Technology Niche Analysis™

Reducing Rejection in Renal Allografts

September 6, 2011

Developer's NAIC: 541711 Research and development in biotechnology
Science/Technology Fields: Biotechnology, Polymer Engineering,
Arena NAIC: 541711, 622110
Technology Type: Product, System
Supply Chain: Design & Development
International Patent Classification: B82Y 30/00 Nanotechnology for Materials or Surface Science
Geographic Region: Global

Project Number: NIH0793TN
Breonics, Inc. (1R43AI081372-01)
was
Prepared by

Maura Lane Warner
617-512-2493
Maura.warner@foresightst.com

Foresight Science & Technology, 430 Angell St., Providence, RI 02906
Voice: 401-273-4844; Fax: 401-273-4744; Web: http://www.foresightst.com/

1 Introduction

The following is a generic description of this technology.

Description of Technology
A method to prevent or delay graft rejection.

The NBLVF4 technology centers around a bioengineered nanobarrier membrane comprised of type IV collagen, vitrogen, fibronectin, laminin, entactin, glycosaminoglycan and proteoglycans. The components are delivered to the renal vasculature via Breonics Exsanguinous Metabolic Support (EMS) System and then polymerized into a three-dimensional transparent membrane. [1]

The interaction between the vascular endothelial cells and the recognition domains within the barrier membrane is receptor-specific via the laminin and fibronectin portions of the membrane. The membrane is applied to "immunocloak" the luminal surfaces within the vascular space by covering the point of contact between vascular endothelium and the host immune system. The result is a bioengineered apical surface that is non-thrombogenic and non-immunogenic.

The NBLVF4 technology would reduce and potentially eliminate the need for use of immunosuppressive drugs in transplant patients and also significantly increase the pool of potential donated organs. Both of these benefits speak to major challenges with kidney transplants. Immunosuppressive drugs carry with them an array of serious side effects. Due to kidney donation currently being restricted to live donors (mainly because of recipients' systemic immunosuppression), there has been a chronic shortage of donor organs. The shortage of donor organs in turn results in increased mortality, significantly increased reliance on dialysis services, use of substandard donor organ with no way to enhance outcomes and poorer quality of life for end-stage renal disease (ESRD) patients.[2]

NBLVF4 is deposited ex vivo as a 28-day pretreatment to facilitate induction prior to kidney transplant. It is known that DCD organs fall short of living donor/HB donor organs mainly in the short-term rejection. If a technology such as NBLVF4 can facilitate the DCD organs to overcome the initial rejection hurdle, then DCD organs become a much more attractive option for transplant and hence, increase the pool of potential donor's organs significantly.

What makes this technology a scientific/engineering innovation is: it facilitates organ acceptance by means other than systemic immunosuppression. The technology acts in a localized manner and does not disrupt other bodily systems.

[1] Brasile, L et al. "Pretransplant kidney-specific treatment to eliminate the need for systemic immunosuppression", Transplantation. 2010 Dec 27;90(12):1294-8.

[2] Tabarrok , Alex, "Meat Market, Tackling the Organ Shortage", WSJ.com, January 8, 2010, http://professional.wsj.com/article/SB10001424052748703481004574646233272990474.html?mg=reno-wsj (accessed August 24, 2011).

Breonics, Inc. wishes to commercialize the technology initially for use with renal allografts. This would be accomplished by partnering with transplant centers to run trials and likely venture capital to fund the development. Corporate partnering may make sense in lieu or in addition to venture funding.

An application is a potential use for a technology that is based on end-user needs and could provide a feasible market opportunity for a technology. The following table is an option for initial market entry.

Viable Application
Renal allografts.

The initial application would be allografts used in kidney transplantation. Kidney transplant represents the largest category of solid organ transplant and also the most constrained.[3] A reasonable means of accessing the market is via patients who would not react well to immunosuppressive drugs. These might include patients who have other ailments.

We also identified other potential applications for the technology.

Other Applications Identified	
Application	***Basis for Feasibility***
Other solid organ transplants (lung, heart, liver)	Immunosuppressive drugs are used in all of these solid organ transplants and there are chronic shortages of all these organs as well.
Burns & skin grafting	If the technology works in solid organ transplant, it would likely work in burns and skin grafting, where rejection is also a challenge. Full immunosuppressive therapy is not used as frequently here. Burn patients require a significant number of skin grafts and long-term allograft survival is a challenge due to immune response.[4]
Regenerative medicine	The technology may have application to simple tissue growth as well.

Skin graft is a second area of application for the NBLVF4 technology. Breonics' technology has been shown to delay the onset of acute allograft rejection. As a topical treatment, the technology could easily be used to improve wound coverage in patients with extensive burns. This is a large market that could be accessed more readily than renal allograft and may offer a promising parallel strategy for commercialization of NBLVF4.

2 Methodology Used for this Study

Foresight uses a methodology called Technology Niche Analysis (TNA™). This method filters applications through a series of funnels. Funnels are decision gates in which we eliminate some options but allow those meeting the decision criteria to pass on for further analysis. Each step

[3] "Advances in Replacement Organs and Tissue Engineering", 2008. Frost & Sullivan web site (subscription required). http://www.frost.com/ (accessed August 20, 2011).
[4] Bart M. Stubenitsky et al, "Delayed Skin Allograft Rejection Following Matrix Membrane Pretreatment", J Plast Reconstr Aesthet Surg (2008), doi: 10.1016/j.bjps.2007.12.001

assesses potential applications in light of pre-determined criteria. Applications may be eliminated at any step. Eliminated applications are not considered further.

Foresight begins solving the commercialization puzzle by using the customer's definition of the technology's performance specifications and characteristics. These are used as guides when conducting on-line data searches and interviews with an expert to identify applications and markets. We also collect our customer's preferences for commercializing the technology and use them as a secondary guide.

In today's rapidly changing global markets, it is unlikely that a single, "best possible" entry strategy exists. Even with the informational resources of the Internet, this remains true, especially for a study such as this that is constrained by budget and time. Of course, budget and time always constrain the data collected and analysis performed for any report. Thus, *the findings and recommendations presented here are preliminary.* Additional market research may lead to modifications or substantial revisions. Although we strive to describe trends that will be important over a five-year window, market and technology developments are dynamic. Events can overtake the data and analysis presented in this report.

3 Competitive Opening

End-users are likely to be interested in this technology because of the following advantages it can bring. We have contacted the following expert to gauge his/her views on the technology's potential competitive opening. These findings are presented in the table below.

Expert on Competitive Opening	
Name	David H. Sachs, MD[5]
Title	Director, Transplantation Biology Research Center Head, Large Animal Transplantation Section Immunologist Paul S. Russell/Warner-Lambert Professor of Surgery, Harvard Medical School
Organization	Massachusetts General Hospital
Phone	617-726-4065
E-mail	david.sachs@tbrc.mgh.harvard.edu
Importance of Need(s) being Addressed	There is a very serious need. We are using [DCD] organs more and more because there is a shortage of living donor kidneys and patients desperately need transplants. DCD organs tend to show delayed graft function at the outset, but if the patient/organ makes it through that, the outcomes tend to be the same as outcomes with living donor kidneys.
Key Specifications and Characteristics to Emphasize for this Niche	Kidney function needs to be maintained along with eliminating the need for immunosuppressive therapy. This has proven quite daunting.

[5] Dr. David Sachs (MGH), 617-726-4065 in a phone conversation with Maura Warner, August 22, 2011.

How long will end-users expect a technology like this to be used before it has to be replaced? If consumables are involved, how often are they purchased and in what lot sizes?	Living donor kidneys usually last 10 years or so. If the technology could deter graft rejection for the life of the kidney (or longer), that would be desirable.
Price and Pricing Factors for this Niche—Specifically what is a price you would expect to pay for such a technology?	Price is a factor in the transplant area. You look at the patient's quality of life and also the cost of dialysis vs. transplant along with likelihood of success. If you can improve outcomes, you can positively impact the cost scenario, especially if you are reducing or eliminating a lifetime of immunosuppressive therapy. Dr. Sachs could not give a specific price.
Key Competitors	Competitors now include living donor transplants and dialysis and to some degree the DCD organ transplants.
How would you commercialize a technology like this one?	Need convincing data first and foremost. Then you run some human trials. I need to see data. Animal data is ok and probably 30 days is all you need to demonstrate efficacy. Need to be careful about what controls your using. Is there a full mismatch? Is there another functioning kidney? Was any drug therapy administered? How much better do the treated kidneys/dogs do?
Potential Roadblocks to Commercialization	The major roadblocks are technical ones; the minor one is economic. First, you have to demonstrate that the technology works without disrupting kidney function and/or causing immune reaction. It needs to be economically viable as well.
Additional Insights	I asked Dr. Sachs about his chimerism program. They have another study in process; need to tweak the protocol a bit before they get going.

Dr. Sachs is a leader in the area of immune tolerance and organ transplant rejection. Dr. Sachs is at MGH as Director of the Transplantation Biology Research Center and as a Professor of Surgery and Immunology at Harvard Medical School. Dr. Sachs has made numerous seminal discoveries in the field of transplantation and has published over 650 articles in scientific journals. He has worked consistently at the interface between basic research and clinical applications. He is committed to developing better therapies for transplant patients, including the induction of tolerance to avoid the need for immunosuppressive drugs and the development of new sources of organs from animals to alleviate the severe shortage. He is the editor of several immunology journals, including Transplantation and Xenotransplantation. He has received many honors and prizes for his work, including the Public Health Service Meritorious Service Award in 1984, the Jean Borel Award in Transplantation in 1998 and the Roche/AST Distinguished Achievement Award in 2005. He was elected to the Institute of Medicine of the National Academy of Sciences in 1996.[6]

Dr. Sachs found the technology interesting and the approach different and compelling. He said it sounds like you're creating some kind of "blood-brain barrier" in the kidney vasculature. On its

[6] http://www.mghtbrc.org/sachs.html, (accessed August 22, 2011).

surface, it sounds like an exciting technology. However, there are a couple of significant hurdles: 1) how do you coat/treat all the lumen in the kidney?; there is such a vast intricate network of blood vessels; 2) secondly, would in effect coating the vasculature impede function? The membrane is integral to the proper functioning of the kidney and disruption of that membrane could be quite problematic. He expressed questions about how the technology could work and kidney function be maintained simultaneously. Secondly, he thought stronger controls would be required to really demonstrate proof of concept. Ideally you would test the 'worst case scenario' – mismatched HLA types, no immunosuppressive therapy, and donor kidney. Also he thought some means of quantification of the polymer barrier in terms of extent of coverage would need to be figured out.

Overall, Dr. Sachs was encouraging and indicated a positive impression of the technology and, like most who know this area well, has more questions about how it would work. This reflects the stage of the technology rather than the soundness of the concept.

We have also contacted the following end-users to gauge their views on the technology and the marketplace. In some arenas, the population of end-users is such that these end-users are also the experts. In this case, they were asked to comment from both perspectives in order to gain the necessary information.

End-User on Competitive Opening	
Name	David Perkins, MD[7]
Title	Director, Transplantation Research Professor Division of Nephrology-Hypertension
Organization	University of California, San Diego
Phone	858-534-9664
E-mail	davperkins@ucsd.edu
Importance of Need(s) being Addressed	The kidney organ shortage is easing somewhat as NHB (non-heart-beating) donor organs are being used more often now. They are used with patient consent, more for the highly-sensitized, hard to match patients or perhaps older patients. The problem with NHB donor organs is time delay to harvest; and you can assume there has been a period of time with minimal perfusion prior to that as well. So a better alternative is certainly needed.
Key Specifications and Characteristics to Emphasize for this Niche	Allowing for access to DCD (donation after cardiac death) organs would be a good thing if the outcomes can be improved. However, organ rejection usually doesn't occur during the first week; it's generally in 7-14 days. There is late graft failure as well. So a key question with this technology would be is if the effect is long-lasting enough.
How long will end-users expect a technology like this to be used before it has to be replaced? If	As this technology won't extend the life of the donor kidney, the average transplanted kidney lasts 10-15 years. 90% of grafts survive a year or more.

[7] Dr. David Perkins (Director, Transplantation Research, UCSD), 858-534-9664 in a phone conversation with Marua Warner August 12, 2011.

consumables are involved, how often are they purchased and in what lot sizes?	
Price and Pricing Factors for this Niche — Specifically what is a price you would expect to pay for such a technology?	"Tough question". Pricing in this area is really a moving target, especially with Obamacare. If the pricing zeroed out the cost of lengthy dialysis plus the cost of immunosuppressive therapy, that would be quite beneficial. Not sure that down the road if an increase in the overall cost would be well-received.
Key Competitors	Not aware of any competitors. Many trials going on with immunosuppressive drugs; mainly incremental improvements however. Artificial kidneys have replicated the tubules, but not the organ.
How would you commercialize a technology like this one?	First step, you would need animal data.
Potential Roadblocks to Commercialization	How long the technology lasts and demonstration of the cost-benefit relationship.

Dr. Perkins is skeptical. Dr. Perkins is a clinical attending physician in the Renal Transplant Program. He also serves on the Kidney and Pancreas Selection Committee, The Kidney and Pancreas Q & A Committee and the Lung Transplant Selection Committee.[8]

Dr. Perkins finds the promise of the technology compelling, but is questioning whether it would actually work. There are major technical hurdles to overcome in having the treated kidney work effectively. He indicated there is really nothing promising on the horizon for improving the kidney transplant situation. There is a sense that expectations were dashed relative to artificial organs and novel technologies in kidney transplant; perhaps this adds to the questioning relative to Breonics' technology.

End-User on Competitive Opening	
Name	Laurence A. Turka, MD[9]
Title	Physician Lecturer The Transplant Institute
Organization	Beth Israel Deaconess Medical Center Harvard Medical School
Phone	617-735-2899
E-mail	lturka@bidmc.harvard.edu
Importance of Need(s) being Addressed	The need is critical – the shortage of kidneys is well-documented. DCD organs do get used now and sometimes they are acceptable, though the question of how long has organ been non-heart-beating do factor in. Immunosuppressive drugs are always

[8] http://nephrology.ucsd.edu/faculty/profiles/Perkins.shtml, (accessed August 10, 2011).
[9] Dr. Laurence Turka (Physician-Lecturer, BIDMC), 617-735-2899 in a phone conversation with Maura Warner, August 12, 2011.

	used and do have some serious systemic side effects. They also are imperfect and do not always work.
Key Specifications and Characteristics to Emphasize for this Niche	
How long will end-users expect a technology like this to be used before it has to be replaced? If consumables are involved, how often are they purchased and in what lot sizes?	A successfully-transplanted kidney that is not rejected can last 10-12 years or longer. For the kidney, each one would need to be treated individually.
Price and Pricing Factors for this Niche — Specifically what is a price you would expect to pay for such a technology?	There is cost pressure in this area. Though if you could counter the increased cost of the technology with a reduced usage of drugs for example, you might have a convincing case.
Key Competitors	Tons of new immunosuppressive drugs are being developed, but Dr. Turka is not aware of any technologies like Breonics'. Some localized immunosuppression has been tried, but the problem is really a systemic one due to vasculature.
How would you commercialize a technology like this one?	You would need to demonstrate the technology works.
Potential Roadblocks to Commercialization	For this, the main roadblock is going to be demonstrating that the rejection rate without use of immunosuppressive drugs is lower. Challenge is in designing an ethical trial.

Dr. Turka thinks the idea seems far-fetched. How would you get enough contacting with all of the blood flowing? Tissues and organs are very different. Another roadblock is damping down the potential systemic effect by doing something locally in the kidney.

Dr. Turka has dual appointments in the Departments of Surgery and Medicine as Co-Scientific Director in BIDMC's Transplant Institute and as Co-Director of the Division of Transplant Immunology in the Department of Medicine. He is also a visiting professor at Harvard Medical School. Dr. Turka is involved in the Immune Tolerance Network and his research is focused on transplantation immunology.[10]

Dr. Turka is also skeptical of the technology until he sees more data. He thought the idea seemed far-fetched and unlikely to work, citing the intimate relationship between the kidney and the systemic immune system.

[10] http://www.immunetolerance.org/professionals/staff/laurence-turka-md, (accessed August 12, 2011).

End-User on Competitive Opening	
Name	Eric A. Elster, MD, FACS[11]
Title	Deputy Department Head for Regenerative Medicine
Organization	Naval Medical Research Center, Silver Spring, MD
Phone	301-319-7201
E-mail	Eric.Elster@med.navy.mil
Importance of Need(s) being Addressed	It is well-known that treatment of ESRD is inadequate and none of the options are optimal. The rate of kidney rejection is too high; there is a shortage of good organs for transplant and dialysis certainly is not great, even on a short-term basis. An enormous amount of money is spent on ESRD and new ideas are really needed.
Key Specifications and Characteristics to Emphasize for this Niche	Kidney function is a delicate balance and manipulating it can have a cascading effect. The same is true with immune response.
How long will end-users expect a technology like this to be used before it has to be replaced? If consumables are involved, how often are they purchased and in what lot sizes?	It sounds like the technology will be used for a month or so as pretreatment. The polymer barrier solution would need to be new for each new organ and the perfusion equipment would be a capital investment that would be used for several years.
Price and Pricing Factors for this Niche — Specifically what is a price you would expect to pay for such a technology?	Key inputs into the pricing equation: 1) Dialysis cost = $100K per year 2) Transplant cost = $100K for the transplant itself; $20-30K/year maintenance costs; there are also organ acquisition costs. If you can price it so you are still within these cost parameters, perhaps even a little bit higher, the economics make sense. Campath 1H and Thymoglobulin are used as induction agents for renal transplant.
Key Competitors	The market today really just consists of transplant as it exists currently and dialysis. There are some warm perfusion systems in trials, but none marketed yet. Dr. Elster's group is set to test a warm perfusion system next month. Nothing that addresses the shortcomings of kidney transplant in the same way as the NBLVF4 technology.
How would you commercialize a technology like this one?	Since it is such a novel approach, you need really convincing animal data. Some small companies skimp in this area and think that just getting some data is good enough. It's usually well worth the effort to get practitioners' input on even animal studies. It sounds novel enough that if warrants further study.
Potential Roadblocks to Commercialization	Main roadblocks are technical ones that center on having the intended effect on immune response and avoiding unintended effects. Not having the correct modulation of immune response or failing to demonstrate efficacy in either animal or human studies.

[11] Dr. Eric Elster (Deputy Director, Regenerative Medicine, NMRC), 301-319-7201in a phone conversation with Maura Warner, August 24, 2011.

Additional Insights	Dr. Elster thought the technology was "a big leap, but that's OK" and "could be good, could be bad".

By bad, Dr. Elster means it could be an oversimplification of how the kidney functions. It's very complicated; how do you know which immune cells should be blocked and which shouldn't be? For instance, blocking T cells is beneficial and reduces the immune response, but some of the inflammatory proteins are needed. What if an infection occurs and there is no immune response? You end up with a bad case of pyelonephritis.

Dr. Eric Elster is a Transplant Surgeon and Associate Professor of Surgery at the Navy Medical Research Center.[12] Dr. Elster was encouraged by this new unique technology, but cautioned that any new technology gives rise to a lot of questions. Design of key canine studies will be critical in moving this forward and advised that giving careful thought to the study design would be time/money well spent.

Overall, the end users are skeptical, which is somewhat to be expected, given the disruptive nature of the technology and the fact that large amounts of data have not yet been generated as the technology is early-stage. However, the end users could also be described as intrigued and supportive of further exploration of the technology.

In this case, the benefit of these discussions is to determine what the questions will be and what the biases are so future discussions and presentations of the technology can be honed. From the discussions with the four expert/end-users, some themes emerge:

1) Definitely a novel approach. This comes with it a large proof of concept burden.
2) It is difficult to explain the technology, where it fits into the transplant technique and what the intended benefit is. Being crystal clear on this is important to get people to see appreciate the potential benefit in a short period of time.

   For instance, Dr. Turka was hung up on the feasibility of treating systemic response via localized technique. I believe a more detailed discussion of the pretreatment method and how it would stave off systemic immune response could have colored his opinion more favorably earlier in the conversation. For practical purposes, whether someone is reviewing a grant application or just reading a paper, they want to quickly assume they understand something and may not want to dedicate the time to fully understand the concept, especially if it takes effort.

3) Again, large burden of proof. Main concern is around "will this impede kidney function"? Other questions were more along the lines of engineering and 'how will this work', which are likely more readily addressed.
4) Design of canine trials. Getting this right will be critical. Dr. Sachs emphasized use of proper and thorough controls. Dr. Elster emphasized practitioner input.

[12] http://usfalumni.org/s/861/internal.aspx?sid=861&gid=1&pgid=1956&cid=3801&ecid=3801&ciid=9766&crid=0, (accessed August 22, 2011).

Given our own research and the views of the above expert and end-users, we anticipate the following parameters will be significant when this technology is evaluated by end-users. It is critical to understand engineering requirements for the primary application. If the technology does not meet and/or exceed current requirements for **performance**, it will be difficult to commercialize.

Our Current View of End-User Requirements/Specifications			
Engineering Requirement	***Units***	***Value Desired by User***	***Why Desired***
Useful life of transplanted organ	years	10-12+	Want to at least meet the current life of living donor organs.
Sufficient contact with blood	%	High enough level to deter immune response	Sufficient lumen coverage and contact with blood in the vasculature is important to deter a systemic immune response.
Blockage of immune response during induction period		Below immune response levels	Measurement of lymphocyte subsets, mitogen-induced T-cell proliferative responses, neutrophil phagocytic capacity and reactive oxygen species (ROS) generation.[13]
Blood pressure, anemia		Normal levels	Increased blood pressure and also anemia are signs of organ rejection.
Deposition of polymer on lumen	%	Coverage	Is equipment able to treat vasculature surface in a reproducible manner.

With the NBLVF4 technology, performance is based on two things – 1) that the polymer is deposited correctly and 2) that is blocks the immune response for the desired period.

Similarly, technology characteristics can make a substantial difference for **ease-of-use**, and therefore affect how quickly a technology will be adopted by end-users.

Characteristics	
Technology Characteristic	***Ease of Use Implications as Applied to This Technology***
Maturity — measures how close the technology should be to commercial introduction.	Must have convincing proof of concept data. This type of technology will have to be fully mature and validated in a clinical study with a sufficient number of patients before it will be adopted by transplant surgeons.
Complexity — measures the number of "layers" of technology that must be integrated into this technology.	This technology needs to be used with the EMS system, so it is relatively complex.

[13] Paul Hutchinson et al. "Laboratory assessment of immune function in renal transplant patients", Nephrology Dialysis Transplantation, Vol. 18, Issue 5, 2003.

Scalability — measures how easy it must be to duplicate the technology to meet market demand. Highly scalable technologies are easily replicated (i.e., software or plastic cups).	The technology is scalable as it is utilized on a single-organ basis to meet the demand. As demand grows, the number of EMS units would be increased.
Packaging — measures how much special infrastructure must be provided with the technology in order for the end-user to capture its utility.	This technology will require a fair amount of extra "infrastructure" for adoption, both in terms of equipment and process.

Because this is a new and unique technology, it will not be a direct replacement or enhancement of something else. As such, new infrastructure will be required for the technology to be implemented and utilized effectively. It is expected that the technology is scalable, but training will be critical. The technology will likely be used in conjunction with the EMS system, which is new capital equipment and will require new costing systems, along with maintenance and training.

Users' abilities to buy the technologies they want are constrained by relevant federal, state, and local government regulations and by relevant standards and certification requirements. These requirements indicate test and evaluation procedures that can speed market acceptance if incorporated into concurrent engineering.

Examples of Regulations, Standards, and Certifications

Identifier and Promulgator	***Description***	***Comments***
United Network for Organ Sharing (UNOS)	UNOS is the private, non-profit organization that manages the nation's organ transplant system under contract with the federal government. UNOS manages the US national transplant wait list and oversee organ allocation policies.	Any company commercializing new technology in the organ transplant area should have interaction with UNOS.
FDA approval process	IDE (Investigational Device Exemption) is required to run clinical trials of NBLVF4	It will be critical to understand which pathway this technology will be in and how that is dependent upon approval of the EMS system.
Code of Federal Regulations (CFR) 42 CFR 482.104 – Condition of participation: Additional requirements for kidney transplant centers.	The final rule sets forth new conditions of participation (CoPs) with data submission, clinical experience, and outcome and process requirements. The requirements focus on an organ transplant center's ability to perform successful transplants and deliver quality patient care as evidenced by outcomes and sound policies and procedures. The CoPs include requirements to protect the health and safety of both transplant recipients and living donors.[14]	This technology is expected to be used at major transplant centers.

[14] https://www.cms.gov/cfcsandcops/11_transplantcenter.asp (accessed August 31, 2011).

The technology will be folded into the current transplant center procedures and equipment. It is key to understand these as it will be critical for adoption and success.

Finally, **price** is always a concern for new technology.

Price
Campath is $1400 per induction and Thymoglobulin is $7000 per induction (3 doses).[15] We suggest these may be benchmarks. Dr. Elster advised: that the key inputs into the pricing equation: 1) Dialysis cost = $100K per year 2) Transplant cost = $100K for the transplant itself; $20-30K/year maintenance costs; there are also organ acquisition costs. If you can price it so you are still within these cost parameters, perhaps even a little bit higher, the economics make sense. Campath 1H and Thymoglobulin are used as induction agents for renal transplant. Dr. Turka suggests the net price of the therapy has to remain at least constant so there needs to be savings elsewhere to cover your costs.

The NBLVF4 technology price differential would be mainly due to the kidney reparation/nanobarrier coating costs and the use of the EMS system.

Comparative effectiveness research will have an impact in the kidney transplant area. The current state of renal dialysis and transplant outcomes is coming under increased scrutiny.[16] In a report issued June 30 [2009], the Institute of Medicine listed its top 100 priorities for comparative effectiveness research. Dialysis and kidney transplantation were high on the list.[17] Current cost for dialysis is $20 billion per year in the US (6% of total Medicare budget).[18]

There is overall price pressure in the kidney transplant area, but the public health need is significant. Therefore, a general guideline would be that pricing that fits within the existing budget but improves mortality and morbidity would be accepted.

4 Competition

There is a range of competitive technologies to consider when comparing this technology to those on the market now, and those that may be available in a five-year window from the date of anticipated market entry. The products, services, and technology below demonstrate the range of potential substitutes from which customers will be able to choose.

[15] Drug Topics, Voice of the Pharmacist, http://drugtopics.modernmedicine.com/drugtopics/Modern+Medicine+Now/Transplant-induction-agent-leads-in-clinical-trial/ArticleStandard/Article/detail/647898, December 11, 2009. (accessed August 24, 2011).
[16] "How Hemodialysis is used to treat kidney failure", USA Today, 8/23/09.
[17] "How Hemodialysis is used to treat kidney failure", USA Today, 8/23/09.
[18] "In Dialysis, Life-Saving Care at Great Risk and Cost", ProPublica, Robin Fields, 11/9/10.

We conducted a search for relevant products, patents and projects using Google, using the terms renal allograft technology, kidney transplant, immune tolerance and rejection. Boolean operators "and" and "or" were used in combination with key words for broad to narrow searches.

Examples of Relevant Products/Services Identified			
Product Name	***Manufacturer***	***Relevance***	***Web site/Phone***
Renal dialysis	Fresenius, Davita	Dialysis is the only option other than transplant for those with ESRD. With the kidney shortage, patients stay on dialysis while waiting for a donor organ.	http://www.fresenius.com
Transplant – living donor; HBD	Transplant centers	HBD donors are the vast majority of kidney donors at present and offer the best outcome for the ESRD patient.	Organ Procurement and Transplantation Network 804-782-4730 http://optn.transplant.hrsa.gov/members/directory.asp National Kidney Registry 631-517-9546 http://www.kidneyregistry.org
Tranplant - DCD	Transplant centers	DCD donor organs are utilized now, but are associated with poorer outcomes due to immune response.	Organ Procurement and Transplantation Network 804-782-4730 http://optn.transplant.hrsa.gov/members/directory.asp National Kidney Registry 631-517-9546 http://www.kidneyregistry.org
Immunosuppressive drug therapy	Abbott, Argos, Amgen, GSK, Novartis	NBLVF4 would be expected to displace a certain percentage of immunosuppressive drug therapies	http://www.abbott.com
Perfusion systems	Smart Perfusion	VasoWaveTM technology for more effective organ preservation; potential to expand pool of potential donor kidneys	http://wwwsmart.perfusion.com 704-241-5029

There are no commercialized technologies that are similar to Breonics'. The competition at present consists of dialysis centers, living donor & some DCD donor organs transplanted in standard fashion with immunosuppressive therapy. Perfusion systems represent the only technological competitive option and are really adjunct to the NBLVF4 technology. The expectation is that perfusion systems will provide incremental benefit and may improve outcomes somewhat, but the kidney shortage will not really be addressed by them.

We search the following data sets: *INPADOC*, which contains patent family documents from 71 world patent signatories and legal status information from 42 patent offices; *WIPO PCT Publications*, which contains abstracts, full document images, and full text from over a hundred member countries of the Patent Cooperation Treaty; *European Patents and Applications* from the European Patent Office; and *US Patents and Applications* from the US Patent and Trademark Office. Searching these data sets simultaneously often does lead to multiple counts of the same

patent, as both the application and patent may be retrieved or the item can show up in multiple databases. This procedure highlights applicants who file, pursue the patent, and protect it in multiple jurisdictions and the presumption is a patent protected in multiple jurisdictions is more important to its owners than one which is not.

Given this procedure, the following assignees appear to be among the major patent holders of technology found using the following search string "renal allograft". We identify these assignees by looking at the ultimate company (parent) of the assignee as identified with the aid of Thomson Innovation. Overall, the string produced 14 hits. Other search strings used:

- renal allograft – 35 hits.
- transplant immune tolerance – 33 hits.
- transplant AND "immune tolerance" – 14 hits.
- "kidney transplant" AND rejection – 13 hits.

The following patents and patent applications indicate kinds and range of technology that show up in the patent literature. We emphasize that we look at patents from the standpoint of market competition. We have no opinion on the patentability of your technology. Please consult with qualified legal counsel for opinions on Breonics' freedom-to-operate and extent of Intellectual Property protection. Material in quotes is from the patent abstract unless otherwise noted.

Examples of Relevant Patents and Patent Applications Identified

Patent or Patent Application Number	***Patent Title***	***Date***	***Relevance***	***Assignee***
WO2011054100	Stem Cell Extracts and Uses Thereof for Immune Modulation	11/5/2009	Use of stem cells for modulating immune response in a variety of transplants.	University of Ottawa
US2010267042	Antigen-Presenting Cell Populations and their Use as Reagents for Enhancing or Reducing Immune Tolerance	4/12/2022	Reagents for detection of IDO, useful for tumor detection and assessment of relative risk of organ rejection.	Medical College of Georgia
WO2010085509	Compositions and Methods for Induction of Antigen-Specific Tolerance	1/20/2009	The present invention utilizes carrier particles to present antigen peptides and proteins to the immune system in such a way as to induce antigen specific tolerance. The carrier particle is designed in order to trigger an immune tolerance effect. The invention is useful for treatment of immune related disorders such as autoimmune disease, transplant rejection and allergic reactions.	Northwestern University; Myelin Repair Foundation
US2007009517	Method of Inducing Immune Tolerance	8/25/2003	The methods comprise administering multiple doses of a therapeutically effective amount of a CD40 antagonist alone or in combination	PanGenetics

			with a CD86 antagonist, wherein the first dose of the antagonist is given before or at the time of transplantation; and administering multiple doses of a therapeutically effective amount of an immunosuppressive drug, wherein the first dose of the immunosuppressive drug is given at least several days after transplantation.	
WO03141884	Building Identification and Application for Heterogenic Interbone Marrow Filling Stem Cell Transplantation Chimeric Model	7/29/2003	This invention relates to the method of establishing long term heterogenic skin transplant surviving model with heterogenic marrow mesenchyme pleuripotent stem cell to induce stable chimera and for immune tolerance formation. The present invention also relates to the method of inducing stable chimera in heterogenic tissue and organ transplant to form immune tolerance and further making the heterogenic transplant survive for long term.	Chinese Academy of Medical Sciences
US6060049	Surrogate Tolerogenesis for the Development of Tolerance to Xenografts	5/9/2000	Xenogenic organ graft where certain lympho-hematopoetic donor cells are introduced into the recipient prior to transplant.	Ximerex
UA20920	Method for Preventing Ischemic Damage of Renal Allograft in Donor's Body	9/6/2006	Intravenous dropwise infusion of medicinal substance, namely quercetin, to the NHB donor organ prior to transplant.	Zohrabian Ruben Ovakimovych
UA62838	Method for Renal Allografting Accompanied with Graft Perfusion with Blood of Recipient	7/2/2003	This method for the renal allograft accompanied with the graft perfusion with the recipient's blood is performed by intraoperative perfusion of the donor's kidney with the recipient's blood.	Buovyna State Medical Academy
WO2006121445	Therapy of Kidney Disease and Multiorgan Failure with Mesenchymal Stem Cells and Mesenchymal Stem Cell Conditioned Media	5/10/2005	Methods and a composition for the treatment of organ dysfunction, acute renal failure, multi-organ failure, early dysfunction of kidney transplant, graft rejection, chronic renal failure, wounds, and inflammatory disorders including media conditioned by mesenchymal stem cells are provided.	University of Utah; USA Department of Veterans Administratio n
US2003225045	Use of Vitamin D Compounds to Prevent Transplant Rejection	3/20/2001	A method of stabilizing kidney function in transplant patients is disclosed. In one embodiment, the method comprises the steps of kidney transplant patient, wherein the transplant patient is undergoing	Wisconsin Alumni Research Foundation

			immunosuppressive therapy, with a sufficient amount of vitamin D compound whereby the kidney function stabilizes.	

Patents and patent applications aimed at addressing the challenge with kidney transplant include incremental advances in immunosuppressive therapies, stem cell therapies, bone marrow treatments and biomarkers of organ rejection. Key areas which appear relevant to the Breonics technology include stem cell therapies, immune tolerance induction and a couple of preventative measures which could deter rejection.

There were no patents or patent applications noted in the searches outlined above that had a similar approach to Breonics NBLVF4 technology. Other approaches being developed for the kidney transplant rejection challenge could be considered as possible "combination" technologies.

Others are researching and developing technology that may become a threat within the next five years.

Examples of Relevant R&D/ Clinical Projects Identified			
Project Title	***Performing Institution***	***Performance Period***	***Relevance***
Artificial kidney	UCSF	2005-present	If it works, the artificial kidney could potentially eliminate the need for dialysis and ease or eliminate the kidney shortage.[19]
Chimerism	MGH/Dr. David Sachs	2007-present	Chimerism[20]
Neo-Kidney Augment (NKA)	Tengion	2006-present	Tengion Neo-Kidney Augment is being developed with the goal of using a patient's own cells to augment or replace renal function for patients with chronic renal failure who are dependent on dialysis treatment and for patients who receive medical treatment for chronic anemia.[21]
Warm perfusion system	TransMedics	2004-present	Not directly competing with NBLVF4, but has a similar system to the EMS. TransMedics has developed the first commercial, portable warm blood perfusion system that allows for a new type of organ transplant, called a *living organ transplant*. This technology, called an Organ Care System, or OCS, is designed to maintain organs in a warm, functioning state outside of the body during transport from organ donor to recipient. The OCS could potentially increase organ availability and improve outcomes for the growing population of patients with end stage organ failure in need of a transplant, bridging

[19] http://www.ucsf.edu/news/2010/09/4450/ucsf-unveils-model-implantable-artificial-kidney-replace-dialysis (accessed August 27, 2011).
[20] http://protomag.com/assets/organ-rejection-chimerism?page=2 (accessed August 27, 2011).
[21] http://www.tengion.com/pipeline/kidneys.cfm (accessed August 27, 2011).

			the widening gap between the number of organs available and the number of recipients awaiting transplants.[22]

There are a number of approaches to immune tolerance induction in renal allografts. Regenerative medicine efforts are also underway, but likely not going to be commercialized in the next five years. Some are incremental improvements, others are more revolutionary, but all are worth noting.[23]

Competitive Landscape
Currently, the competitive landscape consists of organ pretreatment solutions, immunosuppressive drugs and warm perfusion systems, all of which have been used for quite some time. Some artificial organ technologies are in development, but are far off from commercialization.

The competitive landscape includes a variety of technologies and therapies, though none appear to address the overall market need in the same manner as Breonics' NBLVF4. The landscape includes incremental improvements in immunosuppressive drugs, improved dialysis systems (such as home/portable dialysis units), those aiming to improve organ preservation (warm perfusion systems and organ preservation solutions) and artificial/stem cell based organs.

Typically, the kidney can withstand 24-48 hours of cold storage time. Warm perfusion systems and organ preservation solutions have been utilized and improved over the past twenty years and are used to improve upon cold storage/perfusion during the first 24-48 hours and perhaps extend that time. Even with warm perfusion, however, the challenges of kidney shortage, graft rejection and immunosuppressive therapy remain.[24]

Dialysis has become a large money machine for nephrologists and entrepreneurs.[25] Dialysis became big business, with free-standing centers established in hundreds of cities by corporations, not hospitals. The number of U.S. centers has increased 4% every year, according to a June report by the Medicare Payment Advisory Commission. In 1998, there were 3,394; in 2008, 4,957. About 60% are owned by Denver-based DaVita, a Fortune 500 company, and Fresenius Medical Care North America, a Waltham, MA.-based subsidiary of a German company that operates centers in 28 countries and also sells dialysis machines and other supplies.[26]

And about 70% of Medicare dollars spent on dialysis and injectable drugs goes to DaVita, which runs more than 1,500 U.S. dialysis centers, and Fresenius, which runs more than 1,700. In the first quarter of this year, DaVita's revenues were $1.45 billion, up more than 8% from the first quarter of 2008. Fresenius' revenues from dialysis in North America were $1.57 billion, up 5% over the first quarter of 2008.[27]

[22] http://www.transmedics.com/wt/page/corporate (accessed August 27, 2011).
[23] "How Hemodialysis is used to treat kidney failure", USA Today, 8/23/09.
[24] F. Gage et al, "Room Temperature Pulsatile Perfusion of Renal Allografts With Lifor Compared With Hypothermic Machine Pump Solution", *Transplantation Proceedings*, 41, 3571–3574 (2009).
[25] "How Hemodialysis is used to treat kidney failure", USA Today, 8/23/09.
[26] "How Hemodialysis is used to treat kidney failure", USA Today, 8/23/09.
[27] "How Hemodialysis is used to treat kidney failure", USA Today, 8/23/09.

Since 1983, Medicare has paid dialysis providers, whether for-profit centers, non-profit centers or hospitals, a "composite rate" per treatment, which averaged about $155 in 2007. And because Medicare pays the same amount no matter how long the treatment, there's no financial incentive to dialyze patients longer than a few hours at a time. [28]

On top of the composite rate, Medicare pays extra for newer, expensive injectable drugs — namely erythropoietin, or EPO, a hormone that stimulates red blood cell production, and vitamin D, which plays a role in bone health — and lab tests. These extras added an average of $75, or 50%, to the cost of each treatment in 2007. Countries with national health systems don't use the injectables nearly as much. They use less EPO and prescribe oral vitamin D pills that cost about one-quarter of the injectable versions but, their doctors say, are equally effective.[29]

5 Market

While market sizes are hard to estimate, the following provides an example of how to figure out the total addressable market for this technology. While we seek to be as accurate as feasible in the estimate below, it is budget constrained and thus preliminary. We estimate the total market size, at saturation, for the world, and for all competitors, to be approximately:

Market Niche Size

Market Size in Dollars	***Growth Rate***	***Base Year***	***Detailed Basis for Estimate***
$910 million	5%	2010	Assuming the technology will ultimately be utilized with all the DCD organs now transplanted and allow for doubling of the donor organ pool. Also assuming it will be used in target transplant centers and selling price will include equipment price ($40K), consumables ($10K per organ) and annual service revenue of $250K per unit. The total market equals $303 million in the US. Assume the transplant market ex-US will expand and be roughly 2x that of the US.

The market size and growth rate is a function of the number of people in the market and the anticipated rate of buying. As markets transition between emerging, growth, shakeout, mature, and declining, the basis for competition and the number of competitors usually changes, along with the factors influencing adoption of innovation. The number of and growth rate for customers suggests how many units might be sold.[30]

Our Current View on the Phase of the Market

[28] "How Hemodialysis is used to treat kidney failure", USA Today, 8/23/09.
[29] "How Hemodialysis is used to treat kidney failure", USA Today, 8/23/09.
[30] For a detailed discussion of the "innovativeness dimension," see Everett M. Rogers, *Diffusion of Innovations*, 4th ed. (New York: Free Press, 1995). For further readings related to market phases and innovation, see also James Utterback, *Mastering the Dynamics of Innovation* (Boston: Harvard Business School Press, 1996) and Vijay K. Jolly, *Commercializing New Technologies: Getting from Mind to Market* (Boston: Harvard Business School Press, 1997).

Today	***Trend***
Mature	Emerging

The kidney transplant and dialysis market was essentially established in the seventies with the first successful transplant and the Medicare ruling which covered dialysis services. Since that time, the market size has grown by orders of magnitude, but has remained largely unchanged in structure.[31] With dialysis accounting for 6% of the Medicare budget, the spending is significant and political pressures are mounting in favor of reducing this expenditure. This will spur the development and adoption of new technologies and processes and result in changing market dynamics, i.e. moving from a mature segment to an emerging one.[32]

Markets can also be described in terms of the basis for competition (best technological performance; best value or the price/performance tradeoff that best matches the end-users' preferences; lowest cost; or best availability or the ability to get the product quickly). This dimension helps to define the context in which a commercialization strategy must be developed.

Our Current View of the Basis for Competition in the Arena	
Today	***Trend***
Best Value. Incremental improvements based on side effects.[33]	Best value. Improved outcome rates and cost containment are going to be important factors relative to kidney transplant in the future.[34]

In the near future, basis for competition will be cost-related and whether the product or technology has the potential to improve outcomes. More than ever, costs are being quantified and outcomes measured both at the hospital and hospital system levels, along with the payor level. Demonstration of improvement and benefit in these areas will be critical for adoption.[35]

Entry barriers are obstacles that remove customer segments from the market for some period of time. They limit the size of the addressable market in general or the market share that can be captured. These barriers must be overcome or avoided to have a successful market entry. Our work to date suggests the following entry barriers may prevent customer segments from buying Breonics' technology for some period of time.

Generally Applicable Market Entry Barriers	
Name of Barrier	***Description/Why***

[31] "Lifesaving kidney treatment, but only to a point", New York Times, March 12, 2009, (accessed August 17, 2011).
[32] AWAK Technologies web site, "Renal Disease", http://www.awak.com/renal/market.htm, (accessed August 13, 2011).
[33] AWAK Technologies web site, "Renal Disease", http://www.awak.com/renal/market.htm, (accessed August 13, 2011).
[34] AWAK Technologies web site, "Renal Disease", http://www.awak.com/renal/market.htm, (accessed August 13, 2011).
[35] Axelrod, DA et al. "Innovations in the Assessment of Transplant Center Performance: Implications for Quality Improvement", *American Journal of Transplantation* 2009; 9 (Part 2): 959–969 (accessed August 25, 2011).

Requires Costly or Hard to Obtain Platform Supplies to Use	If a kidney can be considered a platform supply item, then this barrier applies. To get clinical evidence that the technology works, it will need to be tested in humans who have given their consent to the test and surgeons who have agreed to do the procedure.[36]
Cost of Product or Service Generally Seen as too High	The current treatment regimen is firmly ingrained in the reimbursement and cost structure. Trying to disrupt this or change the balance will be challenging and will meet with resistance from existing infrastructure.[37]
Currently Available Technologies Meet Needs	Dialysis centers are big business; about 20% of patients on dialysis die per year.[38]
Basis of Competition in Market Does Not Favor Introduction of New Technology	Medicare pays a huge amount of money for the current setup (dialysis centers, living donors, immunosuppressive drugs).[39]
Regulatory Barriers	The need for proof of efficacy and safety are significant barriers.[40]
No Relevant Standards	It is a new technology as compared to an incremental improvement on an existing technology. This path is always more difficult.[41]
Potential Partners Have Competing Technology or Just Not Interested	In the case of Breonics, potential partners may have competing technologies, specifically in the warm perfusion equipment category. Some of the potential partners may be involved in developing or marketing immunosuppressive therapies.[42]

The major barrier would be introduction of a new complex technology into a system that is currently well-defined and profitable for numerous players. Clearly, the need addressed by the technology exists, but the data will need to be quite convincing to overcome the naysayers.

The barriers for the NBLVF4 technology are significant and having a strong alliance with one of more of the major [aspects] would be valuable. In this case, having strong ties to the transplant surgeon segment could help facilitate adoption. Being aligned with the transplant centers, or at least a handful of key ones, would help as well.

The likelihood of buying at any given point of time is a function of a number of individual decisions. Therefore, there is a distribution, or wave, of possible outcomes, which reflects the probability of individual buying decisions. The market drivers identified below are statistical tendencies that will influence buying by accelerating or retarding it to a greater or lesser extent.

---

[36] Opar, Alisa, "As demand for organs expands, so does treatment technology", *Nature Medicine* **14**, 225 (2008) doi:10.1038/nm0308-225 (accessed August 18, 2011).
[37] "Lifesaving kidney treatment, but only to a point", New York Times, March 12, 2009, (accessed August 17, 2011).
[38] "Lifesaving kidney treatment, but only to a point", New York Times, March 12, 2009, (accessed August 17, 2011).
[39] "Lifesaving kidney treatment, but only to a point", New York Times, March 12, 2009, (accessed August 17, 2011).
[40] AWAK Technologies web site, "Renal Disease", http://www.awak.com/renal/market.htm, (accessed August 13, 2011).
[41] Opar, Alisa, "As demand for organs expands, so does treatment technology", *Nature Medicine* **14**, 225 (2008) doi:10.1038/nm0308-225 (accessed August 18, 2011).
[42] Dr. Eric Elster, in a phone conversation with Maura Warner on August 24, 2011.

Market drivers are forces that strengthen or weaken the importance of end-user needs over time. Practice level drivers are micro-economic; they affect the end-user directly. They influence the selection of substitutable goods and thus affect market share. Arena level drivers affect the organizations and industrial sectors in which the end-users work. They influence the overall demand for goods like this technology and its substitutes. They affect when and how much of the total addressable market is actually going to be in the market and buying.

Drivers Identified as Important		
Level	***Today***	***Trends***
Affecting Market Size	Growing size of wait list and those on dialysis. Increased use of DCDs[43]	General increase in the patient population and increased use of DCDs.[44]
Affecting Market Share	Impact of warm perfusion systems and improved immunosuppressive therapies. Habit /safety net works somewhat (drug therapies, dialysis).[45]	Cost pressure coming from Medicare. Development of artificial kidney technology.[46]

How much focus the cost side of the kidney dialysis and transplant market gets will determine market size and relative market share for new technologies.

The window of opportunity is that time period when a market can be entered successfully. In light of the above discussion, we currently see the window of opportunity for this application roughly in this range.

Likely Window of Opportunity
2015-2020

The window of opportunity for Breonics' technology is estimated at 2015-2020 as response to cost pressure with regard to reimbursement will be staged. At that point, adoption of new technologies will be easier.[47] This time frame is likely to be 2015-2020.

The following venues can be used for additional market intelligence gathering and communication with potential end-users and targets.

Examples of Organizations, Meetings, and Publications to Use for Networking, Promotion, and Competitive Intelligence

[43] AWAK Technologies web site, "Renal Disease", http://www.awak.com/renal/market.htm, (accessed August 13, 2011).
[44] AWAK Technologies web site, "Renal Disease", http://www.awak.com/renal/market.htm, (accessed August 13, 2011).
[45] Opar, Alisa, "As demand for organs expands, so does treatment technology", *Nature Medicine* **14**, 225 (2008) doi:10.1038/nm0308-225 (accessed August 18, 2011).
[46] Opar, Alisa, "As demand for organs expands, so does treatment technology", *Nature Medicine* **14**, 225 (2008) doi:10.1038/nm0308-225 (accessed August 18, 2011).
[47] Park, Alice, "Building a Better Kidney Transplant", Time.com, December 31, 2008 (accessed August 25, 2011).

Organization	***Utility***	***Point of Contact***	***Phone Number & E-mail or URL***
United Network for Organ Sharing	UNOS is the private, non-profit organization that manages the nation's organ transplant system under contract with the federal government. UNOS manages the US national transplant wait list and oversee organ allocation policies.	Walter K. Graham Executive Director President & CEO, UNOS Foundation grahamwk@unos.org	804-782-4800 http://www.unos.org
Immune Tolerance Network	The Immune Tolerance Network is an international clinical research consortium founded by the NIAID and JDRF, whose mission is to accelerate the clinical development of immune tolerance therapies through a unique development model.	Gerald Nepom director@immunetolerance.orgI TN Office of the Director, Administrative Operations Benaroya Research Institute Seattle, WA	206-342-6901 http://www.immunetolerance.org
Association of Organ Procurement Organizations (AOPO)	This organization serves organ donor groups through advocacy, support, and development of activities that will maximize the availability of organs and tissues and improve the donor process.	Elling Eidbo, Interim Executive Director	703-556-4242 x204 http://www.aopo.org
AOPO Annual Meeting	This is the annual meeting, which happens to be in Baltimore, MD on June 15-18, 2010.	Summer Kendall Skendall@aopo.org	703- 556-4242 x 202 http://www.regonline.com/builder/site/Default.aspx?eventid=825143
National Kidney Foundation	This organization is dedicated to preventing kidney disease.	Danielle Green Director of Global Activities danielleg@kidney.org	212-889-2210 http://www.kidney.org
American Society of Transplant Surgeons	The society fosters advances in practice and science of transplantation.	Katrina Crist, MBA Executive Director/CEO katrina.crist@asts.org	703-414-7870 http://www.asts.org/
BMC Nephrology	This is an open access journal publishing peer reviewed articles related to all aspects of kidney disease. We found two of our experts on this cite as authors of relevant articles.	Matthew Cockerill, Managing Director of BioMed Central (BMC) Matthew.cockerill@biomedcentral.com	+44 (0) 20 3192 2000 http://www.biomedcentral.com/bmcnephrol/
Journal of the American Society of Nephrology	This journal serves kidney specialists in the U.S.	Eric G. Neilson, MD, Editor in Chief	352-335-1100 http://jasn.asnjournals.org/
OCT News	This online journal serves the OCT community. It lists companies selling the equipment and those companies may make good commercialization partners. It also discusses other medical uses for OCT which	Eric Swanson, Editor	No phone listing. http://www.octnews.org

	may lead to new markets for this type of technology.		
US Renal Data System (USRDS)	The U.S. Renal Data System (USRDS) collects, analyzes, and distributes information about the use of dialysis and transplantation to treat kidney failure in the United States. The USRDS is funded directly by NIDDK in conjunction with the Centers for Medicare & Medicaid Services.	Lawrence Y.C. Agodoa, MD NIH / NIDDK / DKUHD Democracy 2 6707 Democracy Blvd. Bethesda, MD 20892-5458 agodoal@extra.niddk.nih.gov	301-594-7717
The Renal Association	This is the British association serving nephrologists in the UK.	Professor Peter Mathieson Academic Renal Unit Southmead Hospital Bristol BS10 5NB 0117 959 5438 P.Mathieson@bristol.ac.uk	0870 458 4155 renal@mci-group.com http://www.renal.org

The U.S. Renal Data System (USRDS) collects, analyzes, and distributes information about the use of dialysis and transplantation to treat kidney failure in the United States. The USRDS is funded directly by NIDDK in conjunction with the Centers for Medicare & Medicaid Services. The USRDS publishes an Annual Data Report, which characterizes the total population of people being treated for kidney failure; reports on incidence, prevalence, mortality rates, and trends over time; and develops data on the effects of various treatment modalities. The report also helps identify problems and opportunities for more focused special studies of renal research issues.[48]

There are quite a number of organizations devoted to transplant, international, by country and more local organizations as well. Some of the key ones are listed above.

6 Entry Strategy

Using the data we have collected, we now turn to the question of how to accomplish market entry in order to sell the technology to end-users.

6.1 Objectives

Market entry in the kidney transplant area must be carefully considered. A key relevant factor will be transplant surgeons' confidence that the technology works and understanding of in which scenarios it makes the most sense to utilize.[49]

The initial objective is as mentioned before, to gather convincing animal data. From there, initial human trials can be conducted. As a general plan, the first human trials should likely be done in the "worst case" scenarios in patients with not many other options, for whom a living donor

[48] USRDS (accessed August 27, 2011).
[49] Opar, Alisa, "As demand for organs expands, so does treatment technology", *Nature Medicine* **14**, 225 (2008) doi:10.1038/nm0308-225 (accessed August 18, 2011).

and/or HBD are unlikely. They would not be candidates for DCD either as the usual immune response would yield an unfavorable outcome.[50]

From there, treatment of DCD organs in a more general setting could be done. These are used now, but are in the minority and are not the preferred type of kidney to use. Demonstration of improved outcomes with NBLVF4 in DCD kidneys will be critical, especially during the first few weeks post-transplant when most DCD organs fail.[51]

Once the technology has been shown to be effective, the pool of DCD organs to be used for transplant can be increased with confidence.

6.2 Advantages

Advantages of the technology include the potential for increasing the pool of available donor organs and associated with that, reduction or elimination of immunosuppressive drugs and their associated side effects.

The technology could offer some cost-benefit. Though the pretreatment costs will increase, they payoff will be in the improved mortality & morbidity rates and reduction in the use of dialysis and immunosuppressive drugs.

6.3 Obstacles

Generation of statistically-significant proof of efficacy for the NBLVF4-treated organ may be tricky and take a long time given the treatment population and other factors that determine outcome.

From there, adoption by transplant surgeons may be slow, due to the training required and the need for confidence in the technology.[52]

6.4 Strategy

A well-thought-out clinical plan is a key first step along with early interaction and input from the transplant/transplant surgeon community

For purposes of introducing and explaining the technology, development of a concise graphic showing how it would fit in to the transplant center processes and procedures would be helpful.

7 Target

The target is the organization(s) that will partner with Breonics to commercialize this technology. There are feasible and viable targets. Feasible targets have relevant product lines and appear to have an established presence in the market. In short, they are probably worth checking out to see if they make good candidates for partnering. We seek viable targets that appear to be in good financial health, are established in the market with a relevant product line, can provide capabilities that are relevant for commercializing this technology, and possess good absorptive

[50] AWAK Technologies web site, "Renal Disease", http://www.awak.com/renal/market.htm, (accessed August 13, 2011).

[51] Axelrod, DA et al. "Innovations in the Assessment of Transplant Center Performance: Implications for Quality Improvement", *American Journal of Transplantation* 2009; 9 (Part 2): 959–969 (accessed August 25, 2011).

[52] Park, Alice, "Building a Better Kidney Transplant", Time.com, December 31, 2008 (accessed August 25, 2011).

capacity.[53] Viable targets, unless otherwise noted, are those that still appear to be good candidates after we have spoken to them on the phone to confirm their potential interest in this technology.

We cold called several targets to assess interest in this intellectual asset package. We presented this technology's attractiveness as follows:
The technology called NBLVF4 consists of a bioengineered Nano Barrier membrane comprised of type IV collagen, vitrogen, fibronectin, laminin, entactin, glycosaminoglycan and proteoglycans. The components are polymerized into a three-dimensional transparent membrane. The interaction between the vascular endothelial cells and the recognition domains within the barrier membrane is receptor specific via the laminin and fibronectin portions of the membrane. The membrane is applied to "immunocloak" the luminal surfaces within the vascular space by covering the point of contact between vascular endothelium and the host immune system. The result is a bioengineered apical surface that is non-thrombogenic and non-immunogenic. The technology would potentially eliminate the need for use of immunosuppressive drugs in transplant patients and also significantly increase the pool of potential donated organs. Both of these benefits speak to major challenges with kidney transplants. Immunosuppressive drugs carry with them an array of serious side effects. Due to kidney donation currently being restricted to live donors (mainly because of recipients' systemic immunosuppression), there has been a chronic shortage of donor organs.

NBLVF4 is deposited ex vivo as a 28-day pretreatment to facilitate induction prior to kidney transplant. It is known that DCD organs fall short of living donor/HB donor organs mainly in the short-term rejection. If a technology such as NBLVF4 can facilitate the DCD organs to overcome the initial rejection hurdle, then DCD organs become a much more attractive option for transplant and hence, increase the pool of potential donor's organs significantly.

We begin with examples of at least one viable target and then provide a way to find other likely feasible targets. The following table summarizes key information on an identified viable target.

Target Profile	
Name of Target and Relevant Unit	Genzyme, a unit of Sanofi
Address of Unit	500 Kendall Street, Cambridge, MA 02142
Point of Contact in Target with Position	Ted Ashburn, MD, PhD[54] Sr. Director, Business Development Transplant & Immune-Mediated Diseases
Phone of Point of Contact	617-252-7500
E-Mail of Point of Contact	ted.ashburn@genzyme.com
Current Customer Base	Transplant patients and those with ESRD.
Target's Reason for Interest	Genzyme has stated that they are interested in technologies for improvement of solid organ transplant. They have active programs in

[53] Absorptive capacity measures the degree to which the potential partner's staff has the scientific and engineering education and know-how to help commercialize this technology without having to "come up to speed" on generic technical issues.
[54] Dr. Ted Ashburn (Sr. Director, Business Development, Genzyme), ted.ashburn@genzyme.com, in an email to Maura Warner on August 27, 2011.

	renal therapeutics and in allografts. Breonics' technology fits nicely with the areas in which they are active currently.
Example of Prior Acquisition of Technology from the Outside, if Relevant	2006 acquisition of AnorMED and with it Mozobil, a therapy for stem cell transplant, which was synergistic with their Transplant and Oncology franchises.[55]
Criteria Likely to be Used to Evaluate This Technology	Is it effective in reducing organ rejection rate in a manner that doesn't cause harm.
Likely Information Desired	Animal data that clearly demonstrates the technology's efficacy.
Anticipated Time to Decision from Initial Expression of Serious Interest	Estimate one month.
Name, Title, Phone, and E-mail of Likely Champion for Technology in Target if One can be Suggested	Ted Ashburn, MD, PhD Sr. Director, Business Development 617-252-7500 ted.ashburn@genzyme.com
Likely Preferred Legal Structure for Deal	It depends.
At What Stage in Maturity does the Target Prefer to Obtain Technology	We would need proof of concept data.
Will the Target Participate in Concurrent Engineering or Test and Evaluation	Likely yes.
Who is the Ultimate Decision-Maker(s)	The business unit.

Target Profile	
Name of Target and Relevant Unit	Medtronic (Tengion)
Address of Unit	710 Medtronic Parkway Minneapolis, MN 55432
Point of Contact in Target with Position	Darrel F. Untereker, PhD[56] VP, Research and Technology
Phone of Point of Contact	763-505-4511
E-Mail of Point of Contact	Darrel.untereker@medtronic.com
Current Customer Base	None current, have made investment in regenerative medicine for transplant patients.
Target's Reason for Interest	Medtronic is interested in regenerative medicine and cell therapy, particularly in the kidney area as evidenced by the investment in Tengion.

[55] "AnorMED and Genzyme reach agreement on acquisition", October 18, 2006 Press Release, http://webcache.googleusercontent.com/search?q=cache:6rk9-vT6QbgJ:www.lifesciencesworld.com/news/view/11681+anormed&cd=1&hl=en&ct=clnk&gl=us&source=www.google.com (Accessed August 26, 2011).

[56] Dr. Untereker (VP, Research and Technology, Medtronic), 763-505-4511, in a phone conversation with Maura Warner on August 18, 2011.

Example of Prior Acquisition of Technology from the Outside, if Relevant	Medtronic bought a 17% interest in Tengion in April 2011, including right of first refusal for product rights to Tengion's Neo-Kidney Augment Program.[57]
Criteria Likely to be Used to Evaluate This Technology	
Likely Information Desired	Anything that's been generated so far, but mainly patents, preclinical and clinical data.
Anticipated Time to Decision from Initial Expression of Serious Interest	A few weeks.
Name, Title, Phone, and E-mail of Likely Champion for Technology in Target if One can be Suggested	Darrel Untereker, PhD 763-505-4511 Darrel.untereker@medtronic.com
Likely Preferred Legal Structure for Deal	Various, probably either exclusive license or acquisition.
At What Stage in Maturity does the Target Prefer to Obtain Technology	No real preference, we get involved with early stage technologies, it just depends on how well they fit with our existing businesses.
Will the Target Participate in Concurrent Engineering or Test and Evaluation	Yes.
Who is the Ultimate Decision-Maker(s)	It depends on the cost – business unit leadership committee.

Due to the novelty of Breonics' NBLVF4 technology, it would not be a direct replacement for an existing product or technology. In this case, targets are considered to be firms active in the transplant market with either therapeutics or organ preservation products or devices. Regenerative medicine and tissue engineering companies might also be considered targets or potential partners.

We recommend that you contact the target listed above as soon as possible. Even if you feel that your technology is not mature enough at this time to pursue partnerships, it is important to establish lines of communication and keep them open so as not to lose out on an opportunity for partnering.

We have also contacted the following companies.

Name of Company or Unit	***Address, Web site***	***Reason for Recommending***	***Name, Title, Phone, and E-mail of Point of Contact***	***Number of Times Contacted***

[57] http://www.massdevice.com/news/medtronic-eyes-regenerative-medicine-market-with-tengion-investment (accessed August 29, 2011).

Tengion	3929 Westpoint Blvd Winston Salem, NC http://www.tengion.com	Regenerative medicine company	Mark Stejbach Chief Commercial Officer mark.stejbach@tengion.com 336) 722-5855	2
Abbott Laboratories	100 Abbott Park Road Abbott Park, IL 60064 http://www.abbott.com	Abbott is one of the world's largest healthcare companies. They are active in both the medical device and therapeutics areas.	William King Director of Licensing and Acquisition 847-937-0552 william.king@abbott.com	2
Isotechnika Pharma	Isotechnika Pharma Inc. 5120 - 75th Street Edmonton, AB T6E 6W2 http://www.isotechnika.com	Therapeutics for transplant rejection	Daniel Park Chief Business Officer 780-487-1600 dpark@isotechnika.com	2

As noted in the table above, we have contacted all the companies listed two or more times and were not able to get responses in the time allotted for this report.

Once the next set of canine data is available, initial partnerships discussions would be appropriate. Currently, the potential of the technology is compelling, but there is not enough data for companies to make a decision about partnering.

We recommend developing a preliminary plan for deal-making before meeting with targets. This plan should be openly discussed with the target and a consensus one developed if they are interested in exploring being an investor/partner/licensee after meeting with Breonics.

8 Revenue Projection

Market and revenue projections are always an educated guess based on the relevant information available. Because markets are changing and technology is constantly advancing, it is not possible to make a definitive projection, yet it is possible to make a well-informed estimate. In our projections, all revenues are derived from sales because, as Foresight Chairman of the Board David Speser says, "Nothing happens without a sale."

For TNAs™, Foresight employs two widely used methods to estimate total addressable market and potential revenues: Bottom Up and Top Down. We then calculate a growth rate and market share. If we cannot get the data we need, we try to do a Threshold Analysis. How each of these works is described below. What is important to realize is that our estimates are like tossing darts. An experienced player can make a better toss than a novice, but there is always a margin of error. As our budget and time is limited, what is important is to see how we constructed the estimates and use this information to inform subsequent estimates. These estimates should not be taken as definitive. They are merely preliminary.

Bottom Up Approach: In this method, we arrive at the potential revenues by estimating the number of units that can be sold. The estimated number of units is a product of how many buyers are likely to be in the market and how many units each one will purchase in the time frame of

interest. In difficult cases, where a single unit is combined within a platform or system technology, which in turn, is then integrated into a more complex product or system, we calculate the total number of units by multiplying out to the final application. For instance, a microelectronic pressure sensor might be integrated into a component system, which is then used in the production of a more complex device, which might incorporate multiple component systems into the end product. In this example, it is necessary to multiply the number of units not only by the number of end products sold over a given time frame, but by the number of units used in each component or subsystem of the end product. The resulting number times the price gives us the potential revenues.

Top Down Approach: In this approach, we look at a larger market and slice it down to arrive at the total addressable market for this technology. The slice represents the percentage of the larger market that is the total addressable market for this technology. This percent is determined by using data obtained from market research reports, interviews with the expert, historical data from equivalent technology in the market niche of interest, and other sources. Once the total addressable market is determined, the market share can be calculated as above.

Growth Rates: Once we develop a baseline for the estimated potential revenues, we factor in a growth rate. We look at such growth rates in light of the phase of the market. This is because market phase influences the slope for product sales, which directly affects the sales growth potential for the technology. Other points of consideration that are common across both approaches for revenue projections include the overall competitive advantage of this technology, how much education and awareness building will be required to allow buyers to appreciate these advantages, and the potential for stakeholders and others to create pull-through by advocating this technology.

Market Share: Unless clear market data is available, we typically estimate market share by beginning with the total addressable market in any given year. We then consider the current phase of the market (which influences what percentage of the total addressable market might be buying), barriers to entry (which eliminate potential customer segments), drivers (which skew buying forward or backward in time and affect what the buyer might seek in new technology), and the competitive landscape (which influences how the buyers might be divided up among competing offerings). Once we obtain a suitable estimate for the number of buyers and the number of units that each will purchase, we can easily calculate an estimate for the total number of units that can be sold. Multiplying this number by the unit price (as mentioned in the Price Table above) gives a revenue projection that was built from the bottom up. Dividing the revenues by the market size gives a potential market share, which should be taken as a sales goal or objective for this technology.

Threshold Analysis: Sometimes, despite our best efforts, we cannot find data to support a market size or market share estimate. In that case, we try to do a threshold analysis. In this approach, we see how many sales we feel might occur, based on expert and end-user feedback and other data. If that looks sufficient to justify moving forward with commercialization, we say the threshold is passed.

Again, these are the methodologies we use to compile the revenue projections in our TNA™ assessments. More sophisticated methods may be used for valuations and other services. The projections here should serve as a starting point for making a more detailed and definitive estimate of the potential revenues for this technology.

There is no set standard for calculating market share. In the end, it is important to be conservative because something can always go wrong or influencing factors can be missed.

The text below uses this methodology to compile the revenue projections for this technology. Again, these revenues projections should serve as a starting point for deeper discussions about the issue of revenue. The methodology described above should serve as a guide for future projects.

Potential investors/partners/licensees will want to know how much money they can make with this technology. Given the analysis to date, we can make a very preliminary projection of gross revenues the technology could generate using $1.2 million as the price per unit.

1) Year One: $10.5 million based on 5 units installed
2) Year Two: $22.1 million based on 16 installed
3) Year Three: $58.0 million based on 38 installed
4) Year Four: $97.5 million based on 74 installed
5) Year Five: $127.9 million based on 107 installed

There are several major assumptions which go into the market model for the NBLVF4 technology. These include:

- Price – assuming the "price" will include the cost of the EMS unit ($40,000 per unit; one for each transplant center); consumables ($10,000 per kidney); and service revenue for each installed unit ($250,000 per year).
- Expanded donor organ pool – assume expansion by 2x with the extra being DCD organs
- Target transplant centers – 80 in the US; these are where the first units will be placed and the NBLVF4 technology used first; assume 80/20 rule (targetcenters do majority of the transplants).
- DCD organs used currently – assume 15% of the 18000 kidney transplants done in the US annually are with DCD organs.
- Failure rate for DCD organs – estimated at 10-40%; assume 25%. Assume 6% failure rate for HBD organs.
- Global market – assume global market is 3X the US market.

By taking the total market gross revenues and each year's preliminary revenue estimate, we can derive a preliminary market share goal that begins at 1% and ends at 10% after five years from the date of market entry.

Overall, adoption rate will be slow as it is first dependent on having installed EMS systems at the individual transplant center. Training is the second factor. Depending on how sensitive the technology is to operator variation, this could be a small or large concern. If for instance,

optimal deposition of the polymer barrier is largely dependent on human factors, training will take quite a while and there may be variation in success rates because of it.

Because these costs will be at first added on top of other cost and cost categories in the transplant center, getting reimbursement codes will take time and again also take training to code correctly.

An important point to evaluate when refining the market estimate is that of cost savings and avoidance. Quantification of this will allow for optimization of NBLVF4 and EMS pricing.