put together by Michael Baram for Boston University's Center for Law and Technology and by Steve Bauer and the people at Testa, Hurwitz & Thibeault, LLP.

I also was told that today you would be discovering a lot about a topic I know nothing about, which is regeneration. I am actually a specialist in degeneration which is what got me the deanship. I have asked Michael if he can let me know at what part of the day we can discover how to regrow hair, and at that point I will be back. Meanwhile, let me turn it over to Michael. I hope you have a wonderful day.

Prof. Michael Baram:

Thank you, Dean Cass, for getting us all loosened up with a good joke: that regeneration, degeneration bit. My name is Professor Michael Baram and I direct the Center for Law and Technology here at the law school. Today's meeting is the third annual Technology Law Symposium to be held here, sponsored by the high technology law firm of Testa, Hurwitz & Thibeault, LLP and the Center for Law and Technology.

Our meeting today is focused on an exciting area of research and product development. This area involves the use of conventional as well as new genetically engineered biomaterials in new medical device configurations for implantation and with the purpose of restoring bodily functions, regenerating tissue, bone, cartilage, even organs, and limbs someday. This is a field that has great promise for improving health care in the United States. Some people have even said it offers the great promise of perpetual life.

Dean Cass is referring to a recent *Boston Globe* article regarding the merger of three biotech firms.[1] The new firm will focus on regenerative medicine. The ability to restore and regenerate is apparently leading to the creation of at least a nomenclature of regenerative medicine. Living tissue, as you all well know, recently approved by the FDA, was a major break through in this direction. Very soon we will conclude mapping the human genome and, with the advent of bioinformatics and sophisticated computer analysis techniques, it is very clear that many such developments will be coming forth in the near future. But, what this conference is about is the problem of transforming research into product and therapies into use in health care.

Moving from basic research in universities and research labs to applied research and experimentation in hospitals and companies and then on to enter the commercial market for health care is not necessarily an easy timeline to follow. One has to deal with many issues that are going to be discussed today. These issues include timely and appropriate financing of research and development ("R&D"), effective partnerships between diverse organizations, property rights and other incentives for performance, protection of human subjects, satisfaction of FDA and other regulatory requirements, health insurance coverage, ongoing attentiveness to regulatory compliance, and to avoidance of malpractice and product liability.

These are the topics that will be discussed today by our distinguished speakers and there will be full time for audience participation and questions and answers at the end of each session.

We are on a strict schedule, and I do not want to start by violating it, but there are many topics to deal with in short order. Before I turn the meeting over to Steve Bauer, an attorney from Testa, Hurwitz & Thibeault, LLP, I just want to mention a few things. Steve and I have collaborated on the production of these annual technology law symposia and we have been helped a lot by our law students, especially by the students who work on our innovative *Journal of Science & Technology Law* here at Boston University School of Law. The staff has been extremely helpful and will be responsible for publishing the proceedings so you can expect that a copy of the proceedings will be published later this year.

Moderator: Steven Bauer, Esq.
Panelists: Prof. Joyce Wong
Prof. Martin Yarmush
Mr. Rufus King
Mr. Joshua Tolkoff

Professor Michael Baram:

I would like to introduce Steve Bauer. Steve will chair this next panel, and will make the introductions. Mr. Bauer holds several degrees from M.I.T. and graduated with honors from Boston University School of Law. At Testa, Hurwitz & Thibeault, LLP, he is a partner and specializes in protecting the intellectual property rights of clients, litigation, licensing and patent prosecution strategy. He has been an Adjunct Professor at BU School of Law since 1987. He serves on the Advisory Board of our *Journal of Science & Technology Law*. It is a great pleasure to turn this over to Steve Bauer.

Prof. Steve Bauer:

Thank you, Michael. I am lucky enough today to be able to simply introduce the panelists at the table. I am not going to be saying anything else besides that I will be taking questions afterwards. The way this is going to work is that each panelist will get about ten minutes. This panel will talk about technology and financing issues. These issues are the background that will lead to the rest of the day's material. Each panelist will briefly speak, followed by a question and answer session.

Our first speaker today is Professor Joyce Wong, Ph.D. Professor Wong is a Clare Boothe Luce Assistant Professor in Biomedical Engineering at Boston University. She received a Ph.D. in Polymers and Biomaterials from M.I.T. in 1994. Her main research interest is using biomaterials to probe and control cell behavior in drug delivery and tissue engineering applications.

Prof. Wong:

What I would like to do today is to give an overview of biomaterials science – its origin, the current state of the art, and where I think the future of biomaterials is going. First, I would like to define "biomaterial" and "biocompatibility." As you can imagine, the definition of "biomaterial" depends on whom you ask, but in 1987 there was a consensus definition of a biomaterial as "a non-viable material used in a medical device intended to interact with biological systems." The term "biocompatibility" was defined as "the ability of a material to perform within an appropriate host response in a specific application." For example, in a vascular graft, you would want to avoid processes such as thrombosis that would result in blockage of the graft.

This table gives an overview of the different types of biomaterials that are used for various biomedical applications. Note that all material classes are represented, namely metals, ceramics and polymers. Today, I would like to focus on polymeric biomaterials. One example is the use of polyurethane for the artificial heart. For skin repair, there are several products that are available commercially. To date, artificial skin is probably one of the most successful examples of tissue engineering.

The next slide gives some background information on the history of the use of materials for biomedical applications. Originally, some of the materials that you saw in the previous slide (types of materials used for various biomedical applications) were chosen by surgeons who took off-the-shelf materials that possessed properties close to their surgical needs. For example, you can see that with the artificial heart, they chose the same material that was used in the ladies' girdle. For the vascular graft, nylon or clothing was used. In the 1950s, a surgeon went to a fabric store and cut some nylon fabric to use for a vascular graft, and this appeared to work. For a number of years, many of these materials were and are still routinely used for biomedical applications. Note that these materials were being used before there was an FDA approval process for biomedical devices and were thus grandfathered in. In essence, these materials were put into the body, and they happened to work. Today, the procedure for FDA approval is much more stringent. Thus, the first generation of biomaterials consists of *existing* materials that closely match the desired application.

The next generation of biomaterials has been focused on the rational design of biomaterials. One way to classify polymeric biomaterials is to divide them into two different categories. The first is absorbable – i.e., biodegradable. The other category is non-absorbable – i.e., a material that needs to maintain its integrity and does not degrade. On this incomplete list of rationally-designed polymeric biomaterials, some of these materials are FDA-approved, but the number of FDA-approved materials is quite low. This brings up the issue of legislation regarding the liability for biomaterials. I believe that, in 1998, Congress passed legislation to limit liability to essentially protect the material suppliers.[2] But this legislation is very recent, and I am not sure how this new legislation is going to affect smaller companies in terms of introducing new biomaterials into the market.

Teflon and Nylon are examples of non-absorbable materials and are routinely used as vascular grafts. The next slide highlights several novel classes of polymeric biomaterials whose biomedical application is currently being studied mainly at the basic research level. One example are photopolymerizable *in vivo* polymers, so named because they undergo gelation once they are inside your body. Possible applications are to prevent surgical adhesions and reduce restenosis after angioplasty. Electrically conductive polymers are being considered as substrates to guide nerve regeneration, and finally researchers are moving more towards "bio-inspired" polymers, for obvious reasons, but mainly to address issues of biocompatibility. This is by no means a complete list, but it at least gives you an idea of the wide variety of new classes of polymers that are being developed for biomedical applications.

Let us consider again the example of the vascular graft since it illustrates the different types of problems and issues that one faces when using synthetic materials. If you place a graft made of Teflon or Nylon inside the body, once it is exposed to the blood and plasma proteins, the body considers the graft to be a foreign object, and a cascade of events occurs, eventually leading to thrombosis, i.e., the blood vessel will have blockage. Essentially, this is failure of your vascular graft and the patient will require repeat surgery.

Well, you may ask, what does a native blood vessel look like? This slide shows a simplified diagram of a blood vessel. Clearly, there are many differences between an artificial graft and a native blood vessel. However, I have highlighted one of the more important

differences: the native blood vessel has an endothelial cell lining. These cells are extremely important in that they secrete many factors that inhibit thrombosis. These factors include prostacyclin, heparin, tissue plasminogen activator ("TPA"), and nitric oxide. Thus, one approach has been to embed these factors into the polymeric scaffold such that these factors are released in a controlled manner.
However, ultimately, one would like to have the vascular graft contain an intact endothelial cell lining.

18. This leads to the issue of controlling the interactions between cells and biomaterials. One of the goals in creating an engineered tissue is to recruit a desired type of cell onto the medical device. For example, in the vascular graft, you would like the endothelial cells to populate the inside of the graft and, at the same time, you would like to keep away undesirable proteins (e.g. those leading to thrombosis). Thus, what you would like to be able to do is to (a) promote adhesion of desired proteins and/or cells and (b) prevent adhesion of certain proteins and/or cells.

Let us first consider promoting the adhesion of a desired cell type. In this extremely simplified schematic of a cell, note that there are some proteins on the cell surface that bind to different proteins on a surface. Each protein pair is specific – much like a lock and key. One approach to recruit endothelial cells onto the vascular graft would be to adsorb the proteins that endothelial cells recognize onto the graft surface. However, it would be more desirable in terms of cost and processing to isolate a small region on the protein that is involved in cell adhesion.

In the early 1980s, there was a breakthrough when Pierschbacher and Ruoslahti found that the cell attachment activity of a particular protein could be duplicated by small synthetic fragments.[3] The implications of this finding were that one could now synthesize this small, 3-amino acid sequence (RGD) and attach it to virtually any surface to promote the adhesion of a cell that normally adhered to this particular protein. To date, this sequence has been tested on polymers and metals. One example of a polymer that combines this feature of controlled cell adhesion that is also biodegradable uses lactic acid (polylactic acid is FDA-approved), which imparts the biodegradable property, and a modified lactic acid to which one can attach any peptide sequence.[4] The basis for using biodegradable polymers for tissue engineering applications is that the polymer serves as a scaffold – much like the scaffolding you see on buildings – onto which one then attaches the cells while the scaffold slowly degrades away to let the body take over.

In addition to the RGD sequence, a number of other short peptide sequences have been identified, and this slide shows the native protein, its peptide mimic for a specific function such as neurite extension and cell adhesion.[5]

Another desired property for biomaterials is to prevent adhesion. One faces a similar problem in the targeted drug delivery community. Targeted drug delivery is simply the delivery of a drug to a specific location in the body. Before the 1980s, one method involved the use of antibodies to target specific sites in your body. However, *in vivo* studies showed that these drug carriers had extremely short circulation times. It was later found that these particles were being cleared by the body's immune system. Fortunately, in the late 1980s, it was discovered that when you decorate these carriers with polymers (maybe you heard in the news recently about how researchers are using these same polymers to decorate blood cells to create "the universal blood donor"), one is able to protect this drug delivery vehicle from the immune system because you are essentially covering these molecules that your body would recognize as foreign. Today, the challenge is to use some type of optimal combination where you still have the targeting property but at the same time hide from the immune system. This idea has been adopted in the tissue

engineering field by decorating or covering the surface with different polymers that either repel or promote adhesion of proteins and/or cells.

I would like to end by commenting on the recent advances in genetic engineering and bioinformatics. As I mentioned earlier, the discovery of RGD was extremely important in allowing cell attachment to essentially any surface. Since this discovery, the crystal structure of a portion of the native protein has been solved, and this slide shows the structure of a portion of fibronectin. Note that the RGD is sticking out on a loop and is thus very accessible. From the structure, one can easily see how one could cut off the RGD, attach it to a surface and be able to have cell attachment. How bioinformatics and genetic engineering become important is that one can use information from the human genome project. The idea is then to use this information to help predict what functions other proteins or other regions of proteins are involved in – not only cellular adhesion but also other cellular roles such as cell death, growth, and migration and differentiation.

I think that it is a very exciting time for biomaterials because of these developments, so the remaining issue is how can we integrate this information into making new biomaterials for biomedical applications.

Steve Bauer:

Thank you. Our next speaker is Prof. Martin Yarmush. He is the Helen Andrus Benedict Professor of Surgery and Bioengineering at Harvard Medical School, and he is the Director of the Center for Engineering and Medicine at the Massachusetts General Hospital. Prof. Yarmush's research interests span a wide range of topics from tissue engineering and artificial organ development to gene therapy and metabolic engineering. He has his B.A. degree from Yeshiva University and did Ph.D. work at Rockefeller University in immunochemistry. He got his M.D. degree from Yale and his Ph.D. from M.I.T. in chemical engineering.

Prof. Yarmush:

I am going to begin where Joyce left off. She spoke of materials innovation primarily. I will discuss some additional issues that focus on the future. To begin, I would like to comment on the bibliography in the handout under the topic of *Advances in Biomaterials and Medical Devices* that includes a few articles in *Scientific American*.[6] If you read these articles you will become very excited. A great deal of the content of these articles, however, is very "far-out" and one or two figures can be characterized as pure fantasy, sounding more like science entertainment. Certain industrial concerns, in their desire to generate an image of success, have also frequently contributed to the fantasy part and thus overheightened expectations. One must be careful and critical in evaluating the scientific worth of the ideas proposed within the regenerative medicine field, in general. I suggest to those in the audience who wish to live a long life, take your younger brother or sister, child or grandchild to Disney World every six months; that alone will probably extend your life by about five years. I'm not sure that any of these futuristic materials will be around to do that for us.

For any given biotech material, its development and its road to implementation in the field are very long and drawn out processes. Given this fact, are they promising investments? When I say investments, it is not just in the context of monetary investment, but whether it is a promising investment from the standpoint of human effort. I believe the answer is that it depends. It depends on whether the field boldly attacks major problems versus the often minor cosmetic challenges that, for example, face the plastic surgery business. In the past, the human race fought big things – it was the saber-tooth tiger or the wooly mammoth that plagued us. But when we conquered these big things, by god, there were small things lurking around the corner,

like heart disease, cancer, diabetes, Alzheimer's, liver disease, the HIV virus, malaria, TB, and antibiotic resistant organisms. In the jungle of today, if biotech materials serve only a small group of limited health problems that are "doable," but do not impact upon the big killers, then I feel it may not be worth our while.

With that out of the way, I will talk about some broad issues with an emphasis on critical technologies that are poised to perform an enabling function for the field. There are a number of promising technologies which can help energize and expand the horizons of the biotech materials field. These include gene therapy, cell and tissue preservation, microfabrication, metabolic engineering and functional genomics.

The definition that Joyce listed for "biomaterials" was established by a group of biomaterial scientists.[7] I prefer a different definition. They, that is biomaterials, are not just non-living materials. They can be any material including living components such as cells. So, I posit that there is a broader definition of biomaterials that the lay public understands which includes synthetic materials, semi-synthetic or hybrid materials, as well as living materials. A biomaterial could be a patch that you put on your skin, or could be something that you place in your body. These are different than medical devices which are purely mechanical that are exterior to the body or implanted within the body, each of which have no biologically derived or engineered materials.

Perhaps we should begin to discuss some examples of these biotech materials and devices. Artificial skin was among the first commercially available biotech materials. The first version was a purely synthetic material and is currently produced by Integra Life Sciences in New Jersey. It is basically collagen, which is derived from bovine tendon. The collagen is chemically modified by linking glycosaminoglycans to the collagen. This artificial skin had no cells.

Advanced Tissue Sciences is a company in San Diego that produces an artificial skin product which uses a nylon matrix with fibroblasts included within the matrix. There is another company here in the Boston area, Organogenesis, that produces an artificial skin comprised of a collagen matrix and cells called keratinocytes which sit upon the matrix.

It is interesting that none of these companies is making a great deal of profit on these products. The reason for this is quite complicated, involving an imperfect medical effectiveness record, the lack of reimbursement, high costs for manufacture and distribution, as well as certain weaknesses in marketing and sales.

33. A promising set of emerging preservation technologies could impact on part of this problem, especially with materials that contain live cells. For example, there are frogs that are capable of freezing themselves in a very peculiar way so that they can survive the winter in frozen ponds. Each frog's cells overproduce glucose as a replacement for the intracellular water, which can be very damaging during the freezing process through ice crystal formation. There are also examples in nature of organisms that can naturally survive dehydration or drying. If we can harness these biological processes or mimic their essential elements, with the idea of incorporating them into the manufacturing process, then products could be manufactured with an exceedingly long shelf life which could lead to more routine handling and distribution methods.

The technology of gene transfer might also be applied for the treatment of diabetic or venous ulcers, in which case the artificial skin product could serve a direct healing function rather than that of just a wound covering. A genetically engineered graft could stimulate new blood vessel production as well as new dermal tissue generation. Moreover, some of these skin beds are filled with bacteria, so an artificial skin that is genetically engineered or chemically modified to release antibiotics might be more clinically effective.

Another area that Joyce mentioned was immune reaction control.[8] Sometimes immune reaction control does not matter that much as in the case of skin, where rejection may set in after the patient's skin has had time to regenerate. However, this area is of vital importance to other materials, and technologies which bring immune neutrality through chemical modification or genetic engineering will have a tremendous impact on the medical effectiveness of many products.

I would like to discuss another example in the device area, which relates to some of our work on development of an artificial liver device. The idea is to have a device that contains liver cells, so that when a patient faces acute liver failure, the device could serve the patient like a kidney dialysis machine. Some of the development issues that one is required to consider seem incredibly mundane, but yet are very important. First, the human liver has over 100 billion cells. Even placing ten percent of these cells into a device is a difficult feat. So, reducing the dead volume of our device design is extremely important and the technologies of microfabrication and nanotechnology hopefully will help in this regard. Another problem is cell source. Where do the liver cells come from? Are you going to harvest them from a pig? Each pig liver you use for a device will have to be tested extensively, which is a costly process. It would be best to use that pig liver to fill more than one device. Thus, technologies for stem cell isolation, cell expansion, and cell culture become important.

Another technology that bears mention is metabolic engineering, where the question to be answered is how well is this device operating? Do you check certain enzyme levels, or check a couple of other distinct functions, or do you have a more integrated approach to evaluating the device? We may know what's coming in and coming out, but we need a better understanding of what's happening within the device when it's treating the patient, as well as during the manufacturing process and prior to use. The analytical tools of metabolic engineering can be useful in this regard, as can the burgeoning fields of functional genomics and proteomics.

Coordination of technologies is also exceedingly important. In the protein engineering field, molecular biologists can generate great ideas for new drugs, like erythropoetin and interferon, but sometimes it takes years to work through the scale-up and manufacturing issues that make production scale outcomes possible. Another issue is market suitability; an in-depth understanding of the true market, and of the likes and dislikes of the end-user who is typically a physician or skilled healthcare professional.

A final issue is FDA approval and reimbursement. FDA approval and reimbursement are critical issues for industrial concerns. Criteria for approval and reimbursement, in the not-too-distant future, may go beyond safety and medical effectiveness, and also include the cost of the material or device.

I hope that I did not stir the pot too much. But, I wanted to emphasize that the field of biotech materials has many exciting practical aspects, and that one of its greatest challenges is to coordinate the growth and application of certain emerging critical technologies so that true solutions to significant medical problems emerge.

Thank you for your kind attention.

Steve Bauer:

Our next speaker is Joshua Tolkoff. Josh has been active in the R & D and manufacturing of medical devices for twenty-five years. He's currently the managing director of a new company called Seedling Enterprises, which is a company looking for new medical device concepts, and then helping those products get to market, and get commercialized. He's also Chairman of ACT Medical, which is a contract developer/manufacturer of medical devices such as catheters. Before that, he was Vice President of Medi-Tech, which is now a Boston Scientific

subsidiary. He's a graduate of Harvard and M.I.T., and has twenty patents in the medical device area.

Joshua Tolkoff:

Good morning. It is my role to give you the medical device and industry perspective, so ten minutes should be enough. I should probably tell you how I got here, because it really relates to health care financing. I visited Ashley Stevens, who is here today, at the technology transfer office at BU (Boston University). I know that he has contacts within BU, and we went to see if there was a possibility of BU investing in Seedling Enterprises, this sort of incubator or hatchery of medical ideas that I have started. Before we sat down to give our pitch, he said, "How would you like to speak?" So, you always say "yes" to a potential investor, so here I am.

I am going to give you a quick summary, since I only have a short period of time, of medical devices, and health care since one million B.C. From one million B.C. up to 1900, was the "watch out" time of medical devices and medical practice. "Watch out" meant to stay away from the problem, or keep the problem away from the patient. In fact, during that period, the two greatest devices in the history of medical care were invented. Those two devices were the flush toilet and the shoe. Only one of those is a biomaterial. But, that was the time of the earth, fire, and water perspective of life. The shoe and toilet kept the problems from the earth, parasites for example, out of the body. Of course, they helped keep many diseases transmitted by water away from the patient as well. So, we have a lot of catch up to do to equal those two inventions.

From 1900 to 1970, health care really changed. There was a change from the "watch out" medical practice to a practice of finding the problem, performing some surgical intervention, and then allowing the body to fix itself. So the surgeon was really removing a problem, removing an obstruction, removing a joint that did not work properly, and then perhaps putting something back in to hold that position, but really letting the body heal itself.

What about the last period, from 1970 to the current period of time? It is very similar except procedures are done non-invasively, or less invasively. We're in the age of finding the problem less invasively. What do I mean by that? I mean using new imaging technology instead of doing exploratory surgery. When was the last time you heard of someone having exploratory surgery? It's hardly ever done anymore. So, instead of surgery, physicians use catheters and imaging devices, biopsies, needles, etc. to find the problem in a less invasive way. The procedure after that detection step is the same as in earlier surgery, removing the problem or helping to remove the obstruction and allowing the body to repair itself. Where possible, however, these are done less invasively or non-invasively.

The 1970s period was when I began my experience in the health care device industry. It is also when I recognized the two most important watch words of life. This has little to do with health care devices specifically, but how I like to live my life. One is: "Don't get sick" and the other, which is equally important, is: "If you do get sick, don't tell anyone."

What is the future? Where do we go from here? Well, the future will be moving from passive devices, passive interventions in the body, to harnessing biology itself. Basically, (1) harnessing our understanding of biology, as our two previous speakers have described, to make better materials, and then (2) flipping that and in fact using those materials or that biological understanding, to actually create organs: to recreate functional components of the body. This will be a huge step forward, if in fact the promotion that Prof. Yarmush was talking about in fact turns into reality.[9]

Let me shift from health care to biomaterials. The first materials used as biomaterials were really shielding the body. That includes clothing or shoes, as I mentioned. Also, the first metals were used to make surgical instruments to take out splinters, to lance boils, etc.; basically

removing problems. The earliest catheters were feathers, hollow quills. In fact, the very earliest catheters, long before polymers were developed, were demineralized bones.

And that leads us up to this century. In this century, we generated materials, many that came from industrial work, having to do with armaments, and certainly from governmental research. This gave us other materials that could be used to replace or restore structural components of the body. This includes metallic implants, hip implants, things like that. Silicone implants have been used for different prosthetic applications in the body , and many legal and public issues revolve around use of those devices. We have many plastics or tubes. There are tubes that now can be used to provide fluid transport within the body or from inside the body to outside, draining things, catheters, grafts, all used to restore flow in the body.

Most of the things up until the present time have been used in the body for short term applications or intervention in the body. There is no committee that determines exactly what "short term" means, so I will give you my determination: it is not enough time for the body to really care very much about the device. So you put the device in, you may prevent the body's reaction, like using Heparin to keep blood from clotting on it, but you do that for a short period of time and then take the device away. The body does not have much time to react or you prevent the reaction. Long term device use is more challenging because those are devices or things that have to be left in the body and the body has to be at least sanguine about them. The term biocompatibility has been discussed today. I think it is important to consider what that term means in relation to the function of the device. I will talk a little bit more about that later. Up until the last ten or fifteen years, biocompatible basically meant that if you put something in the body for a long period of time, the body kind of left it alone. The body generally would cover the device with cells, encapsulate it, or wall it off in some fashion so the body existed with the device and was satisfied with it being there; maybe not happily, but just left it alone. Obviously, with the new functional device technology that we're talking about, that is not the case; devices must react directly with biology and vice versa.

What about problems with devices and materials? Well, materials degrade, and we have heard about infection risks of devices. Things get pinched off, they break, they leak. Materials degrade over a long period of time in the body, since they are not restored. There is no regeneration as there is with natural biological materials. So biomaterials wear out. In addition, biology is not really happy with things staying inside the body. For example, blood clots on catheters or grafts that are left in place for a long time. Devices get clogged, tissue grows inside of drain tubes and anything else which is left inside the body. Catheters get clogged off, pinched, and bacteria grow on the surfaces of devices inside the body because the body cannot clean artificial surfaces the way it can a biological system.

The next generation of materials and devices that use biomaterials uses more active materials. These are materials that try to avoid these problems. For example, coatings that help to keep blood from clotting on surfaces, anti-microbial coatings that slowly come from a device to defend against the body being attacked or against the body's immune response (being inside the body is a pretty hostile environment for medical devices), and harder wear surfaces for orthopedic implants. The goal is to improve the function of the devices by understanding what the body was trying to do to the device. The concept is to prevent the body from attacking the device or material and causing it to fail. The coming generation of biomaterials requires a better understanding of biology. If there is anything I have learned in the last twenty-five or thirty years, it is that biology is extraordinarily complex. Whenever we think we have a solution to something and we put that solution first into ten people, then 100 people or 1,000 people, you find out things at each level that you never expected. This is particularly true as we explore device-drug combinations and we begin to harness biology in active devices.

What about the practical side? How do we get people to pay for new materials? What gets paid for? What's interesting? What makes economic sense? Ten years ago, if you made a catheter, a guide wire, a hip, or some other medical device and added an improvement, a slippery coating, a non-thrombogenic coating, an anti-microbial coating, you would demonstrate that in the laboratory, in a petri dish, it worked. Then it was possible to get people to use them and you could get people to pay more for them than for the standard device that did not have the improvement. These enhancements were viewed as good and therefore people would pay for them.

That is not the current situation. The current situation is that if you have something that you think is good, you have to prove that it is good. You have to prove it not only in a petri dish, but you have to demonstrate that the clinical outcome, that the actual clinical use of this improvement, gives you a better outcome for the patient. Once you have done all that, and you have demonstrated that the device adds value, you get to charge just the same for the improved device; you can no longer charge more for these things.

Some of the significant challenges include the testing and modeling of medical devices, implants, and tissue engineering. The most common ways devices and materials are tested in the laboratory do not mimic very well the actual human environment. And I am not just talking about the species differentiation, from an animal species, or to cells in a petri dish, but really the healing of someone who is elderly, someone who is sick. I am aware of some very interesting problems with a heart valve where a new sewing ring was tested and it used a silver coating to enhance the defense against infection. This is a wonderful idea because infection risk is a rare problem, but a really devastating problem when it occurs. Well, the new device was tested in animals and it passed all of the FDA tests for safety and was approved. Now it has been implanted in many hundreds of patients and in almost all of those it has worked fine. It appears that there is a small subset of patients who do not heal well and in these patients the silver on the device may slow down the healing even more so that problems occur. So you now have, instead of a device which has been endothelialized, a device that is exposed to blood for a longer period of time, leading to clotting or other problems.

The very subtle biological problems that may occur will not be discovered in the normal modeling and device testing process. This poses a significant challenge: How do you better model the biological environment? The future, as I see it, is understanding biology and replicating function through harnessing that biology. We have many significant challenges. I like to think of the magnitude of the challenge in terms of the natural materials. As we age, the normal biological materials, the ones that we are born with and that are replicating, fail. I think that it is unlikely for us to do better than the actual natural arteries, and veins, and other materials. So if those fail over time, I think our expectations should be in relationship to ultimate failure of the best. We should probably start to consider the proper expectations and challenges we are going after. As far as I know, we will not live forever; we should keep that in perspective.

The legal issues, of course, are real ones. I mentioned earlier in my discussion that because of lawsuits, silicone implants have been in the public eye quite a bit. Silicone is still probably the best and most inert polymer material for use in the body. But once there is a public perception of a problem, manufacturers will no longer even provide it. There are many material manufacturers who will not send you product literature if the name of your company has anything relating to health care. That is a challenge for future biomaterial development.

I am excited about the next phase that we are moving into, but I also take the words of the previous speakers that biology is quite complicated. It will take us quite a while to really understand the complex interactions between biology and devices.

Thank you.

Steve Bauer:

Thank you, Josh. Our last speaker has two qualifications that make him unique of all the people sitting up here. First, he is the only one up here who has not gone to M.I.T. at some point, and second, he only knew about speaking yesterday morning. So, the next person is my partner, Rufus King. He is in the business practice group at Testa, Hurwitz & Thibeault, LLP. He specializes in public and private companies, their formation, raising capital, and doing the licensing work that relates to it. He has his undergraduate degree from Dartmouth, a graduate degree from Oxford University, and he went to Harvard Law School.

Rufus King:

Thank you Steve. I am going to talk about financing, and I thought I would start by saying: what a difference a year makes. Going into my clippings file, I have found an article from February 1999, which says, "Wall Street's Zeal for IT Prompting Some Firms to Curb Health Investing."[10] The article describes one medical device company laying off one third of its workers, and about how many venture capitalists are getting out of investing in health care altogether.

That was then. This is now. January 23, 2000 in *The New York Times*: "Another Boom in Biotechnology Stocks."[11] *The Boston Globe*, January 30, 2000: "Biotechnology is Back and Genomics is Leading the Way."[12] February 15, 2000 in *Wired* (and if it is on the internet, it has to be true): it says, "Biotechnology is About to Rock."[13] And just today, in the *Boston Globe*: "On Wall Street, a Buzz Over Biotech."[14] So, perhaps things really have changed (or at least the perception is that things have changed) and I think they are right. I am going to give you some data to show that there is a perceptible upward trend in funding for health care companies and part of that will be for medical devices and medical materials companies.

The question is, why? What has happened in the last year to change things? Clearly, as these articles indicate, genomics is leading the way. As it says in the *Boston Globe* article, many of the genomics companies are located right here in New England.[15] They are clearly the media darlings. I think we are going to have something like a "homerun derby" going this summer, not between Sammy Sosa and Mark McGuire, but between Celera and the Human Genome Project to finish sequencing the human genome.

I think one reason for the buzz about genomics is that there is a real affinity between information technology ("IT") and genomics. I see a lot of the same issues, the same technology can be used in the data mining and bioinformatics fields. So that is one reason for the change in attitude.

Another reason is that the health care and biomedical sectors have been down so long that there really are a lot of opportunities there. There is a lot of pent-up research here at Boston University and elsewhere that has not been able to get funded by investors, but has continued to percolate along. I think investors are beginning to see some low-hanging fruit: ideas that are ready to be commercialized, and not just at the concept stage.

Finally, some of these articles say that there may be a pendulum swing back towards long-term investing, long-term value, real profits, and real intellectual property assets. I think that may be debatable. As we have heard this morning, the profits from medical devices do take a long time to materialize. I do not think that anyone has any impression that this is going to

change anytime soon. It is just that so much money has gone into IT that investors may be thinking that it is time to diversify.

What does this mean for medical device companies and medical material companies? It means that now is a relatively good time to get financing, either in the public markets or from venture capitalists. In 1999, there was a discernable upward trend. This is from *Venture Source*: first quarter, $680 million; second quarter of 1999, $719 million; third quarter, $824 million. [16] More money appears to be going into private health care companies. Of course, this is dwarfed by the amount going into IT, which is $4.4 billion. But things are definitely looking up.

So, if now is a good time to start looking for financing, what are investors looking for? Well, the first thing is always good technology. You have heard today about what would go into a good medical device product. The second thing, that was also alluded to, is good management. Experience counts in this field. This is not a field where two twenty-year-olds can get lucky and create a billion-dollar company. It takes a long time, it is hard work, and knowledge of the markets really is important. Experience is crucial to avoid some of the traps that are out there for medical device companies. In particular, as has also been said, it is a very highly regulated field.

One thing I wanted to point out anecdotally is that regulation is not just by the FDA, which everyone knows about, and Medicare and Medicaid reimbursement that we have talked about, but there are other miscellaneous laws. For example, as was mentioned, some of the new medical devices use human skin that comes from donors: neonatal foreskin cells, for example. On the federal and state level, there are laws governing tissue donation and organ donation, [17] and you have to make sure that you are in compliance with those laws before you can start selling your product. There are laws about informed consent. Are you sure you got the proper consent when you took that neonatal foreskin to generate the cells that were incorporated into your device? These are issues that executives who have been around the industry might be aware of; scientists who have solely worked in the lab might not be aware of them.

Those are the things that investors are looking for. What should people who are trying to raise money privately be looking for? They should be looking for investors who are the long-term health care players. As that article from a year ago reported, some groups that have been investing in health care were dropping out, because the returns were not particularly good. But other groups have stayed the course, in good times and bad, and those are the types of investors that entrepreneurs should look for. Health care investing involves a different funding model. You don't put twenty billion dollars into your companies at the earliest stage. Investors need to be able to pace themselves, and give these health care companies the funding when they need it, over the time period it takes: from lab, to product development, through clinical trials. It is important that you have got investors who can stay that course, and have plenty of cash in reserve to do that, so that they will be there the next time we have the inevitable down cycle.

So that is my view on financing, and I am happy to answer any questions.

Steve Bauer:

At this point, we can take questions for any of the panel. We have about twenty minutes.

Audience Member:

My basic question is actually something I saw in the *Wall Street Journal* a few weeks ago, or within the past couple of weeks, about the use of phage technology, or the use of phage as antibiotics, or in an antibiotic capacity. Is that just something that has been used in the former

Soviet Union, or is there potential to this research? Does anybody know anything about that particular issue?

Prof. Yarmush:

Can you describe it a little better?

Audience Member:

Essentially, they're using bacteriaphages and simply giving it to people as a sort of a serum, as opposed to potentially more expensive-to-manufacture antibiotics. The basic question I have there is, is that an actual technology that will actually migrate to the United States, or is this not something that people are familiar with yet?

Prof. Yarmush:

I don't know about this specific area, but in a related area, in the infectious disease field, investigators are looking more carefully at how bacteria kill themselves. Bacteria seem to experience the same sort of programmed cell death that we find in eukarocytes. Colonies of bacteria thus have a self-regulating aspect that controls colony growth by generating autolysins. For example, penicillin may not necessarily only block synthesis of the cell wall but also trigger this autolysin pathway.

Audience Member:

Seymour Lederberg, Department of Biological Medicine: Molecular, Microbiology & Immunology at Brown University. Bacterial viruses (bacteriophage) were discovered by F. W. Twort in 1915 and perhaps first pursued as a therapeutic agent by Felix D'Herelle from 1917 through 1922. The antibacterial use of bacteriophage has a few practical problems, one of which is that bacteriophage that kill sensitive bacteria strongly select for the outgrowth of resistant bacterial mutants that are always found in large populations of sensitive bacteria. The resistant bacteria can multiply and replace the dead sensitive ones and continue the infection, thereby impacting a patient's health.

A second problem (that possibly will also occur with approaches that induce bacterial apoptosis) arises from the release of surface fragments of gram-negative bacteria if they lyse after a successful infection by bacteriophage. These fragments include endotoxins which can provoke a systemic shock response in a patient. These problems are similar to beasts around the corner. As one problem is overcome, and there may be ways to solve it, another problem surfaces around the corner.

Joshua Tolkoff:

I just have a comment. I cannot let our last speaker's comment about the ease of financing in health care go without some debate. I think it is dismal out there for early stage to first-round financing, particularly for venture capital in the medical device arena, notwithstanding what the *Boston Globe* says. Certainly, there has been a resurgence of interest in biotech. I think that is correct, although I do not know how much early stage financing there is for biotech either. And with the amounts of money that are going in, I think you have to look a little bit more carefully at where the money is going. Those larger investments are placed, so that total amounts of money are decent, but what that typically means is they are not going in the early stages. Early stage money is very difficult. The number of venture capital companies who are playing in that area (now I am talking about medical devices) is fewer than it was a year ago, no question about that. Even those who are still in health care talk about dot-com health care

kinds of things, as being where they are interested. My experience comes first hand. I am on the board of about four or five early stage health care companies, device companies, and they go a lot further on angle investments, and beg, borrow and steal wherever they can. It is a difficult period right now for early stage investments. We have a couple of technology licensing people and other people in the audience; I do not know if their experience is different. It seems to be a hard time now.

Rufus King:

My point was that it has been bad for a long time, so any change in the public attitude toward it can only help. The stock market is one area where appearance does become reality. If the top-tier medical devices can get funded, then that has a halo effect for the startups. There is no question that it has been very tough for a long time in the medical device area. You can only hope that things will change.

Ashley Stevens:

I think you are probably going to see some kind of trickle-down effect. A couple of fairly major early stage health care funds have closed in the last year or two. Oxford Bioscience has raised a quarter of a billion. Domain did the same. I think this resurgence in the public markets in biotech might allow some of the other funds, that perhaps have not been doing as well, to show the sort of return to their investors that will allow them to attract follow-on funds. I think, over the next year or so, if the markets hold up, you might see the situation start to improve.

Steve Bauer:

What do you see at Boston University in terms of raising money?

Ashley Stevens:

I agree with Josh. It is difficult. I can think of one startup, a medical device startup, which was being done by angels. When I asked the guy how it was going the other day, it did look as if a venture fund might be interested in picking it up. You do get this area of what we call the "valley of death." It is relatively easy to raise a quarter of a million dollars, let us say, from angels, from friends and family, from taking out a second mortgage on your home. Beyond that, you get transaction costs that make it uneconomic to raise really much below two million dollars, and perhaps getting toward raising less than five million dollars. When you get to a venture route round, they demand a downtown law firm doing the legal work. Thus, there is a very difficult period, which is where I think a lot of the companies that Josh is talking about fall into the middle of.

Steve Bauer:

Any other questions?

Michael Baram:

I was struck by the formidable challenge of being able to market a biotech material. Martin Yarmush mentioned the problems of shipment and prevention of contamination of the product. I wanted to ask all of you, and Josh especially, in entrepreneuring in this area, and in investing in this area, how important are these downstream marketability issues – the product being able to be shipped and used by a health care provider, uncontaminated and effective? Are there special problems in this regard? And who's dealing with these problems?

Prof. Yarmush:

I think there are special problems for this field, because the end user is not some kid at the end of the computer terminal. Here you have hospitals and skilled individuals that are the users, at least with many materials and devices. The downstream portion, the marketability, is not just telling everybody about it. It is actually getting the users to overcome barriers. Some of the barriers are monetary; if the patient is not reimbursed, the doctor will probably not offer it. Some of the barriers are the doctors' attitudes themselves. I think there are barriers with the very nature of a start-up company. Ideas within this field usually start off in small conglomerations. If you are with Big Pharma, on the other hand, with their development experience, workforce, regulatory affairs know-how, and connections to the medical community, it is a totally different story. I think when you are starting from scratch, you must, at least, have some knowledge of the program downstream if you want to stay in business for the long haul. If you want to sell yourself off in five years, then you probably don't need to consider any of these issues.

Prof. Wong:

Another issue on developing new materials that you have to think about is prevention of bacterial infection. A lot of times you must use sterilization methods before a material can be implanted. If you are doing fancy chemical modifications, you may just be destroying your engineered surface after you use, say, UV irradiation. This is just one issue in taking something from the research lab. Just a simple thing like irradiation can obliterate everything you've done to the material.

Josh Tolkoff:

Clearly, what we are talking about is a field where commercialization is expected at the end, so those challenges are critical. I think there are a couple of things that are in favor of biomaterials and devices. One is that the distribution companies have gotten larger. The training and expertise that is required to bring new ideas to the marketplace and train health care providers is best done through the larger organizations. As things changed more quickly, for example laparoscopic surgery, where in a very short period of time, literally a matter of a year or two, gall bladder removal converted from an open surgical procedure to a laparoscopic procedure. I can assure you that the manufacturers had a huge role in that, including setting up their own animal testing labs, where they would train as many as twenty-five physicians a day, learning how to use the new devices. That is an enormous effort, but obviously companies want to be able to economically change the way things are done. That is a positive example of an economic industry solution. The other is that there will need to be other models in the way in which money is made. For instance, if you have cartilage taken out of your knee, you can have a procedure to grow more of those cells and put them back in. It is not clear that there's a device sale there. It may be a service that is provided. If tissue engineering is done, you may end up paying for the service that provides the tissue, or you may pay for the processing to move it to where you are, rather than a device sale. There may be other models of the economics that make sense.

Michael Baram:

Just a quick follow up. Obviously, if I have developed a new biotech device, and I want to sell it to the health care providers, I have to fully inform them about how to maintain and keep that material or device so that it is suitable for effective and safe use. In my instructions and warnings to my customers, I may be stating such formidable requirements of refrigeration or sterilization, that they just simply cannot accommodate this product. I'm just wondering, is there

a growing infrastructure? You mentioned larger distributors. Is there a growing infrastructure in the health care sector that is capable of responding to these new technological materials and devices? Or, what can prompt such an infrastructure? Otherwise, the market is obstructed.

Prof. Yarmush:

I think that's part of the problem. On the development side, there's no one large company, or group of companies that's capable of taking on some fundamental issues, like Bell Labs or IBM did for the communications field, where people had free reign to investigate some important downstream issues, so to speak. The tissue preservation business, which I think applies not just to shipping skin but to distributing many other things, needs to be taken off-line, and invested in. With everybody's quarterly report facing them, it's very difficult to do that. I don't think there's the capacity out there now nor the patience required. The cell-sourcing problem is another area. This is something you need to take off-line, as well, not just for liver, but pancreas, kidney, cartilage, or whatever organ you wish to develop. I'm an advocate for basic research and development, because it is important from the standpoint of long-term commercial value.

In another vein, two aspects of the legal profession impact on some of these devices and industries: the liability issue and the amount of money spent on intellectual property battles. From my read of the situation the latter is incredibly large. With companies trying to protect their patents, it seems like there's an incredible drain. I realize it's a drain into lawyers' pockets, which is a good thing for you folks, but it seems like it's an incredible drain on the field. Is the magnitude unique to this field? How does it compare to the dot-com companies?

Steve Bauer:

The next whole panel is going to talk about intellectual property issues, but they are going to talk about why people should be litigating. In the biotech and chemical areas, there is a big difference on the patent side, and that is, the patent at issue is probably going to cover a product, and a variable product, for twenty years. There is big value to monopolize. A biotech patent gives you that industry monopoly. That has big value. On the Internet side, the patent just forces people to tinker a little bit. And the patents take three years to issue, while the technology is moving so quickly. So you do not see it on the other side. But the patent industry was what created the pharmaceutical companies. And you are just seeing it now, on a smaller scale, with the startup companies. You read about all these mega-companies, and the drug prices – that is all patented.

Audience Member:

Are there lower regulatory barriers to the approval of a medical device that would be used as a sensor or a test, as opposed to a material that would be implanted in the body or a procedure that would be used on an actual patient? Or are the hurdles just of a different character? And that, I suppose, would also tie into financing questions. Would it be easier for a company developing, for instance, a biosensor of some kind, to achieve financing, than it would be for somebody who is developing a material that would be used in and permanent in the body?

Josh Tolkoff:

With a lot of industry experience, I think I can give you some comments on that and also reflect on the investment side of that. Investors know if they are investing in a company where the regulatory barrier is what is called a Class III. The classifications by the FDA relate to how

life-threatening or life-sustaining the device or technology would be, three being the most severe. There are not many Class III devices that get reviewed by the FDA in a year, in the tens of devices a year. There are many hundreds in Class II, which do not require nearly the same level of testing. Most diagnostic sensors or other devices fall into Class II, which still require a variety of testing. How much testing depends on how the company presents the material, and how well they have done the background work, long or short tests, depends on open discussions with the FDA, etc. Absolutely there is an understanding by investors that with a Class III device you are probably looking at a twenty million dollars (or more) kind of clinical trial effort to bring a device or material to market. In Class II devices, you are looking in the million dollar range, perhaps, or perhaps even less if have some infrastructure already.

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[1] Ronald Rosenberg, *Three Biotech Firms to Merge: Out of the Union, Curis Inc. Will Focus on Regenerative Medicine; No Layoffs Planned*, BOSTON GLOBE, Feb. 16, 2000, at D7.

[2] *See* Biomaterials Access Assurance Act of 1998, 21 U.S.C. § 1604 (Supp. IV 1999) (providing that biomaterials *suppliers* are not liable unless they qualify as a *manufacturer* or *seller*, as defined in the Act, and other law exists defining their liability).

[3] Michael D. Pierschbacher & Erkki Ruoslahti, *Cell Attachment Activity of Fibronectin Can Be Duplicated by Small Synthetic Fragments of the Molecule*, NATURE, May 3, 1984, at 30.

[4] *See* Denise A. Barrera et al., *Synthesis and RGD Peptide Modification of a New Biodegradable Copolymer: Poly (lactic acid-co-lysine)*, 115 J. AM. CHEM. SOC. 11010 (1993).

[5] *See* Yoshihiko Yamada & Hynda K. Kleinman, *Functional Domains of Cell Adhesion Molecules*, 4 CURRENT OPINION IN CELL BIOLOGY 819 (1992).

[6] *See* Robert S. Langer et al., *Tissue Engineering: The Challenges Ahead*, SCI. AM., Apr. 1999, at 86; Michael J. Lysaght et al., *Encapsulated Cells as Therapy*, SCI. AM., Apr. 1999, at 76; David J. Mooney et al., *Growing New Organs*, SCI. AM., Apr. 1999, at 60; Nancy Parenteau et al., *Skin: The First Tissue-Engineered Products*, SCI. AM., Apr. 1999, at 83; Roger A. Pedersen, *Embryonic Stem Cells for Medicine*, SCI. AM., Apr. 1999, at 68.

[7] *See supra* ¶ 11.

[8] *See supra* ¶ 22.

[9] *See supra* ¶ 36 (discussing the development of artificial liver devices).

[10] Asset Alternatives, Inc., *Wall Street's Zeal for IT Prompting Some Firms to Curb Health Investing: With Quick Gains Promised by Internet, VCs Find It Difficult to Be Patient*, VENTURE CAP. & HEALTH CARE, Feb. 1999, at 1.

[11] Lawrence M. Fisher, *Another Boom in Biotechnology Stocks*, N.Y. TIMES, Jan. 23, 2000, at BU9.

[12] Ronald Rosenberg, *Biotechnology Is Back, and Genomics Is Leading the Way*, BOSTON GLOBE, Jan. 30, 2000, at F1.

[13] Kristen Philipkoski, *Biotech Is About to Rock*, WIRED NEWS, Feb. 15, 2000 (visited May 3, 2000) <http://www.wired.com/news/business/0,1367,34361,00.html>.

[14] Ronald Rosenberg, *Darlings Include N.E. Firms Deciphering Genetic Code*, BOSTON GLOBE, Feb. 18, 2000, at C1.

[15] *See id.*

[16] *See* VentureSource News, *Q3 1999 Venture Capital Financings Top $8 Billion* (visited Feb. 17, 2000) <http://www.venturesource.com/cgi-bin/vs.pl?sid=1228462&srid=2029124297&rtype=news>.

[17] *See, e.g.*, National Organ Transplant Act, 42 U.S.C. § 274e (1994) (prohibiting the sale of organs); MASS. GEN. LAWS ch. 113, §§ 8-9 (1998) (governing persons authorized to make organ and tissue gifts and those that may become donees of such gifts).