The Potential Commercialization of Neuronal Replacement Therapy using Smart Polymers

by

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Abstract

NeuroBioChip Device is a programmable, biocompatible, biodegradable, polymer matrix which allows the growth and programming of donor neurons. It creates a microenvironment conducive for neuronal outgrowth and promises a novel cure for neurological disorders caused by localized sites of brain damage, such as Parkinson's disease, stroke, and spinal injury. This chip is being researched in the MIT laboratories of Drs. Robert Langer and Mriganka Sur. My thesis addresses the challenges and possible strategies in commercializing this technology.

The need for this treatment was evaluated in the context of current therapies available for the treatment of relevant neurological disorders. Extensive field interviews were conducted. Among other factors, the varying clockspeeds between different components of the device, the unsustainable cost structure and the emerging status of complementary technologies suggested that the development of the therapy is best pursued in collaboration with a large biopharmaceutical or medical device firm.

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This final thesis I wish to dedicate to a few very special people
Those who have made the difference in my life and my academic career, nurturing me to be who I am today…

Monimala Dutt, my grandmother who lovingly gave me my name which means "The Perfect One",
Sukumar-Arati Mitra, my maternal grandparents for their endless affection,
Samir-Protima Dutt, my ever-supportive parents,
Abhijit Dutt, my affectionate brother,

Lorainne Rita Lewis, my 8th grade teacher who taught me the courage and will to be different,
Prof. Madhusudhan Ghosal, my undergraduate mentor who encouraged me to aim higher,
Dr. Cary Lai, my Ph. D. mentor who helped me survive a new Country, and
Dr. Matthew Shapiro, a tireless mentor in my professional life.

"....the ability to evaluate the viability of science with respect to business and the commercialization of an idea, is not just about understanding the design phase or coming up with new technologies. But knowing when to deploy them, when to hold off on them, and how to come up with a successful venture that employs that idea."

Ziv Katalan,
Co-director of Executive Master's in Technology Management
Adjunct Associate Professor in the Operations and Information Management Department
Wharton.

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Contents

Chapter 1: Introduction to Neuronal Replacement Therapy

What is a Neurodegenerative Disorder?

The brain and the spinal cord make up the nervous system. Together they not only coordinate the activities of all the organs in the human body, but also contribute to the human element by creating thoughts, emotions and by forming memories. The Brain and Spinal Cord are made up of neurons, glia and astrocytes. The neurons are the fundamental functional component of the brain and the spinal cord. The glia and astrocytes form the structural components by engaging in maintenance and repair of the nervous system. The neurons communicate with each other by means of electrical signals at specific locations called "synapses". The average number of inputs and outputs a neuron receives and sends, lies in the order of 10,000, with some managing up to a million points of contact. There are 10^{12} neurons in the human brain[1]. The fact that each neuron establishes approximately 10^4 connections demonstrates the complexity of the human brain. There is considerable redundancy and plasticity in the complexity of the human brain. It is not one continuous circuit which would be debilitated by the death of a single neuron. The brain can be impaired to a very large extent before functional discrepancies begin to appear. In Parkinson's disease 80% of the brain is lost before functional deficits are observed.

Neurodegenerative disorders cause deterioration and death of neurons in the brain and spinal cord. These disorders negatively impact a person's memory, cognition, and voluntary movements, driving him to the point of becoming unsociable. Examples of neurodegenerative disorders include: Parkinson's disease, Multiple Sclerosis, Alzheimer's disease, Huntington's disease and Macular Degeneration to name only a few. Neurodegenerative disorders do not merely affect the afflicted individual but disrupt entire families,

[1] Freed, Neural Transplantation (complete references are to be found in the bibliography).

emotionally, socially and economically. Therefore, it is extremely important to find cures for such diseases.

Since neurons communicate with each other by means of electrical signals, scientists have been trying to cure neuronal disorders including Parkinson's, Epilepsy and even depression by means of purely electrical implants surgically inserted into patients' brains. Examples of such companies are Cyberonics and Medtronic, which sell electronic implants to treat epilepsy and Parkinson's disease, respectively. In sharp contrast to these electronic devices are brain grafts. The sources of brain grafts are often fetal tissues, but sometimes they are autologous[2], such as chromaffin cells obtained from adrenal medulla of the patient himself. These tissue grafts are implanted at multiple sites in the patient's brain. Sometimes, dissociated embryonic neuronal cells are injected into the brain, close to sites of damage. The technology discussed in my thesis is a hybrid technology which strikes a middle path between the purely electrical implants and the complete brain grafts. The NeuroBioChip Device is a polymer-neuron assembly which is technically and scientifically many steps ahead of either of these technologies. It aims to produce brain grafts by impregnating new neurons on electrically conducting biodegradable matrices. Such brain implants have the potential to revolutionize medical devices just as the pacemakers have revolutionized the treatment of heart disorders early in the last century. My thesis explores the potential challenges in commercializing the NeuroBioChip Device in the following sequence:

1. Chapters 1 and 3 identify the need for Neuronal Replacement Therapy in treating a variety of neurodegenerative disorders by looking at the disorders and the present treatment modalities.
2. The technology will be discussed in detail in Chapter 2.
3. Chapter 4 involves an interview with a neurosurgeon to gauge physician willingness to use the new technology.

[2] An autologous graft is one in which the donor of the tissue and the recipient is the same person. This avoids any kind of adverse immune reaction.

4. Chapter 5 involves interviews of several senior executives from a company which unsuccessfully tried to commercialise cellular therapy.
5. Finally, Chapter 6 draws lessons from the entire thesis and applies them towards the commercialization of NeuroBioChip Devices.

The Need for Neuronal Replacement Therapy

The reasons why neuronal replacement is necessary are as follow:

1. Firstly, not much is known about the molecular pathology of most of the neurodegenerative disorders to enable rational drug therapy.
2. Traditional preventive or corrective drug therapy is not as effective in treating brain and spinal disorders due to the presence of the extremely selective blood-brain-barrier (BBB).

   The nervous system is a delicate organ performing by far the most important task of coordinating all physiological functions such as heart rate, digestion, liver function and so on. It is responsible for our thinking, learning and motor abilities and our personalities. Therefore, almost by natural selection, the nervous system is protected by a semi-permeable membrane which allows extremely few and small molecules to go from the blood into the nervous system. While all other organs draw their nutrition in forms of amino acids, proteins and carbohydrates from the blood, the brain lives primarily on glucose. Therefore, delivering a drug to the brain, past this semi-permeable barrier, is an enormous challenge.
3. Delivering a drug systemically dilutes the dosage of the drug to the brain and causes the drug to have secondary effects on other non-targeted organs.
4. The Central Nervous System is extremely limited in its ability to repair itself.

An advantage of the very restrictive nature of the blood-brain-barrier is that the brain is highly immune-compromised compared to the rest of the body. This means that exogenous tissue can be relatively easily

transplanted into the adult brain without triggering an immune response. However, no matter how small, there is always a possibility for an antigenic reaction and the consequences of such an event are disastrous. However, most often grafts are immature tissue from embryonic or fetal donors lacking in molecules which are responsible for initiating an immune response in host systems.

Methods of Delivery to the Nervous System

Grafts: In the grafting method, stem cells are grown in a dish, allowed to differentiate and then implanted into a specific region of the brain. It should be noted that re-establishment of neuronal circuitry is not always mandatory for the restoration of function. Tissue grafts used in the brain have served a variety of purposes, such as:

1. A source for replenishing a missing or reduced neurotransmitter or hormone
2. A support for brain repair and growth[3]
3. A bridge to restore communication between disrupted networks (as in Spinal Injury)
4. A support for re-myelination[4] (Multiple Sclerosis is caused by demyelination)[5]

The alternate approach researchers have taken in executing neuronal replacement is to inject younger undifferentiated Neural Stem Cells into the Ventricle[6,7] and allow the cells to migrate. Reportedly, the Neural Stem Cells injected into the ventricle are transported by the cerebrospinal fluid directly to damaged regions of the brain[8,9]. While both the methods have achieved encouraging results they are definitely handicapped by the poor survival of exogenous neurons.

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[3] Raisman, G. (1997)
[4] a layer of protective insulation present on every neuron
[5] Duncan, I. D., et al. (1997)
[6] Qu.T., et al. (2001)
[7] "empty spaces" in the brain.
[8] Hoehn M., et al. (2002)
[9] Modo M., et al. (2002)

Mechanical Pumps: Technologically, mechanical pumps are no match for cell therapy for the following reasons:

1. Cells are much more efficient since they secrete the necessary compounds according to physiological needs instead of a constant rate all the time.
2. Cells manufacture secreants on site and are likely to last much longer where as mechanical pumps would need replenishing after a year or so.
3. Cells migrate and send out processes to become more widely distributed and deeply integrated with the host tissue thus have a far greater efficiency in delivery.

The primary concern with cells in grafts is causing an immune response. There is very well established protocol to eliminate or minimize the immune reaction, while surgical insertion of pumps in the ventricles is more vulnerable to infection. Yet, mechanical pumps have experience greater commercial success because of the ease of delivery, low cost of production and a clear FDA approval process.

Managing patient expectations

Brain transplantation is fundamentally a technique for repairing localized neuronal circuits in the brain. The purpose is to restore lost function. It is not a perfect structural restoration of the brain which promise to take a brain damaged by disease and return it to its initial virgin state. The human brain functions as a systemic whole with enormous redundancy in function performed by an individual neuron as well as considerable plasticity in the strength of its connections. Brain implants aim to restore function not by replacing the specific damaged neuron, but by forming a "relay network" or a bridge between the truncated ends so that the pathway is operational.

A second "anomaly" about neuronal replacement therapy is that the therapy can be classified as successful or unsuccessful depending on the characteristic symptoms of the disease. While the therapy might significantly improve some features that had been lost, it may have no impact on the other debilitating aspects of the disease. In other words, the same patient can be categorized as cured or not, depending on the parameters chosen. In the case of a patient suffering from Parkinson's disease, while the tremor might have reduced, slowness of movement might persist undeterred.

It is extremely important to condition the recipients of brain transplants about the extent of recovery they might expect. The lay person very often hopes to get better than he ever was and brings depression upon himself.

Where will the neurons for replacement come from?

Success of cell transplantation depends on the ability of the transplanted cells to migrate and integrate into the host tissue both physically and functionally. This is extremely challenging. Neurons have lengthy processes which travel long distances to connect with cell bodies of other neurons and enable communication between the two via synapses. The nature of the connectivity both in terms of cell types involved and in terms of the type of connection, inhibitory versus excitatory, is vital to say the least. Neurons are best able to integrate if the donor neurons are immature, i.e. they are terminally differentiated but yet to form extensive connections. Reciprocal connections form relatively easily if the recipient's brain is also young. However, neurons grafted into the adult brain can also establish functional connectivity. Consequently, fetal and embryonic brain tissues continue to be used. It is expected that in future neural stem cells will be in frequent use.

The ability of stem cells to give rise to a variety of cell types has become a common knowledge. There are many types of stem cells[10]. Without getting into the intricacies of stem cell differentiation, Pluripotent Stem Cells are earlier in their development stage and are not yet committed to forming a specific tissue. Thus they may give rise to some unwanted cell types leading to tumor formation[11]. Multipotent Neural Stem cells (MNC), are further along the path of differentiation and are committed to forming cells that belong to the nervous system. However, they still retain the ability to form different types of neurons, or form glia or astrocytes. These are the most promising candidates for neuronal replacement. Stem cells can be obtained from a variety of sources, such as early embryos, fetal tissue and even some adult tissues. For a very long time it was believed that the adult nervous system does not regenerate. However, recently MNCs have been discovered in the adult human brain even though restricted to specific regions such as the dentate gyrus and the adult human hippocampus[12]. This has been a major breakthrough for scientists and a major encouragement in the ability to use neuronal replacement therapy to cure neurodegenerative diseases. To quote Dr. Eriksson from the Salk Institute[13]: "Our study demonstrates that cell genesis occurs in human brains and that the human brain retains the potential for self-renewal throughout life... Studies in rodents have shown that the adult hippocampus contains progenitor cells that can be expanded in vitro and grafted back into the adult brain, where they can respond to regional cues by differentiation into site-specific phenotypes, including neurons. The presence of progenitor cells in the human dentate gyrus, reported here, indicates that these cells also may be used for in vitro and in vivo studies of cell differentiation and possibly subsequent transplantation studies."

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[10] Stem cells are undifferentiated cells with the ability to give rise to a variety of cell types depending on the culture conditions. There are essentially two broad classifications of Stem Cells: the Pluripotent ones which give rise to three tissue types, namely, ectoderm (skin and nervous system), endoderm (stomach lining) and mesoderm (muscle, bone and blood). And then there are the Multipotent stem cells have been a major discovery. Multipotent Stem Cells are more limited in their ability to give rise to a variety of cell types.

[11] Bjorklund L. M., et al. (2002)

[12] C shaped structure in the human brain responsible for much of memory formation.

[13] Eriksson, 1998

Studies have explored the possibility of using pig neurons in humans[14]. This will remove the dependence on the availability of human fetuses. The added advantage to using pig neurons is that the pig can be tightly screened to obtain high quality and an unrestricted number of neurons whenever the need arose. Perhaps, the neurons could be even genetically modified for superior performance. Pigs could be breed with decreased immunogenicity, as suitable for human brain transplants.

[14] Bjorklund, Lindvall, 2000.

Chapter 2: An Introduction to NeuroBioChip Devices

NeuroBioChip is a novel approach in trying to cure neurodegenerative disorders caused by localized brain damages as in Parkinson's disease, stroke, and spinal injury. The proprietary technology invented in the MIT laboratories of Drs. Robert Langer and Mriganka Sur aims to produce brain grafts by impregnating new neurons on electrically conducting biodegradable matrices. Though the system is biodegradable and biological, it mimics the electrical implants in being programmable. NeuroBioChip Device bears similarity to the brain tissue grafts by restoring neural circuits with exogenous neurons. It is superior both to the pure electronic implants and tissue grafts because prior to implantation, the neurons are pre-programmed for optimal integration into the brain circuitry. In addition, the supporting implant scaffold is coated with dopants to create a microenvironment favorable for repair and healing of brain tissue. The scaffold degrades in a time-dependent fashion, just as the implanted neurons integrate with the host brain. I interviewed Nathan Wilson and Paul Matthew George, graduate students working on this project, in the laboratories of Prof. Mriganka Sur and Prof. Robert Langer respectively, to know further details about the technology in terms of the device composition and what it can do. While the interview is written in first person, much of the interview has been modified to make it easy to comprehend by non-technical readers. Some parts of the interview have been retained in the original deep technical form, to satiate the curiosity of the more technology-savvy readers.

1. How does the biochip work?

The biochip at its core is a scaffold on which neurons will be laid out. The scaffold is made from a biocompatible polymer, modified to support neuronal growth. The uniqueness of the biochip lies in the fact that this novel biopolymer conducts electricity. This feature allows them to work like "biowires", emulating electric wires. A scaffold made from these polymer "biowires" behaves like any programmable chip which can be connected to a standard electronic system. Eventually neural stem cells will be placed on the biochip. Since neurons communicate with each other and respond to electrical stimuli, the lattice of microelectronics embedded in the polymer scaffold will be able to guide the anatomical and functional organization of the neural network by means of high-precision electrical patterns. In this way, a mass of undifferentiated nerve cells will be converted into a functional circuit. Following this, the polymer scaffold with the programmed neurons will be implanted in the brain, in areas of localized neuronal death.

The integration of the new neurons with the surrounding circuitry is facilitated by presence of dopants such as nerve growth factors, immuno-suppressants, hormones and drugs that are imbued within the

scaffold to create a microenvironment conducive to neuronal regrowth and tissue repair. This is particularly helpful in cases of neurodegenerative disorders where neurons are dying and their survival is dependent on creating a microenvironment conducive for recovery. Finally, the scaffold itself is extremely pliable and can be inserted with minimal damage to the brain tissue.

The efficiency expected from implanting such preprogrammed neurons should by far exceed the efficiency of a simple tissue graft left to reconnect on its own. The biochip is also programmed for gradual degradation by the brain, such that it disappears from prominence leaving behind only the rejuvenated neural circuit and the rehabilitated function that the damaged brain circuit represented.

2. How do you make an electrically conducting chip out of a polymer?

The scaffold polymer is Polypyrrole (PPy) which is an electroplated polymer. It can also be doped with various agents to improve its properties for this application. In a publication in 2000, Chen et al. demonstrated PPy as a promising scaffold material for nerve regeneration. McCaig et al. in 2000 showed that the combined application of electrical stimulus and neurotrophins altered neuronal growth to a great extent. That's what got us thinking.

Successful implantation required us to manufacture working arrays that can be patterned and oriented to sub-millimeter levels of precision required for physiological integration with cortical cell populations. We are able to fashion PPy-based multi-electrode arrays with such acuity, which possess different geometries to suit our various applications. We have now even fashioned implant chips which utilize micro-patterned PPy for the wired circuitry, and biorubber for the structural base. Biorubber has been shown to be unusually biocompatible, and biodegrades with a time course similar to that of PPy. It provides the chip with the much needed flexibility to gently insert into the cortical tissue and adapt to its contour. We felt that the combination of the two, one for flexibility and the other for conduction of charge, would provide the synergy necessary for the next generation of our implants. Using fluorescent imaging we have demonstrated that cells do indeed extend processes and form synaptic partnerships with their neighbors on our PPy chips.

3. Can cultured cortical networks be patterned by external electrical stimulation?

It is possible to grow neural circuitry outside of the brain in a dissociated culture. The "pro-neural" forms of PPy doped with substances like laminin and BDNF, induce the formation of a neural network from

previously dissociated cells. This made it possible to interface these neural networks with arrays of multiple electrodes connected to a computer, to study the electronic relationships of the neuronal networks. We used our system to map the connectivity between neurons by injecting current to stimulate neurons in one area of the array and using the other electrodes in the array, to measure the bioelectric response to the stimulation. Using hippocampal brain slices we found that electrical impulses injected at one point in the network (to stimulate the local cells), gave rise to synaptic communication which could be detected in the rest of the neuronal network (much like the seismic waves of an earthquake spreading from the epicenter). The strength of the signal detected varied depending upon the strength of connection between the individual neurons. In this way we were able to generate a "network influence" map.

4. You have told me about being able to study and follow how information flows in these networks. Are you able to influence these information flows within the neural network?

Naturally at this point we asked ourselves whether we would be able to actually use this bio-electric system to "program" the neural circuitry to our desire. And, we have had particular success in using our system to modify specific connections between neurons! We have been able to alter the functional properties of neural pathways.

A more challenging question was whether we could create a "functional" architecture in an untrained, neonatal network. For this, we started by optimizing conditions for growing dissociated cultures of neonatal neurons on our multi-electrode arrays. The cells extended their pathways in multiple directions forming haphazard connections across the dish. Although this was very much, in sharp contrast to the well-patterned brain slice mentioned above, the connectivity was still quite reliable. We know this because the cells repeatedly fired the same "output" pattern across the network, in response to the same "input" stimulation.

Next, we wanted to see if we could alter this map and modify the input-output relationships of neurons. For this, one input pattern was immediately followed by another input pattern. We repeated this pair of stimuli hundreds of times. This eventually brought about a change in the network, which is called "associational" learning. When associational learning takes place, then stimulating any point within the first subset of neurons, elicit substantially greater activity than that elicited before the execution of the pairing protocol. In this manner it was possible to etch changes in the network which depended on the informational properties contained in the stimulus itself and not merely on how frequently a site was

stimulated. The ability to encode information at the network level in this manner is a significant step forward.

5. Can you measure the role of individual neurons in the context of the network?

Another major advance this year has been the addition of intracellular patch clamp into the electronics of our array measurements. Intracellular patch clamp allows the recording of individual synaptic inputs into a specific neuron, while also enabling the measurement of the response of the neuron to that input. You might be able to visualize, the micropipette probes of the patch-clamp extending into the network from above, while the multi-electrode activity is being acquired from below the chip, without the two interfering electrically with one another. In this way, by combining patch clamp with multi-electrode arrays, we were able to directly observe an individual cell's participation in the global dynamics of the neural network. While the patch recorded activity within a specific neuron, electrodes continued to monitor activity at different sites across the network. Thus, simultaneous patch clamp allowed us to correlate the activity of the specific neuron with the firing observed in other areas of the network, and conversely map the input strength of those areas into the cell of interest.

6. In a functional neural circuitry dynamic information patterns change rapidly. Are you able to mimic the fast time-switching time in your network?

You are correct. In order to induce a comparable neural structure in the trained networks, we need our input to be able to shift along a similar rapid timescale. We constructed a "stimulation controller", which allowed the gates to the electrodes to be rapidly opened and closed in a programmable manner. Stimulation can now be applied to a bank of the electrodes, but only some of the electrodes receive it. Any degree of input complexity is in theory possible with this manner of stimulation, with micro-second time resolution.

7. Have you conducted any experiments implanting the NeuroBioChip in neonatal or adult animals?

This year we surgically inserted various geometric and chemical versions of implant into the rat cerebral cortex. After the surgery, animals were allowed to recover and live normal behavioral routines. At various time points after the surgery, such as one week, or one month, the animals were sacrificed and histological (tissue) sections were taken to observe the degree of integration of the implant with the

surrounding host cortex. Post-mortem analysis of the implant integration came as a big surprise and a relief. We were very happy to see that the implant had not triggered any noticeable immunological response. Several of our implants had been fitted with holes to help us determine whether host neural tissue might penetrate the implant. By conducting histological analyses at the site of implant holes we discovered that host neurons seemed to reach through and around these holes. In fact, the host neural tissue had, formed an indistinguishable seal around the implants and had established elaborate processes into these spaces (which had been intentionally designed into the chips to assess the integration). The host tissue thus appeared receptive to fostering integration. This suggested, that in future, if neurons were provided on the surface or even inserted inside a hollow PPy implant, functional integration might follow from the spread of host tissue into and around the implant. With time the bio-erosion of the implant material would leave only an array of host cells intertwined with recently delivered, newly functional neurons.

PPy is an exciting possibility for neural interfaces. If we are successful, the NeuroBioChip will offer the first treatment that will cure diseases such as Parkinson's.

Table 1: Proposed Operational Process Flow Diagram for NeuroBioChip Devices

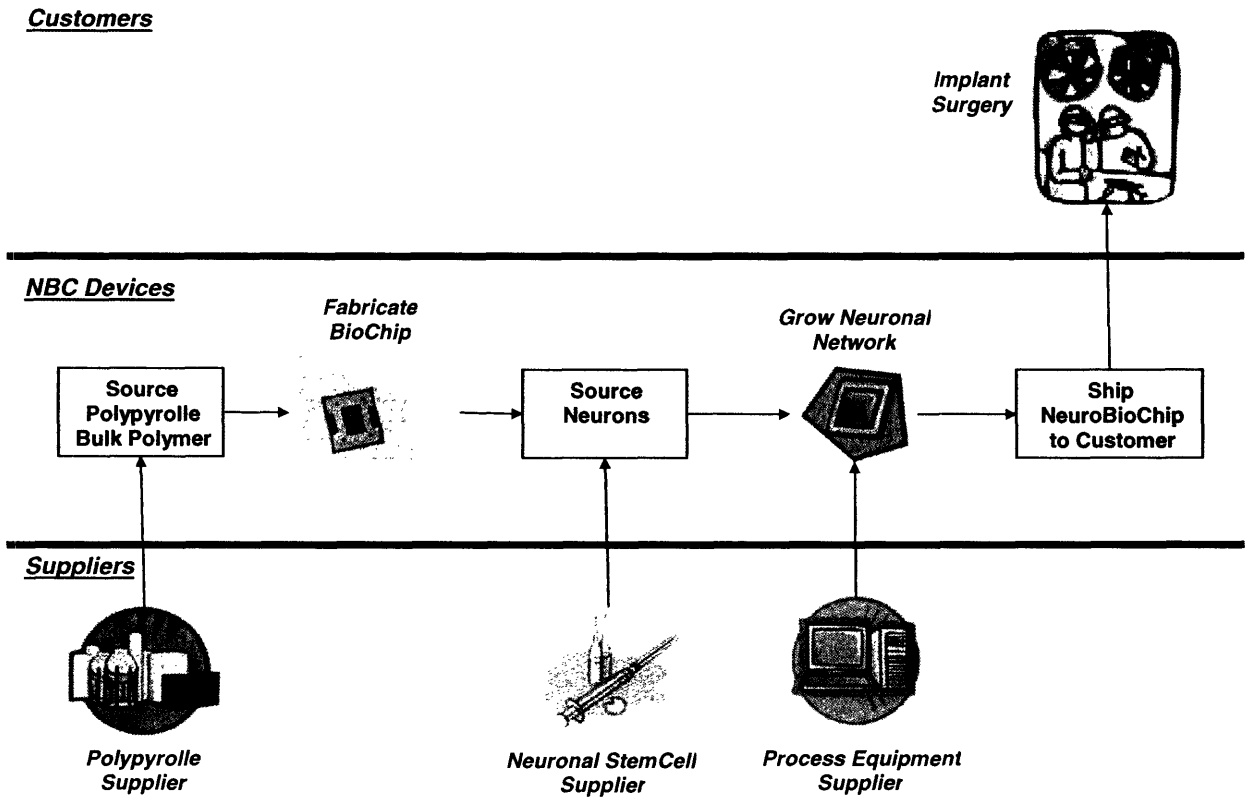

Diagram courtesy: Matt Vokoun, team member, NeuroBioChip Devices, 50K Business Plan Competition.

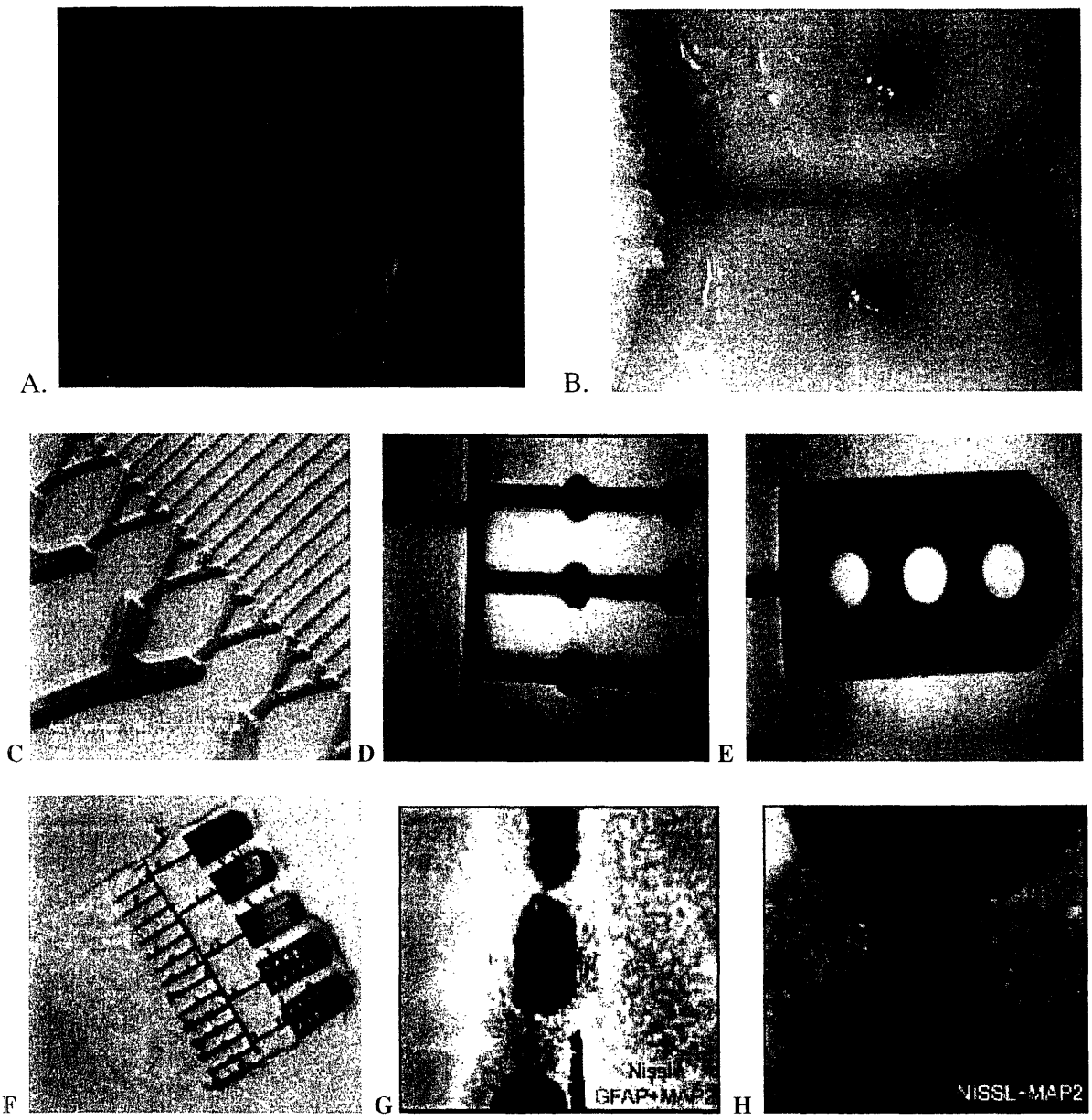

Figure 1: A. Visualisation of neural circuits on opaque polypyrrole. The cell bodies of neurons are depicted in blue (DAPI), while the dendritic processes are shown in green (MAP2). Glial support cells are also visible in red (GFAP). B. Implantation of chips into rat cerebral cortex. C. Patterning of the PPy circuitry. D. Conductive wires are patterned inot the ends of the implant. E. Holes are fashioned to assess host neuron in growth. F. Integration of the PPy circuitry with biorubber for enhanced flexibility. G and H.Integration of host nervous tissue through the holes designed in to the implant chip.

Diagram courtesy: Nathan Wilson and Paul George Matthew.

Chapter 3: Introduction to neuro-degenerative disorders suitable for cell therapy

Neural transplantation is a therapy for diseases that have well-identified, easily accessible and localized sites of brain damage. The diseases include Parkinson's disease (PD), Huntington's disease (HD), Stroke, Epilepsy, Macular degeneration and Spinal injuries.

Animal models

Experiments are naturally conducted on rats and mice, followed by monkeys, prior to clinical trials in human patients. One of the biggest hindrances to research in this space has been, finding the appropriate animal models in mice, rats and monkeys. Though in all cases the animal models are simulations of the human disease, no case is perfect, but some are better than others. In PD, for example, MPTP causes severe Parkinson's like symptoms in monkeys. Unfortunately, in mice very high doses of MPTP are needed to create merely a reversible PD effect. While rats are entirely resistant. However, injection of 6-hydroxydopamine helps simulate PD in rodents. In the case of HD, there are no suitable animal models. Perhaps because of the limitation in finding the perfect animal model (and the cost involved in conducting monkey experiments), Neural Replacement is one area in which clinical studies have preceded substantial animal studies.

Parkinson's Disease:

PD was initially described by James Parkinson in 1817. Today there are about 1.2 million PD patients in the United States and Canada, giving a ratio of 3500 patients/ million people. The number of new patients diagnosed every year is approximately 480 PD patients/million people. The peak onset is around 60 years of age. PD affects 1% of people at age 60+ years and 2% of people at age 70+ years. However, PD is not just a disease of middle or old age. 15% of PD patients are 50 years or less and 10% are 40 years or less.

PD even appears in teen-agers (juvenile PD). PD affects men more than women: 55 men/45 women. PD affects Caucasians more than people of color. PD progresses slowly but is debilitating. It takes from diagnosis to major disability a span of about 10 - 20 years.

There are four primary symptoms of PD, namely,

(1) Rigidity of the limbs very similar to the stiffness of joints as seen in arthritis.

(2) Tremor of the limbs especially hands, is a symptom commonly associated with PD. However, 30% of PD patients do not have tremor and tremor if present could be asymmetric in the two hands.

(3) Bradykinesia is slowness, paucity or incompleteness of movement. It is caused by a difficulty in initiating movement and is the most prominent and disabling symptom of PD.

(4) Postural Instability is the absence of Postural Reflexes. These reflexes empower a normal person to adjust for abrupt changes in position. When a PD patient trips, he is unable to prevent himself from falling and often incurs secondary injury. Bradykinesia can also cause the patient to trip over his own foot.

40% of PD patients are depressed, demonstrating that PD is much more than simply a motor disorder. Though some patients get depressed upon diagnosis, vast majority of the patients suffer from endogenous depression which precedes motor symptoms. 30% of PD patients develop dementia and an overall deterioration in intellect. Dementia develops most often in patients who are 70+ years and resembles Alzheimer Disease (AD). 30% of PD patients develop symptoms related to impairment of the Autonomic Nervous System, the region of the nervous system that regulates among other things, blood pressure, gut motility, and bladder function.

Pathology: Parkinson's disease is caused by a degeneration of dopaminergic neurons in two regions of the brain, namely, the substantia nigra (SN) located in the lower midbrain (or ventral mesencephalon), and the striatum (mesolimbic area). Dopamine is the neurotransmitter responsible for enhancing the

neuronal communication between the SN and the striatum. The histological hallmark for PD is the loss of unique dark pigmentation in the SN neurons caused by melanin and the presence of circular structures with a dense core formed partly of neurofilaments, called Lewy Bodies. Lewy Bodies are observed in other parts of the brain as well, demonstrating that PD affects all areas of the brain. However, the motor impairment is directly correlated to the extent of neuronal degeneration in the SN, and emotional and motivational impairments are associated with the mesolimbic region.

Treatments & Constraints: Since Dopamine is unable to cross the BBB, PD patients are most commonly treated by the precursor to Dopamine, L-DOPA. However, over time the patient becomes unresponsive to L-DOPA treatment and starts spending more time in the "off" state, as if he was not on treatment, versus the "on" state which clearly showed the positive effects of L-DOPA treatment. In advanced stages, even during the "on" days the patient suffers involuntary writhing movements called Chorea. Reportedly, by the time the patient starts to show functional impairment, he has lost 80% of the dopaminergic neurons in his brain. It is speculated that by this stage of the disease, the remaining synapses have also lost their ability to convert L-dopa into dopamine and therefore, become unresponsive. In summary, L-DOPA does not cure PD.

There have been two approaches to treating PD by transplantation. The first approach involving transplantation of chromaffin cells from the adrenal medulla[15,16] taken from young adult donors has been less successful[17,18]. The other more promising approach involves transplanting ventral mesencephalon taken from fetal donors[19,20]. This approach has been successful to the extent of discontinuing L-DOPA

[15] Chromaffin cells secrete the hormones, epinephrine and norepinephrine. Dopamine is the precursor to norepinephrine and is therefore also produced by Chromaffin cells.
[16] Adrenal medulla is an endocrine organ located above the kidney, one on each side of the body.
[17] Goetz et al., 1991
[18] Brundin, 1994
[19] Olanow, 1997
[20] Lindvall, 1997

treatment[21,22]. The tissue is usually implanted at sites where the dopaminergic fibers terminate and not where they initiate. Thus the purpose of the implant is to supply dopamine[23]. It is not to restore the dopaminergic circuitry in the striatum or the SN. Hence, this is "simpler" transplant than HD as we will see later. Human fetuses around 6.5 to 9 weeks old have been found to be optimal for transplantation in PD patients. In a particular study conducted at the University of South Florida, 7 such embryos were used to allow 24-32 transplants of fetal mesencephalic tissue to be made per patient, 5 mm apart from each other. It took 6 months for improvements to show up in the patients, with notable improvements in walking happening after a year later. In some cases, dramatic improvement was seen 2-4 years post-surgery[24] and even six years in some cases[25]. The patient spent more time in the "on" periods. There was marked improvement as well during the "off" times. In a specific patient reported by Lindvall in Lund University in Sweden[26], the time spent in the "off" periods went down from 70% to 40% within 12-14 months and then to zero in 30 months. In unilaterally operated patients the benefit was seen on the limb contralateral to the implant while the ipsilateral side continued to deteriorate. This was confirmed by following the dopaminergic neurons by PET scan. In spite of the improvement observed, in the best of surgeries 200,000 grafted neurons survived, which was only 5-6% of the total number of neurons grafted[27], and which is still only 50% of the total number of dopaminergic neurons in the healthy human brain. In addition, the grafted neurons showed delay in maturation. The fact that most of the patients in the various clinical studies died 18 months post-surgery due to causes unrelated to the transplantation, means limited information is available regarding the long-term success of the therapy. Indirectly this also indicates the physical condition of the patients who agree to undergo transplantation surgery. Patients 60 years and younger were found to be more responsive to cell therapy.

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[21] Olanow, 1997
[22] Lindvall, 1997
[23] Chase, 1989
[24] Freed, C.R. et al. 1998
[25] Wenning, 1997
[26] Lindvall et al. 1990
[27] Kordower et al. 1995

Obtaining fetal tissue of the right amount and the right age is understandably an enormous constraint in this method of treatment. This is further inflamed by the controversy around the ethical usage of fetal tissue[28]. As was mentioned earlier scientists have explored the possibility of using pig neurons. 12 patients received pig neuronal transplants[29,30]. Examination of a patient who died 12 months following surgery revealed the graft to be in good condition and the neurons had even sent out processes to integrate into the host brain. Pigs as a source of donor neurons for neural transplantation continue to be explored as an attractive alternate possibility. It is also encouraging to know that human to human allografts have not reported any immunological reactivity, even after many years of withdrawal of immunosuppressive drugs[31]. In one case, immune cells, namely macrophages, B and T cells were observed in the vicinity of the allografts, indicating the possibility of an aggressive immune response by the host[32]. Attempts at delivering L-Dopa have also included implanting L-Dopa releasing polymers[33] and L-Dopa secreting PC12 cells in polymer capsules[34].

It is not only that the fetal tissue needs to be right, but it is also extremely important that the host brain also be conducive to repair and regrowth. The adult brain having reached full maturity, no longer harbors an environment conducive to neuronal development. This causes poor survival and integration of graft tissue into the host brain. The scaffold of the NeuroBioChip can be supplied with dopants (such as GDNF, BDNF, bFGF[35]) that help create a microenvironment at the transplantation site in the adult brain mimicking that of a developing fetal brain and hence more supportive of axon guidance and survival. It is mention worthy that it is not sufficient for the implanted dopaminergic neurons to survive and secrete dopamine. The secreted dopamine has to be incorporated by neurons downstream in the pathway.

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[28] Boer et al. 1994
[29] Isacson, 1997
[30] Deacon et al. 1997
[31] Wenning, 1997
[32] Kordower, 1997
[33] Winn, 1989; Becker, 1990;
[34] Aebischer, 1994; Emerich, 1993
[35] Sinclair, 1996; Rosenblad, 1996;Yurek, 1998

Dopaminergic synapses are most often located on the dendritic spines[36] of neurons in the striatum. Should these spines have degenerated, even the best donor tissue and implant surgery cannot improve the condition of the patient.

A frequent side effect of neural transplantation has been psychiatric problems. Part of the problem is related to depression seeing the lack of dramatic improvement following transplantation. However, one of the patients reported an increase in the intensity of the panic attacks he was already experiencing prior to surgery. There is a general tendency of psychiatric disorders to get worse afterwards with instances of psychosis and delirium observed long after the surgery.

Spinal Injury

Ironically Spinal Cord injury is a disorder in which the damage and the cause can be clearly identified and yet it cannot be repaired. This is because the spinal cord circuitry is as complex as it is precise. It carries all the connections between the brain and the rest of the body, which includes sensory, sympathetic (involuntary) and parasympathetic (voluntary branch of the nervous system). The most common obstacles to repairing a damaged spinal cord are the formation of scar tissue that prevent regenerating nerve tracts from reaching their destinations, and formation of large fluid-filled cavities. Both the scar tissue and fluid-filled cavities create an area entirely lacking in any kind of intrinsic infrastructural support for repair and regeneration to take place. The peripheral nerve regenerates readily after a transection, but because it regenerates randomly, functional recovery is poor and defective. Substances such as piromen[37] and trypsin[38] inhibit scar tissue formation and promote fiber growth[39] but only to a very

[36] Neurons have processes called axons and dendrites. Axon of one neuron terminates on the dendrite of another to conduct impulses at specific sites called synapses. Dendritic spines as the name suggested are protrusions on the dendrites. Electrical impulses travel from the axon of one neuron to the dendrite of the neuron it is synapsing with.
[37] Bacterial polysaccharide
[38] Proteolytic enzyme
[39] Freed, Medinacelli, Wyatt, 1985

limited distance. Progesterone, the female hormone, is routinely administered to patients with spinal cord injury to prevent the injury from getting worse from inflammation related damages[40]. Much improvement has been observed in patients by such simple prevention of secondary damage.

Spinal cord injuries have a long history of transplantation dating as far back as 1944[41]. Analogous to the adult brain being non-conducive to neuronal regeneration, the spinal cord neurons fail to regenerate not owing to any intrinsic inability of the neurons themselves, but because of the antagonistic environment in the adult spinal cord. The myelin[42] producing cells in the spinal cord called oligodendrocytes actively inhibit axon outgrowth[43] by a form of contact inhibition. Antibodies (IN-1) cultured against this inhibitory protein residing in the myelin sheath enable neurite outgrowth[44]. Transplants containing cells secreting IN-1 promoted neurite growth up to 5-11 mm, up from 2-3 mm[45] but still far short of the required length. Also, growth was found to take place only in the intact portions of the spinal cord and not across the gap. The use of IN-1 is tricky. While it true that myelin is inhibitory to neurite outgrowth, it is also essential to neuronal function. Restoring large tracts of myelin in adult spinal cord has thus far proved to be impossible. This is because the fundamental organization of the myelin in the central and peripheral nervous system is very different. In 1968 Bunge showed Schwann cells to be responsible for the myelination of a single neurite belonging to the peripheral nerve fiber.[46] The Schwann cell continued to remain associated with the basal lamina of the neurite, and provided a scaffold for neurite regeneration in the event of the neurite degenerating. Oligodendrocytes are cells with numerous processes which produce myelin. They do not provide any such infrastructure to the neurons in the CNS. In adult hosts host fibers are found not to grow through the spinal cord grafts to continue their journey on the distal side of the

[40] Young, 1993
[41] Woolsey and coworkers
[42] Since neurons in the CNS communicate by electrical impulses, they are ensheath all along their length by insulating layer of myelin.
[43] Martin Schwab, Lisa Schnell
[44] Caroni, Schwab, 1988
[45] Schnell, Schwab, 1990
[46] Paino and Bunge, 1991

spinal cord. However, if peripheral nerve grafts are used, host neurons do grow through peripheral nerve grafts. It is possible to initiate spinal repair by using a graft containing a combination of Schwann cells, IN-1 and a cocktail of neurotrophic factors, which would induce regeneration of the severed neurons, provide them with a bridge to cross the gap and continue to grow towards the distal end of the spinal cord.

Transplanting fetal spinal grafts might prove to be more beneficial.The primary hope with fetal spinal grafts is that, among other features, they will supply neuronal cells that will develop into relay neurons interconnecting the two severed ends of the pathway. It is important to mention here that spinal cord implants grafted immediately following injury were able to connect the distal with proximal end, across the gap. The adult neurons found to grow through the graft included serotonergic and adrenergic neurons from the brain, and some neurons within the spinal cord[47]. Secondly, being in a developmental stage, the neurons in the fetal graft might cross the gap more readily, while also releasing trophic factors which would serve in checking further deterioration and damage to host neurons at the site of injury[48].

Olfactory neurons present an alternate source of neurons for transplantation since they retain their ability to regenerate even in adults. Ensheathing cells are glial cells belonging to the olfactory nervous system. The ensheathing cells display neuronal outgrowth inducing properties very similar to Schwann cells, however, they closely resemble astrocytes in other respects. In a study in rats, grafts containing ensheathing cells cultured in the laboratory, supported the growth of corticospinal tracts through the graft into the distal end of the spinal cord[49]. In 1996, Vawter et al. proposed the use of ensheathing cells in grafts to repair spinal injuries in human subjects. Ensheathing cells can be easily removed from the patient himself and cultured in the laboratory before being transplanted into the patient. This would subvert concerns about immunoreactivity, availability and regeneration of at least the corticospinal tracts through the gap created by injury.

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[47] Itoh et al. 1996, Shibayama et al. 1998.
[48] Bregmann, 1997; Tessler 1991
[49] Li, Field and Raisman, 1997.

To summarise, the white matter is strongly restrictive of nerve regeneration while the grey matter is more permissive. However, implanting Schwann cells or ensheathing cells can help create a micro environment conducive to regeneration. Adult neurons do not have any kind of intrinsic guidance mechanisms that will lead them to their correct destinations. Guiding the axons to innervate the right muscles remains an enormous challenge. In the fetal brain there are lots of guidance molecules in the extracellular space and receptors complementary to the guidance molecules at the nerve endings called growth cones. Cheng et al. in 1996 used multiple peripheral nerve grafts in a very ordered fashion, to induce an environment favorable for nerve regeneration and in a controlled manner. The NeuroBioChip can certainly help in this regard, by providing a scaffold on which organized restructuring can take place, while the dopants being released by the chip, would provide the regenerating nerve fibers with guidance cues. And finally, the chip could be implanted with neural stem cells to form relay neurons.

Stroke

In the United States, stroke is the third leading cause of death and the leading cause of adult disability preceded only by cardiovascular disease and cancer. Every year about 750,000 Americans experience a stroke; about 160,000 of these people die. This is an attractive candidate for neuronal transplant for two reasons. Firstly, stroke is characterized by easily identifiable, very localized, discrete sites of lesion. Secondly, the cerebral cortex, unlike the rest of the brain, has a high intrinsic ability to repair itself. Following stroke it recovers considerably, entirely by itself. However, it is very unlike PD or HD. Both PD and HD have well characterized symptoms and causes and have very standarised treatments available. Stroke is a cerebrovascular accident such as a blood vessel blockage also called occlusion which can happen anywhere in the cortex. In rare instances it can be caused by a blood vessel rupture as well. In stroke the blood supply to the brain is interrupted[50],[51] and brain tissue that was supplied by that occluded

[50] Occlusion of the cerebral artery
[51] Lee et al., 1999

blood vessel, is deprived of oxygen and nutrients. This phenomenon is known as ischaemia. Within minutes, the brain cells begin to die. Irreversible damage is caused in a core region with reversible damage caused in a surrounding penumbra zone (called global ischemia). The symptoms of each stroke case vary depending on the function performed by the neurons at the site of injury. In other words, the patient population for Stroke is not homogenous[52], as each case of stroke is unique. This makes it very difficult for scientists to get statistically significant clinical data using transplantation methods to cure stroke patients. In spite of such constraints, Stein et al. in 1985 demonstrated that transplantation of frontal grafts taken from fetal tissue showed considerable behavioral improvement. However, the improvement was not a consequence of integration of the grafted neurons into the host brain. It is believed that the improvement was a consequence of increased presence of the neurotransmitter, Acetylcholine (ACh)[53]. It is possible that the graft neurons themselves secreted ACh, or the graft released substances which sensitized the ACh response by the cortical circuitry in its immediate neighborhood. If this is correct, then neuronal transplantation for stroke seems to be overkill. Instead, delivering a local cocktail of substances to boost the ability of the neocortex to repair itself, might be a more practical approach. Simply using the NeuroBioChip scaffold loaded with neurotrophic substances seems to be a suitable for the treatment. It is important to do this transplant as soon as possible, since doing a cortical transplant long after the accident can do more damage to the patient's brain than not receiving any transplant.

Huntington's Disease

Huntington's Disease or Huntington's chorea is a relatively rare disease found in about 50-100 individual per million people. Dr. George Huntington first described this hereditary disorder in 1872. Today more than a quarter of a million Americans have HD or are "at risk" of inheriting from an affected parent. It

[52] Homogenous means all of the same kind. Opposite is heterogenous.
[53] Miranda et al. 1997, Lopez-Garcia, et al. 1990

manifests itself between the ages 35-50 and is characterized by rapid involuntary jerking and writhing movements, rigidity, dystonia, difficulty in speaking and swallowing, with accompanying personality and psychiatric problems such as depression, mood swings and forgetfulness. As the disease progresses, concentration and short-term memory diminish and involuntary movements of the head, trunk and limbs increase. Walking, speaking and swallowing abilities deteriorate. Eventually, the person with HD becomes totally dependent upon others for his or her care. Eventually the person dies from complications such as choking, infection or heart failure.

HD has a clear genetic bias. The abnormal gene IT15 is located at the end of Chromosome 4[54]. When present, this gene causes a long string of the amino acid, glutamine to be connected to the end of the protein Huntingtin[55]. While normal people have 9-34 glutamines attached to the protein, patients with HD have more than 35 repeats. There is a rough correlation between the number of glutamine repeats and the severity of the disease. Huntingtin is expressed in many tissues in the body and even in the brain it is not restricted to the striatum. However, in the striatum the abnormal protein interacts with some other striatal proteins to form toxic insoluble deposits[56]. It is only in midlife of the patient that Huntingtin starts causing the striatal neurons and few other neurons to degenerate, though onset may occur as early as the age of 2. Children who develop the juvenile form of the disease rarely live to adulthood. HD affects males and females equally and crosses all ethnic and racial boundaries. Each child of a person with HD has a 50/50 chance of inheriting the fatal gene. Everyone who carries the gene will develop the disease. In 1993, the HD gene was isolated and a direct genetic test developed which can accurately determine whether a person carries the HD gene. The test, however, cannot predict when symptoms will begin. Therefore in the absence of a cure, some individuals "at risk" elect not to take the test.

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[54] Goodfellow 1993, Huntington's Disease collaborative research group 1993.
[55] HD is thus caused by the presence of the gene (gain of function) versus a loss of gene function. Patients with two copies of the gene (homozygotes) have no more severe a disease than heterozygotes, having one copy of the gene.
[56] Li et al. 1995, Martindale 1998.

Treatments and constraints

Since little is known about the molecular onset of the disease, there is no treatment available for HD. Dopamine receptor blockers called narcoleptic drugs, provided temporary relief. Transplantation studies have taken two approaches to HD treatment: (1) the first approach presumes the excitotoxic model. This model claims the neurotransmitter, glutamic acid, perturbs the ionic balance in the neurons carrying glutamate receptors in their membranes, by keeping the glutamate channels open for long durations. Since glutamic acid activates (or excites) the neuron that responds to it, this is considered excitotoxic[57]. The treatment acts in a preventive mode against the progressive degeneration by implanting cells that would release growth factors such as nerve growth factor (NGF) or Ciliary Neurotrophic Factor (CNTF) in to the vicinity of the striatum. In a very creative approach, Duane Emrich at Cytotherapeutics (CTI) implanted small polymer capsules containing kidney hamster fibroblasts secreating hCNTF[58] into HD models of rats. In 3 weeks time the rats that received the implants were indistinguishable from the rats which had no lesions[59]! Similar results were observed in monkey models as well[60]. However, the animal models were studied over limited time span. It remains unknown whether prolonged infusion of hCNTF would be necessary over the lifespan of the animal to keep HD symptoms in control.

(2) The second approach does not depend on the molecular cause for HD. It acts in a corrective mode trying to re-establish degenerated striatal inhibitory connections. This is no simple task since the medium spiny neurons form a relay between inputs from the cerebral cortex and the SN (pars compacta) and send outputs to the globus pallidus and SN (pars reticulata) among other minor connections. The neurons at the input and output destinations are further connected to complex circuitry involved in critical tasks. (This is in sharp contrast to PD where the inputs to the dopaminergic neurons in the SN did not seem to matter.

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[57] Coyle and Schwarcz, 1976; McGeer and McGeer, 1976.
[58] Human CNTF
[59] Emerich, Linder, 1996; Emerich, Cain et al. 1997
[60] Emerich, Winn et al. 1997

The dopaminergic neurons involved in PD send impulses at a constant rate. Also PD involves a closed looped circuit between the striatum and the SN. For these reasons, perhaps, transplantation in the striatum has been some what successful.) Since, the GABAergic inhibitory inputs to the globus pallidus seem to be particularly important, the transplants will certainly need to carry either cells that secrete the neurotransmitter GABA or GABAergic neurons that will patch the circuit. Clinical trials using fetal tissue transplantations have thus far yielded no significant results. Regardless of the complexity, HD continues to be a very attractive model for neural transplantation because no other modes of treatment exist.

Pain

Chronic pain is not merely a symptom but an illness. It accompanies cancer, nerve damage and abnormal outgrowths[61], arthritis and other significant diseases. It can last from few weeks to months and gets progressively worse with time. Over the counter analgesic tablets fail to provide relief against chronic pain. Chronic pain can disrupt the patient's life causing loss of appetite, irritability, hyperventilation and insomnia.

Treatments and Constraints

Adrenal Chromaffin cells secrete endogenous opiate peptides and catecholamines. Endogenous opiates mimic drugs such as morphine obtained from opium, in alleviating pain by binding to opiate receptors on neurons. The discovery of endogenous opiates has fallen short of expectation as a possible cure for pain, because when they are delivered systemically, they fail to cross the BBB. They also universally affect all opiate responsive neuronal circuits in the body, and along with providing relief from pain, they cause secondary effects such as sedation, euphoria, and cause the patient to become addicted and develop tolerance to pain killers. Jacqueline Segan et al. transplanted adrenal medulla grafts in the spinal cord of

[61] Neuralgia – nerve damage; Neuroma – abnormal growth of peripheral nerve fibers.

rats to control pain[62]. Reportedly the combined analgesic action of norepinephrine and endogenous opiates was much more potent than each one individually[63]. Bovine chromaffin cells transplanted in the spinal cord of mice with accompanying (though brief) immunosuppression, lasted indefinitely and were found to cause analgesic response upon induction with nicotine. The ability of the grafts to release the peptides in response to nicotine was considered particularly favorable for use in human patients. Instead of a continuous secretion of the opiates round the clock, these grafts could be induced by administering nicotine systemically only during episodes of acute pain.

It was found that transplantation of adrenal medulla grafts into the periacqueductal gray stopped all sensations of pain, regardless of their source. However, transplants in the spinal cord provided relief only in those regions of the body with peripheral fibers terminating in that region of the spinal cord. Most of the experiments have focused on the spinal cord instead of the periacqueductal gray. Adrenal medulla grafts have even been transplanted into the spinal cord of cancer patients[64]. It should be mentioned that the pain sensation is a very subjective phenomenon which makes interpreting the efficacy of therapy very difficult. In this particular study, patients were asked to grade their sensation of pain on a scale of 1-10 and also their analgesic intake was noted, assuming it would decline as the pain subsided. Within 5 weeks of surgery, three patients experienced relief, with complete amelioration by the 10th week until the rest of their lives. These patients were suffering from colon cancer. Since then similar clinical trials have been conducted and with similar success[65].

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[62] Sagen, Pappas and Perlow, 1986; Sagen, Pappas, Pollard, 1986; Sagen et al. 1990; Sagen et al. 1991; Sagen et al., 1993; Sagen and Wang, 1990.
[63] Drasner and Fields, 1988; Yaksh and Reddy, 1981.
[64] Sagen et al. 1993; Winnie et al. 1993
[65] Pappas et al. 1997; Bes et al. 1998.

Epilepsy

Epilepsy is a brain disorder in which clusters of neurons in the brain signal abnormally at times. This disrupts the normal pattern of neuronal activity and causes strange sensations, emotions, accompanied by convulsions, muscle spasms, and loss of consciousness. Having a seizure does not necessarily mean that a person has epilepsy. Only when a person has had two or more seizures is he or she considered to have epilepsy. EEGs and brain scans are common diagnostic test for epilepsy. Epilepsy can be inherited as a single Mendelian disorder or a multigene phenomenon[66]. Epilepsy is a disorder with many possible causes. Anything that disturbs the normal pattern of neuron activity — from illness to brain damage to abnormal brain development — can lead to seizures. Epilepsy could also develop as symptom of another neurodegenerative disorder[67]. Just as in Stroke, the symptom of Epilepsy is diverse depending on the function of the afflicted neurons in the brain. Epilepsy may develop because of an abnormality in brain wiring (recurrent excitatory synapses), an imbalance of neurotransmitters, an autoimmune attack on the nervous system, or some combination of these factors. While the causes of epilepsy are diverse and no definite region in the brain has been identified as the epicenter, the proposed imbalance between excitatory and inhibitory neurotransmission has raised the possibility that seizures could be suppressed by transplanting cells that release inhibitory neurotransmitters. (Each gene identified with Epilepsy has been found to encode an ion channel, which if impaired will disrupt the ionic balance of the neuron carrying the channel.) Intracerebral grafting of porcine fetal striatal GABA-rich tissue has been performed in a group of epileptic patients. The effects observed so far have been transient either because the GABA release from the grafts declined over time or the host tissue down-regulated indigenous GABA synthesis, but suggests a possibility of long-lasting inhibition in epileptic brain regions[68].

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[66] McNamara, 1999
[67] Pannacchio, et al., 1996
[68] Bjorklund, Lindvall, 2000

Retinal Implants and Cochlear Implants

"Volta, in the year 1790, became the first person to experience and publish the effects of electrical current on the auditory system. He inserted a metal rod in each ear and then subjected himself to approximately 50 volts of electricity. He reported that the sensation was that of receiving a blow to the head followed by the sound of thick soup boiling."[69] Cochlear implants have certainly come a very long way since then. Currently, there are two major corporations manufacturing cochlear implants for use in the United States: Cochlear Corporation and Advanced Bionics Corporation. Present day retinal and cochlear implants are composed of tiny integrated circuits with platinum electrodes that send electrical stimuli directly into the relevant nerve endings to the brain. The NeuroBioChip because of its electrically conducting properties can definitely find use in both retinal and cochlear implants[70]. However, the precise nature of its application would take us in to the realm of bioelectronic devices, which is beyond the scope of this thesis.

[69] http://biomed.brown.edu/Courses/BI108/BI108_2001_Groups/Cochlear_Implants/history.html
[70] Zrenner, 2002; Rauschecker, Shannon, 2002

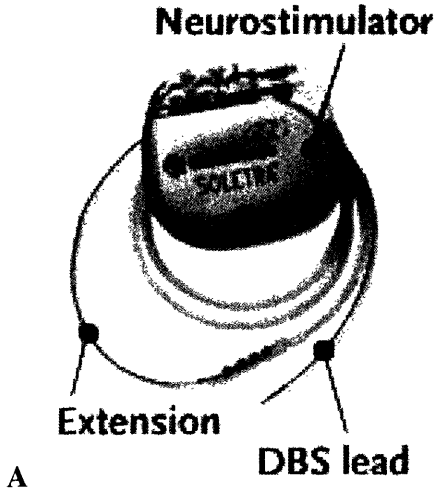
Chapter 4: Practical issues to the neuronal implant: A Neurosurgeon's perspective

The NeuroBioChip device once commercialized will come into direct competition with the Activa Systems sold by Medtronic for symptomatic relief of Parkinson's patients. The Activa System is a deep brain stimulating device. The device is usually given to Parkinson's patients who are unresponsive to medication. There is a central pacemaker (Fig. 2A), called the Neurostimulator, which is very similar to a cardiac pacemaker. It is surgically implanted beneath the hollow of the collar bone. Deep Brain Stimulator (DBS) Leads from this device travel under the skin from the shoulder, go up the back of the patient's neck and terminate in the globus pallidus interna or the subthalamic nucleus regions in the brain, delivering controlled electrical pulses in these brain areas (fig. 2B). Depending on the patients condition, he can have 1or 2 pacemakers in himself. The surgery for installing each pacemaker is 12 hours long. Post surgery, the physician uses telemetry to set the stimulation parameters of the device. Once back home, the patient turns the device on/off by holding a handheld controller over the neurostimulator, which also allows him to check the battery status of the implanted device. The first experience of the using the device is usually painful, but should not last more than a few seconds. Most often the device is implanted in the left side of the brain, as most people are right handed, and can cause slurred speech. There is a rare risk of infection, breakdown of the hardware and the batteries will need to be replaced in a couple of years. Each of these requires additional surgery. There is also a 1% risk of haemorrhage during surgery, which can cause death, coma or paralysis.

Below is an interview with **Dr. Thorkild Norregaard**, a neurosurgeon at Mt. Auburn Hospital, who regularly operates on PD patients, implanting the Activa System. He is also a professor at Harvard Medical School and has extensive research experience with polymer implants in spinal cord injuries. Since the NeuroBioChip would be in direct competition with the Activa System, I interviewed Dr. Norregaard to get a neurosurgeon satisfaction with the Activa System and to learn about a surgeon's receptivity and apprehension towards the NeuroBioChip, should it become available.

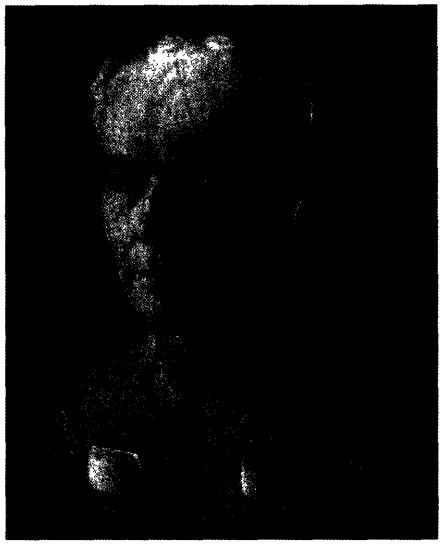
Figure 2:

A. The components of the Activa System.



A

B. Patients with bilaterally implanted devices.



B

Courtesy: Medtronic website

How satisfied are you with Medtronic's Activa Therapy and L-dopa medications?

Dr. Norregaard: In PD certain dopamine producing cells die, and some other centers of the brain become de-inhibited and therefore, become over active. When you put the Activa system or a Deep Brain Stimulator in, you are actually not stimulating to get activity. The electrical stimulation is actually a blockade. It blocks these hyperactive cells. You continuously depolarize them so that they can't fire. That's why the stimulation is a brake you put on, as opposed to a facilitating effect. The same is true of medication. It is a symptomatic treatment. Usually the people who go for the Stimulator are the ones who are taking so much medication that they are experiencing the side effects of Dopamine, a dyskinesia. These are choreatic movements which are dose related. When you reduce the dosage of dopamine you can often times get rid of the dyskinetic side effects. Usually following implantation of the Activa system, patients can reduce their anti- Parkinson medication significantly. Some can even get off medication. Whether or not the patient can reduce the amount of medication he is taking, that the neurologist will have to decide.

But both the medication and the Activa Therapy or Deep Brain Stimulation treatment for PD are truly symptomatic treatments. They don't do anything for the progression of the disease. And PD is by and large a progressive disease. There has been some suggestive data that when you put the device in the subthalamic nucleus, stimulation would alter the natural progression of the disease. But this is by no means proven. Therefore, the only thing we can say at this point in time that it is a symptomatic treatment which does not cure.

The whole concept of having an electrically conducting polymer that can be programmed and that can be altered from the outside so that it can alter its connectivity is fascinating. An approach like what you are describing might help symptoms as well as alter the natural progression of the disease. Anything that

might have more of a restorative effect, I would definitely use it, as opposed to having to put in a clunky electrode and battery.

1. **Could you comment on the infection rate often associated with the Activa system?**

Dr. Norregaard: Infection rate for the Active therapy does vary. It is in the 5-6% which is high. In general, electrosurgery in healthy patients (without diabetes) should be about 1%. So, we are quite a bit higher. When you put in the Activa device, the infection is usually around the battery implant instead of the electrodes. (Is this because the brain is immune compromised?) No, I don't think so. It is simply because it is a foreign body put in. I put in the same device for spinal cord stimulation for pain management, and also for cardiac pacing for pacemakers. There is a known infection risk whenever we put these devices in. At times, the skin can erode over the hardware as it runs down underneath the scalp. Suddenly, the hardware is exposed and you have to take it off because there is infection going in. So, there are some negative aspects in that respect.

At some point the patients will need to have the batteries replaced. Depending on how much stimulation they need, it is about 4 years on an average. There is an emerging technology however, with percutaneuously rechargeable batteries. There is a company in the market with the device and within a short time period you will see the adoption.

2. **Do you feel the polymer implant will be a solution to this infection issue?**

Dr. Norregaard: The polymer implant you are talking about will probably have the same risks and complications in whatever mechanism it is meant to be implanted. You will need to identify the sites for implantation and then some sort of a guide to get there or you will have to inject the polymer. At least you won't have the battery replacement problem, and will be gentler on the skin.

3. **Do you have any other comments on other treatments for PD?**

Dr. Norregaard: There is one other aspect you ought to know about Deep Brain Stimulation. If you do DBS in people with Obsessive Compulsive Disorder, you can cure these people with a stereotactic lesion in the Cingulate Gyrus. It is the same effect as with a stimulator in. A lot of times when can get the same effect as the Activa therapy, with a lesion in the brain. The stimulator is a reversible treatment while the lesion is an irreversible treatment. We don't have the studies to indicate whether to make lesion the accepted therapy; to compare one to the other. Outside of US, e.g. in Britain they have done experiments with lesions in the subthalamic nucleus. If you take a normal person without PD and make a lesion in the subthalamic nucleus he will develop involuntary movements of the arms and legs. But a Parkinsonian patient with a lesion does not experience such involuntary movements. This is because the altered neuronal connectivity that has occurred as a result of PD protects them against developing this symptom.

In cases of Central Tremor, when we use bilateral lesion, there is 10-20% chance of some alteration of speech. Therefore, surgeons have been reluctant of bilateral lesions. But you can do a lesion on one side and install a stimulator on the other side. If they experience alteration of speech, the patient can turn the stimulator off. Some places do practice this form of treatment. Thus, Activa therapy is a blocking therapy and lesion is a destructive therapy. It is crude.

4. **How do the cost and reimbursement work for such surgeries?**

Dr. Norregaard: In Activa therapy, the devices cost close to $25K of just hardware. If we go into a lesion modality, there is no hardware. We can save $25K! If we go to India and buy the same equipment it will cost $10K! Because they have national health insurance, Australia also has a deal with Medtronic for a discounted price. That's the way Medtronic markets it. With the standards of surgery coming up in

India, it is almost cost effective for the patient to fly into India, get treated and come back. The future will be much more a global marketplace or an even market place. Either you buy your stuff somewhere else or you fly the procedure or fly the patient.

The DBS system involves putting in the electrodes and then putting in the batteries. In Europe, often times they put in the battery and the device in the same surgery. Here we don't do that, because reimbursement is poor. So, we have to do a 2-stage procedure. We put in the electrodes and then we discharge the patient. We have the patient come in 10 days to 2 weeks later, and then, we put in the batteries. They get a better reimbursement this way. (How does reimbursement relate to admission?) Suppose you are treated for gall bladder and a skin lesion in the same operation. Then we get 100% reimbursement for the gall bladder and only 50% for the second. When you put in the system for PD there are 4 components: 1 electrode, and a contralateral electrode, 1 battery and a contralateral battery. If you really wanted to get the best economic benefit out of it, you will make it into 4 separate operations. However, putting in the electrodes is so time consuming because you have to put on the stereotactic frame and do calculations, it is not rational to do it twice, but it is rational to send the patient home in between. The entire procedure of putting in the batteries takes only about 4 hours. There were times we kept the patient in the hospital. But we would get only 50% reimbursement in the 2nd operation because it is on the same admission.

Activa therapy involves a lot of programming afterwards. Each electrode requires 7 hours of programming. That's a total 14 hours. We can't charge any money for that, because when you do surgery, any post-operative care within the first 90 days is within the global period and is considered paid for by the surgical fee. When you look at the current reimbursement and you look at the amount of time it takes the surgeon to do the case: the preoperative assessment, office staff and post-operative programming, the entire package, then economically it's a complete fiasco. The DBS is only done in academic centers where some form of funding is available to provide the salary for the nurse who does the programming

after the surgery. If a private physician was to hire a nurse and do the programming, he would lose money. By the time dust settles in the DBS case, the surgeon's hourly fee is about, $60-70 an hour. When I have an electrician come into my house, he charges about $75 an hour and he doesn't have my overhead. (Laughs)

5. **As a physician which indication would you choose if you were commercializing the technology and how would you go about it?**

Dr. Norregaard: Conceptually it is very helpful to any focal neurodegenerative disease: PD, Stroke, spinal injury and even certain cases of Multiple Sclerosis, where there are specific plaques. But pain is a very heterogenous population and also you can't really quantitate it. Spinal cord injury is very suitable because you know exactly where the lesion is and you can get a digital read out. Patients with Essential Tremor would be ideal. When you turn on the DBS in such patients, the tremor stops immediately. With PD patients, when you turn on the DBS, it has to work for a few hours before you see the full effect. In other words, there is a cumulative effect. Also, PD is laborious, as you have to do PD scores and a host of other measures. Essential Tremor is very distinct and clinically a very recognizable condition. You can even see the effect in teens. You don't necessarily have a lot of polluting factor as in PD. PD patients can be old, demented, as well as there can be L-Dopa effect. Both Spinal Injuries and Essential Tremor are easy to diagnose, easy to quantitate and very easy to monitor. I recommend those. Stroke could be made into a potential target by picking patients with very similar types of Stroke. But PD,.... I wouldn't go there to begin with.

In this country it has become very difficult to introduce new therapies, particularly if it is in the Medicare population, because it is where the federal government pays, and they won't pay for anything that is not FDA approved. To complete the cycle, FDA approval is very difficult for a biological implant versus any other device. When I go to Europe and talk to my colleagues in Spain for instance, they can do anything

they want! Therefore, for something like this, it might be smarter to do the development in Europe, as opposed to doing it here. If it becomes a smashing success, there will be a public drive to bring it home. Making the science work almost seems like the lesser of the challenges....

6. **Could you comment on depression being a problematic side-effect in neuronal replacement cases?**

Dr. Norregaard: Depression is part of PD. People do get depressed. I doubt that when they the embryonic cell implant that they get more depressed. You have to distinguish between depression and disappointment. Disappointment is not as serious a disease as true depression is. When we do deep brain stimulation for both central tremor and also perform subthalamic stimulation, we stimulate different areas. I have patients who are awake and suddenly get into absolutely glooming depression. As soon as you turn it off, it goes and the sun comes out again. I have had people suddenly beginning to laugh hysterically. I ask them, "Why are you laughing?" "I don't know why I am laughing!" They have tears streaming down their face. I can put a device in you that will make you always happy. It varies from individual to individual. Some people are more susceptible to that stimulation than others.

One time we tried neuronal replacement using adrenal cells, which did not to work. The only scenario where neuronal replacement seemed to have a beneficial effect was in Sweden, where they used human embryonic stem cells. When stem cell implants were performed, they were put in different areas. So, the observed depression could have been site specific. I wouldn't worry about that.

Chapter 5: CytoTherapeutics: A case study

Why I chose CTI?

Attempts have been made to commercialise brain implants. One of the companies that tried was CytoTherapeutics (CTI). The core technology at CTI was an encapsulation strategy. Fibroblasts would be sealed inside small perforated polymer capsules, such that nutrients would reach the fibroblasts and therapeutic secreants from the fibroblasts would diffuse outside. However, the polymer capsule would shield the fibroblasts from the host immune system, thus preventing an immunogenic response and also contain the fibroblast and keep them from migrating to parts of the host body and give rise to tumors. The polymer capsule containing fibroblasts, thus, defined a platform upon which product development efforts were based to treat a variety of diseases including Parkinson's disease (PD), pain and ALS. Founded in 1990, CTI not only thrived but went public. In 2000, cell therapy efforts at CTI were discontinued and the company was transformed into Stem Cells Inc.. Interviews were conducted of several key ex-employees of CTI to determine the nature of challenges they faced. Whether there were any problems unique to commercializing brain implants. The objective was to put preventive measures in place for similar future initiatives.

I. The Beginnings of CTI (as narrated by one of the founding scientists)

Founding Management: It was around 1988 when two pieces of technology, one at Brown University and the other at Washington University came together in the formation of a company. Dr. Pierre Galletti, a distinguished physician at Brown University had been working with me (Al Vasconcelos) at Pfizer, on a permeable nerve repair device, for repairing peripheral nerve cuts and disconnects. The material we used had a very selective permeability of 50kd, with a very unique surface structure that allowed for vascular in-growth. It became very clear to me that the material was advantageous for cell transplantation. Brown

was already interested in forming a company. The venture capital fund, Mayfield, which funded Genentech, approached Patrick Aebischer, a postdoctoral fellow under Dr. Galletti. Patrick was eager to seize the opportunity and I followed suit. And thus, the original company started at my home office in May, 1996. Late in September, we hired Mike Lysaght, and then Orion Hegre. We were the trio that formed the kernel of the fledgling company. Soon afterwards, we moved to Richmond Square, where we rented a couple of temporary offices. What was then called Cellular Transplants, two years later came to be known as CytoTherapeutics (CTI).

The technology and initial IP involved transplantation of cells into a hollow capsule: a preselected scaffold that helps cells in the purpose of hand-picking protection existed at Brown. The original IP for the central nervous system (CNS) came out of Brown University, while Washington University contributed the ability to isolate the pancreatic islet cells. My job was to expand the base intellectual property. Within 24 months, David Knaac, who was a Neurobiologist as well as a gifted patent agent, worked together with me, to convert the initial IP into a significant cell transplantation IP portfolio, considered one of the strongest IP portfolios in the industry even today.

II. Core technology of CTI (as described by one of the scientists at CTI in a publication[71])

Life Scientist: Delivery of potentially therapeutic drugs to the brain is hindered by the blood-brain barrier (BBB), which restricts the diffusion of drugs from the vasculature to the brain parenchyma. One means of overcoming the BBB is with cellular implants that produce and deliver therapeutic molecules. Polymer encapsulation, or immunoisolation, provides a means of overcoming the BBB to deliver therapeutic molecules directly into the CNS region of interest. Immunoisolation is based on the observation that

[71] Cell Transplant. 2001 Jan-Feb;10(1):3-24. Update on immunoisolation cell therapy for CNS diseases. Emerich DF, Salzberg HC. Department of Neuroscience, Alkermes, Inc, Cambridge, MA 02139, USA.

xenogeneic [72]cells can be protected from host rejection by encapsulating, or surrounding, them within an immunoisolatory, semipermeable membrane. Cells can be enclosed within a selective, semipermeable membrane barrier that admits oxygen and required nutrients and releases bioactive cell secretions, but restricts passage of larger cytotoxic agents from the host immune defense system. The selective membrane eliminates the need for chronic immunosuppression of the host and allows the implanted cells to be obtained from nonhuman sources."

Interview structure

To know why CTI was unable to commercialize their technology, I queried into the following areas:

I. Human Resource Management
    1. Hiring Strategy
    2. Culture at CTI
    3. Organizational Learning
    4. Growth Rate

II. Technological Challenges
    1. Manufacturing
    2. Cost structure
    3. FDA Regulations
    4. Implementation (surgery)
    5. Reimbursement

III. Technology Strategy adopted by the firm at various key junctures
    1. Choosing Pain as a market over Parkinson's disease
    2. Project management
    3. Transformation into Stem Cells Inc.

[72] meaning from different species

IV. Investor effect

V. Lessons Learnt

1. Is now a better time for the technology?

In order to convey the true feelings of the ex-CTI employees, the interviews have been narrated in first person, while revealing the identity of the interviewees only to the extent of the positions they held at CTI. In a start-up the heads of technology divisions very often assume a management role and have been classified as "Technical Head/Management". The beginning of many sections captures the essence of the interview in a collection of quotes marked "snapshot of comments". In addition, significant statements within the text have been underlined to draw the attention of the reader. Quotes from published documents have also been included.

The interviews represent a shadow of what might have happened and might be prevented in similar endeavors in future. What really went wrong, or what could have saved the company, might never be known.

III. Human Resource Management Issues:

Snapshot of comments:

Life Scientist: "... there wasn't a sense of: You have to do A, B, C, D to get this to market..."

Engineer: "Whenever you are making widgets you need to make them all the same. And it was really not my expertise. I never like doing things the same way twice!"

Technical Head/Management: "There were several people within the company with drug development experience."

Management: "What makes cell therapy very difficult is the need for cross disciplinary personnel."

1. Do you have any comments on hiring?

Life Scientist: The firm too often decked for the investors. In spite of the need for a cell biologist, a molecular biologist was hired. The real solution would have been to hire a cell biologist and outsource the molecular biology.

Life Scientist: You needed personnel who are actually trained to work with animals. If you looked at the talent pool that you could draw upon, you would pull out a bunch of good cell biologists and good engineers. You really pulled them out of school, because there were no other companies who had done this, there was no development experience around. You can't expect a bunch of PhDs to know this. They knew how to publish good science and they were doing that. But there wasn't a sense of, "You have to do A, B, C, D to get this to market. Today you can draw upon a much more mature group of people. And there are encapsulation companies out there right now, who have toned down their expectations."

Engineer: Whenever you are making widgets you need to make them all the same. You can't have things work one time and not the next. They need to work every time. You need a process. When I got there they never had anything like that. And it was really not my expertise. I never like doing things the same way twice!

In the beginning you had to interview with everybody. I had to interview with the CEO even though I was low on the totem pole. Everybody's input was listened to. Some good candidates were shot down because

people perceived something in them that they didn't fit the culture and they were right about that. Later on they were a lot less careful to involve wonderful people. They didn't care if people cared about the culture. A guy from (a company out of town) was hired as a VP. Nobody got to interview him. He appeared out of nowhere. He was a big shot and he was gone in 2-3 weeks! The CTI culture spurted him out because of complete disconnect.

Technical Head/Management: There were several people within company with drug development experience. We had a pretty good mix of people relative to what people were trying to do. It was difficult to do.

Management: Mike Lysaght pretty much structured the research. What makes cell therapy very difficult is the need for cross disciplinary personnel. You need wet people who can do cells, you need engineers; you need people who understand in vitro and in vivo applications; you need physio-pathologists, people able to dissect, able to do histology and manufacture polymers. You are having a very diverse cross-section of skills. Therefore, we decided on hiring by key milestones; identified functions necessary to accomplish those milestones and broke them down into subcategories. It is easier today to do that, than it was back then. Part of it might be change in the industry, part of it could be change in us. Since that time I have put together 5, 6 or 7 different very successful start-ups, all of them in cell therapy. Today we have worked with everybody in the industry, since it is a small industry. We know who the players are. We know their strengths and their idiosyncrasies and how to put them together. Because there have been a number of cell therapy attempts, there are a lot of people who have that kind of expertise. Then there were a whole host of people who said they could do it only to be proven that they couldn't.

Management: It was an organizational experiment like most start-ups are. Most employees did not have much experience outside of academia. They were smart people who worked very hard, passionately believed in what they were doing, but not much experience with drug delivery, the disease they were

working on, and the process of commercializing the technology. When I took over the development group, I took the scientists to the local hospital and some of them saw and met PD patients for the first time.

2. **What was the culture like at CTI? Was there enough communication between the different groups?**

Snapshot of Comments:

Life Scientist: "The culture... became an engineering culture and the attitude towards the biologists was not very optimistic."

Engineer: "If I had a problem that I couldn't solve, and it was important, I would spend the night there; spread a mat on the floor because I was so excited about it. Nobody was telling me to do so and often nobody knew. Even the janitor was excited about cleaning the floors because they knew they contributed to the success of the company. Everybody was excited... Initially it was very good. It got horrible towards the end."

Engineer: "Membrane scientists were calling all the shots."

Technical Head/Management: "Reasonable men can differ."

Life Scientist: CTI used matrix management, which is known for its risks. This was necessary because CTI had to manage silos of competency: cell biology, biochemistry, chemical engineering, animal physiology, histology and cytology, etc. The development activity was cross functional. All CTI employees needed to report to both the CTI Product Manager and to their own Department Head. As CTI

grew, many decisions were made in either small work groups closely involved with a specific product development task or in board rooms seeking to navigate corporate growth.

CTI was a dynamic, hard-working, hard-partying crusade in the early days. CTI had to learn how to behave itself as it came under increased investor attention just before and then for long after its IPO. To appeal to investors, CTI practiced a policy of "forward hiring", meaning that once you were in the company, you would rarely get a shot to advance to a level that might otherwise be filled by a high profile and new senior executive. This created a bureaucratic culture that I think contributed to the early departure of one of the artificial organ scientists, a founding scientist.

R&D was not divided into Pain and therapeutics but into engineering and biologics. The technology required a high level of collaboration between the engineering and life sciences groups in the firm. The atmosphere was definitely collaborative, yet the hiring was more impressive, heavy, and accurate for the engineering side than the life sciences side of the firm. This was largely because the Technical Director was a talented engineer who by virtue of his training stressed on engineering the capsule to perfection, undermining the biological challenges. The culture therefore, became an engineering culture and the attitude towards the biologists was not very optimistic.

Besides, the engineering wing was more in touch with the product development. The engineering problems by their sheer nature were quickly resolved and therefore had a higher frequency of success as compared to biological research which has always been challenged by the presence of far greater unknown factors. This painted the biologists in unfavorable light and paved the way for the Life Sciences division to remain unappreciated for their contributions and become progressively lesser in importance, to the point that nobody asked the Life Sciences team about the problems they faced and the solutions they proposed. Decisions were made on their behalf. This also caused more funds to be channeled into the

engineering divisions of the firm. Their frustrations failed to be heard by the management who themselves were under pressure from the investors.

Another reason was that the Head of the Life Sciences division, even though on paper a technical counterpart to the head of the engineering division, in personality he wasn't a match for his counterpart. Though charismatic, accomplished, and very resourceful, he lacked a deep understanding of the technical issues at hand. Consequently he failed to provide strong, well directed leadership to his team even though he recruited a couple of good people to the team. The CEO at the time was from a billion dollar company. While an able leader, he had never been in a start-up culture.

Life Scientist: We had the attitude that, "We've got this really cool technology. It's going to work. We are going to make it work." A lot of companies make that mistake. That really doesn't work. I think it is really important to talk to other people, enter corporate alliances, and look at new ways of doing things. Chances are your technology will not work, just from a statistical point of view. Until you have a technology that works, you've got to develop a culture that works internally very well. From the very early on there was a cultural bias in the company. There were groups within the company that didn't interact as well as they could have. We were set against one another.

Engineer: The early culture under Mark Levin and Michael Lysaght was really progressive. Individuals were empowered with respect and responsibility for their jobs. Mark Levin invited all new employees over to his house for dinner to meet them and welcome them. It didn't matter if you were the person who washed the labware or you were a scientist. There was hardly any difference between the CEO and the janitor.

We met the life science folks a lot. Routinely I would go over to Pierre Galletti's office at Brown. He was the VP and in charge of the entire life science program there. He would give me all the time of the day to

talk about cellular transplantation. There were no closed doors ever anywhere. A lot of important decisions were made with inputs from everybody in the room.

It started to change when the CEO changed and we got bigger. And we had to get bigger. When you get to 200 you are a lot less mobile. To get 200 people to all turn right at the same time is hard. Groups of people disagreed with other groups of people. When you are few people you work out the problem and come to a consensus instead of retreating into a group and standing firm. Besides, we unloaded diabetes to Diacrine with which we lost a couple of important employees whom we sent to California with the new company. There were favorite scientists and other scientists who were equally talented but not in favor because they didn't agree with the company line. There was a lot of discrediting of scientists, some scape-goating, and a lot of negativity that would not have been tolerated earlier. It was when the CEO hired someone to bring in the Stem Cells, that we morphed into the Stem Cells Company and moved to California and that was the end. Even though the CEO was around for a long time, he was replacing people under him a lot. Top leaders came and went. The VPs to senior management was very much revolving door. You needed stable leadership versus people coming and going.

There were some other scientists at Brown and the technology came out of Brown. Sometimes we would try to replicate what they did at Brown and sometimes it wouldn't work. So there was some "us versus them" in the company in the middle of the company's development cycle. The then CEO very wisely hired all the Brown people into the company, to put an end to this divide. Between 30-60 employee strength, CTI was a manageable, well run, very happy place to work and everybody was happy to come to work.

Technical Head/Management: If you start a company one of the 3 things are going to go wrong. Either the technology is not going to work (in Cyto's case I think the technology did work), or if the technology does work, you are going to run out of money (and I think that's what happened with CTI. If they worked

better, longer, they probably could have raised enough money). The third risk is that people are going to stop working together and start fighting each other and that I think was ultimately what got Cyto. There was a breakdown of team work and the company became fractionalized and that was really too bad.

I was in charge of R&D. It was the normal things you do as a manager. To try to build alignment, make sure that everybody had a stake in the company and everybody was excited. It's just good management. It is probably more difficult maintaining alignment in 200 people but it is certainly not impossible and that's clearly the responsibility of the management of the company. Clearly one of the big decisions you have to make is to identify management who are able to achieve those goals. So, you want to choose management not on the basis of technology but on the overall skills.

Technical Head/Management: CTI was an interesting place because there was a group doing standard device work, like making catheters and containers that were going to allow us to test media while keeping the device sterile. People knew how to do that. Nick Warner was trying to do that. Then there was a whole bunch of molecular biologists. They transfected BHK cells to deliver something like NGF or CNTF or BNTF. They knew had to transfect cells, because they used PC12 to deliver dopamine. And then we had a group that knew how to make hollow fiber membranes. When you brought all these groups together, you had some interesting problems.

Management: It is the responsibility of the management to ensure that the tools are in place; that you are capable of bridging the gap between the wet guys and the dry guys. To understand that you cannot use a reagent to make a polymer that would kill the cells. You need to have people who train each other. If you do it properly it is a very gratifying experience. You can build in a leadership that turns an organization into something spectacular. In the early days of CTI there was an excitement and camaraderie, and a result that was spectacular. That was when there were 20-22 people. The company had to grow but the

management had to ensure that the culture remained. It's not easy. Management was fine and had plenty of experience managing people and did a good job.

3. **How did you make sure organizational learning was happening?**

Management: The way you keep people excited in an environment which is lots of work, filled with lots of ups and downs, is you make sure there is personal growth. You sit in with folks and you plan your program, you plan your projects, you plan what's going to happen. And at the same point in time, you take in where possible, you promote from within, you make sure you grow people and make sure that there is cross fertilization. In CTI in the early days, nobody had a bigger office than anybody else. Once a week one of the team leaders, scientists and technicians came and talked to everybody else about what they were doing. It didn't matter whether it was a new histology or a spectacular breakthrough in transplant physiology. They had ownership. There's a limit to what you can do there because there is information that is sometimes difficult for some people to digest in a manner that keeps it in perspective. Wherever possible you make sure that there is communication and there is cross-fertilization, because some of the best ideas come from the strangest source. When people do something they do so because they are energized as a part of a team. They understand that even if you are doing glass washing, if you don't do your job right you can bring the company to its knees. When people understand what they are doing is important they do a better job.

4. **Do you feel the CTI's problems came because CTI grew too fast?**

Engineer: Yes, I do. I was the 17th employee. I finished up school while I was at working there. I got my Engineering BS and ME at Northeastern while I was there. I was actually promoted to eventually manage the Engineering Department which was part of the reason I left because I felt that was outrageous growth. And I wanted to confirm my abilities somewhere else. They asked for me to come back and I did. When I

came back I reported to the manager. When I was there I was at least on a dozen patents. I am not sure how sound all of them are, but some of them are pretty interesting.

Technical Head/Management: When I left, we had hired 100 people, our product was in the clinic, had been successful in proof of principle trial and we had raised a 100 million dollars. The growth rate was pretty good. What limits growth rate is how much money you raise, because every person is going to cost you between 200,000 to 300,000 dollars a year. Your ability to successfully raise funds is ultimately rate limiting. And to raise enough money to support a hundred people of the caliber Cyto had, was pretty good. You can't have too few people to do the job, because you are scared to change the culture. You just have to hire able management.

II. Technological challenges faced by CTI

Snapshot of comments:

Life Scientist: "We did have very encouraging data on monkeys and rats, but then they were monkeys and rats. I have cured lots of rats and monkeys. There is a very grateful population of small animals out there. It's just very difficult to take technologies like that and scale them."

"This novel technique was successfully tested for the in vitro and in vivo delivery of various therapeutic agents, including neurotrophic factors, neurotransmitters and hormones. Phase I clinical trials were reported for the treatment of amyotrophic lateral sclerosis (ALS) and chronic cancer pain." Curr Opin Mol Ther. 1999 Oct; 1(5):645-50. Technology evaluation: CRIB (CNTF delivery) CytoTherapeutics Inc.

1. **Was the technology at a very early stage in its development?**

Life Scientist: If you look at everything that was ever done, you will find the encapsulated cells survived really, really well when they were in a fluid filled setting. Yet you never find a single piece of data showing any cell type in a capsule survives for a long time in implant. We did marketing analysis. Patients and surgeons and clinicians believed that if you get a year and a half for the implant to stay, it was probably an okay interval. If you put the PC12 in a lateral ventricle they would survive a long, long time, (but the drug would dilute). The problem with the technology was when you take those hollow fiber membranes and put them in a tissue they would become clogged, and the cells would die. Cell survival became very poor. The company was never willing to step back and say "We need to take a handful of biologists and engineers and figure out how to put a device that we can put into a tissue." We never did that. We were impatient and never willing to take a step back. Then we began looking into indications for which you could use a fluid filled space. So, you deliver neurotrophic factors in the ventricle, which would be so diluted that it would be so ineffective that it won't treat anything! I believe that you can design fibers that work in tissue and you can make products out of it. Developing materials that cells can grow into and fibers can grow into.

Implanted cells that released CNTF in monkey models of HD went to the clinic. Patrick Aebischer and his group in Switzerland have been running clinical trials on it for several years now. The same group is trying to develop GDNF in PD patients. People are still trying it. CTI became very focused on a couple of things that distracted it. It is not a technical challenge getting into humans. The brain volume from rat to monkey is 60 fold, but from monkeys to humans is not that big an issue. In the HD models, for example, we would implant cells that would release CNTF into the brain. Go back into the same brain area in 2-3 weeks and inject toxins that would produce neuronal pathology that would mimic HD disease. You would see the CNTF release from the capsule had decreased the volume by 50% in monkeys. The effect would be even greater in rodents. In PD you inject MPTP in monkeys. They lose striatal catecholamines and

develop motor impairment. You implant PC12 cellular devices into them and sometimes their motor functions would improve dramatically. The logic for something like that would simply become, "Here's a disease you can diagnose genetically, before the onset of symptoms." and that made it a logical disorder to go after from a neuroprotective point of view. If you can plant these cells releasing the factor maybe you can slow the slope of the progression of the disease.

Life Scientist: The fact that PC12 cells were being used could have made the company vulnerable, as a competitor or a critique could have kicked a row over the fact that PC12 cells are essentially tumorigenic in origin. However, the beauty of the technology lay in the fact that the treatment could be terminated without the introduction of a killer gene. The capsule was inserted into the recipient's brain by stereotactic surgery and later on removed by the same procedure.

The hollow fiber was designed to offer an immuno-isolating environment, inside and outside. The hollow fiber was designed such that only the essential secreants would diffuse into the host tissue but there will be no other exchange or contact between the host tissue and the encapsulated cells within the implant. However, it was very difficult to prove that the porosity of the capsule was extrusive to both immunogenic substances as well as immune cells.

The encapsulated cell replacement can be visualized as a cluster of cells surrounded by porous polymer scaffold. There were some cells in the interior of the scaffold and other more towards the exterior. This set up a nutrient gradient as well as a microenvironment gradient inside the capsule. The cells in the interior were naturally starved and stressed, while those towards the outside were healthier in comparison. The metabolites were found to undergo change depending on the time spent sequestering out of the capsule. The problem of the implant secreting the necessary compound, in the desired concentration, could be solved more appropriately by a cell biologist than a molecular biologist. (However, the firm to

often decked for the investors. In spite of the need for a cell biologist, a molecular biologist was hired. The real solution would have been to hire a cell biologist and outsource the molecular biology.)[73]

In spite of the technical challenges, the technology was sound. As a therapeutic device it had tested well in rats and primates and in order to check the manufacturability of the product the technology had to be brought into a commercial concern, so it was neither wrong nor early to form a company around the technology.

Technical Head/Management: Our problems were more demonstrating efficacy. Often times the CNS physiologists' other choice was to insert a Medtronic pump into the patients. The rate of infection was high so they really didn't want to do that. So, while that played to our advantage, at some point, someone was going to do something more clever. Personally I don't see cell therapy moving forward as a means of delivering drug. I just don't think you can get enough cells or implants to deliver the amount of drug necessary. This was the problem for the artificial pancreas project. You had to be in a position that you could deliver a "sheep t-h-i-s big" and it had to be inserted in a place where it would not get engulfed by other tissue. It wasn't feasible, to deliver that many Islet cells. The same was true for ALS, PD and pain. It was very hard to get enough cells to deliver a meaningful therapeutic dose. The other problem is a dose control hurdle. At one point we discussed the possibility of using these cell lines to treat depression. To have them secrete serotonin. These patients titrate their dose up and down, go from one serotonin receptor uptake to another. There are a lot of doctor manipulations with the dose, none of which is possible with a cellular implant. The same is true for Parkinson's. You don't have dose control the same way as you have in traditional medicine and that is a problem with both PD and pain. PD patients will be on L-dopa and L-dopa agonists as well, not clean cases of PD. The model is not a bad model but not a great model: the MPTP primate is not quite real Parkinson's. There is always an issue.

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[73] Quote repeated from before because of pertinent context.

Management: We had intellectual property but the technology was too early and very complicated. NGF, BDNF were being isolated, purified and how they worked, were beginning to be understood. It was exciting to see what these compounds were doing in vitro to neurons. You couldn't deliver these across the blood brain barrier. So if you could deliver them site specifically then de novo synthesis would be important. Therefore, genetically modify cells with a gene-promoter system to produce these proteins and hopefully that will have a benefit. The pharmacology was a nightmare to understand. Pharmacodynamics[74] was impossible. Firstly, since you are in the brain. Secondly, microtitration techniques available were very crude at the time and they still are. You have substances that are to be used in micromolar concentrations and you have very crude methods of estimation. They had to make serial sections over time, which were expensive, very complex and full of all kinds of measurement error. Looking at any kind of dose response was practically impossible.

2. **Any manufacturing challenges encountered by CTI?**

Snapshot of comments:

Engineer: "We didn't have a successful product that worked every time and we certainly had no business to be in manufacturing."

"Instead of stuffing the cake with the frosting, we could have frosted the cake. Nobody took a step back and looked at that."

Life Scientist: You are basically taking isolated cells into your facility and then encapsulating them. Difficulties include developing a process that ensures sterility through out. It required building an entirely

[74] Understanding the drug metabolism

separate facility, including the surgical and tissue culture technologies involved. That was a significantly expensive undertaking.

One thing CTI was able to do was, they were able to make clean viable encapsulated cell products. These products could be kept in culture for a couple of weeks. They were not cryo-preserved. They could be kept encapsulated for a few weeks. So in some sense you had to be on call because of the unpredictability in demand, they would have to establish herds of animals in stock. That was one of the reasons for having Astra as a partner with deep pockets. It was doable but for many other reasons it never worked. The products went as far as Phase II clinical trial.

Life Scientist: I believe that manufacturing was expected to be a relatively small scale for quite a while -- - based upon the design of the manufacturing facility. Looking for alternative product to manufacture would make sense in terms of generating a high return on assets for the company.

Engineer: [75]Whenever you are making widgets you need to make it all the same. You can't have things work one time and not the next. They need to work every time. You need to have a process. When I got there they never had anything like that. And it was really not my expertise but we started making membranes reproducibly, understanding the permeability, understanding the morphology of the membrane wall. We could make all kinds of membranes. We were able to control that very closely. We made a lot of different nozzles to impart characteristics to permeable and semi-permeable membrane. Challenges included keeping cells alive in the device, allowing nutrients through the membrane to keep the cells alive and allowing them to release e.g. the pain device had to release enkephalins and catecholamines. There were problems that the body would see it as a foreign implant and macrophages would surround the device affecting the release. We overcame some of those hurdles but a lot of them would recur sometimes which was frustrating. I made a machine that spat out the product out on an

[75] Repeated for context

assembly line fashion called the stop start machine. Basically a co-extrusion, the same way they make jelly donuts. It was basically making hollow noodles and what we would do is stop the flow, seal the ends and cut it off. It was making these discrete capsules quite fast and quite consistently. Prior to building the machine it was quite laborious and technique dependant. Technicians would take the hollow noodle and they would block one end and fill it up with cells, and some media for the cells to live in and then cap the other end. And often times the seal would go onto a wet surface. The sinoacrylide wouldn't take it well. The machine solved all the problems. But in the end I don't think we stopped the flow of cells sharp enough to guarantee that the good seal was good enough. It was pretty hard to standardize the technology. This is still pretty much year 1 and year 2. We were making a lot of progress.

At about 150, there were a lot of QA-QC people that were putting breaking on the science too early and demanding documentation and so everyone was paper pushing. We didn't have a successful product that worked every time and we certainly had no business to be in manufacturing. There were a lot of layers that slowed things down. I think there was also some lack of focus. I still think we might have accomplished if things hadn't changed later on.

People were throwing in too much money into the scale up. We were scaling up to do something than we were not ready to do. The product was never really designed, nor specified, but we were all set to manufacture. We went too far ahead, too early.

Technical Head/Management: You have a whole manufacturing issue. How do you know that the product you are making on Monday is the same product as you are making on Wednesday? So you have to device a set of specifications that allow you to specify quality (in this case, release specifications). Those are well worked out for traditional drugs and biologics but they are completely not worked out for anything that is cellular. You have to test for a number of sterility issues which are straightforward. But then you have to test for potency assay, which says it meets the threshold. You have to figure out

something that the cells secrete, measure that and use that as a surrogate. CTI's manufacturing issues were that they had to take Bovine Adrenal Chromaffin cells. Harvest those from calves, demonstrate they were sterile, come up with release specifications that they were potent, put them in a capsule, seal the capsule, come up with a release specification that the capsules were okay and they secreted reasonable amounts of norepinephrine and enkephalin, that they were sterile and they had a shelf life that could be used. These were all big challenges of one kind or another, which the company eventually overcame to have a product that they could make reproducibly and test. This means that the company had reasonable quality control, testing and quality assurance program. The company was definitely able to do that.

3. **How was CTI planning to market a product whose manufacturing costs were so high?**

Engineer: "People assumed they would deal with it later on."

Engineer: Costs were high to make these things. In the beginning we didn't worry about the cost of the product. We assumed we could get the product to cost somewhere in between reasonably. We threw a lot of money at it. Everybody thought including the marketing people, that if we could halt or reverse a disease, it could shift all the normal paradigms even associated with costing medical stuff.

Technical Head/Management: Manufacturing was not expensive relative to the benefits received by the patients. If your product delivers benefits against PD, AD or HD, then the cost of keeping the patient one year in treatment is already up in 50-60K a year to 150K year for AD, so you can afford a fairly expensive product.

Technical Head/Management: The cost of goods sold for anything like this is astronomical. If you are doing anything with cell therapy especially using primary cells, whether that's bovine adrenaline chromaffin cells, or human beta cells, you are going to have pretty enormous costs and limited shelf life.

When you make a dose of erythropoietin, you make it in a batch of zillion. It sits on the shelf for a long period in time. You test 10%. Every time you do a lot of these pain devices, you have to sacrifice in order to test. And if you have to demonstrate shelf life then you sacrifice them again. You have to be very, very sure that there is not a non-cellular way to do this. I design the best cellular implant that I put in the sub-arachnoid space and I deliver enough product, which by itself a stretch. As soon as somebody comes with a non- cellular solution that basically does the same thing that will be immediately cheaper to make, easier to test, there's a regulatory path associated with it already, you can get a 510K. Suppose my device is 5cm by 0.5mm and suppose someone has an elegant way of putting a pump that delivers as much agency as one wants, there's no sterility or infection issues, you can dial that in. All of a sudden they make it for $200 and charge $5000. And you make it for $2000 and have to charge $15000. You have a reasonable margin, but you can't get reimbursed for something like that. That's a big issue in cell therapy. You better be sure that there's a tremendous unmet medical need that can only be met by cell therapy. But this wasn't our problem.

4. **Did CTI encounter any issues with the FDA?**

Life Scientist: "CTI was way ahead of its time and problems came with that. Nobody was familiar; nobody knew what you had to test for. So you had to test for everything. Very elaborate tissue culture was required. You had to invent the tissue culture interface, which with manufacturing and the biological testing, was completely outrageous because it was new..... It was difficult regulatory environment to work because the FDA couldn't provide any guidance. It was just the time. There was a theoretical concern out there of inducing some global pandemic because of a retrovirus in your product.

More fundamentally at that time the FDA had gone from the attitude that a xenotransplant was a desirable thing because if something ever went wrong the body would reject it; to being completely paralyzed and unable to give any regulatory advice. Bovine Spongiform Encephalitis had cropped up and they just

didn't know how to handle the issue of a xenotransplant. So there were really no regulations and that instigated a cycle of biological testing that at the time was extraordinarily expensive. Per sample the cost was approximately $20,000-25,000 for biological testing. Therefore, cost of the full package became a very expensive process. Today it would cost $2000-3000 but at the time it was an extremely difficult process. I am not exact about the figures but it was very, very high. You had to test the cells and maintain the cells once they had been encapsulated for a certain length of time to ensure quality control. You had to develop a very rigorous sterile and controlled process of doing that which required a lot of monitoring.

Technical Head/Management: The FDA will regulate an implant containing cells and biomaterials in the drug regulation pathway. They require you to go through a process equivalent to what you have to go through with drugs. It involves many, many years and a couple of 100 million dollars in expenses. One of the problems CTI had, was that, other people were proposing to treat the same diseases with devices, particularly electro stimulators which go through a very different approval process that costs a great deal less. So even though both products provided equivalent risk to the patients and pretty much did the same thing for the patients, just by the nature of the regulation, the CTI product had a much more expensive regulatory pathway. These laws were written in 1962 for drugs, 1976 for devices tend to be obsolete and are very hard to change. A product that has to be fundamentally regulated by a very expensive pathway which may or may not be in competition with a device that is regulated by a much cheaper pathway sets up very high and real barriers.

Technical Head/Management: There are a number of things: if you are the first person to blaze the path, then you have to set guidelines for everything that you do. You have to set what the appropriate pre-clinical model is, what the appropriate toxicity model is, how this thing gets modulated. The FDA visited CytoTherapeutics. CTI petitioned the FDA for an export permit because they wanted to send some devices to Europe and that triggered an FDA visit. You are in the company one day, there's a knock on

the door. There are 2 people from the FDA to inspect the facility. At the end they filled out the 483. There were no major items on the 483 even though the inspection was relatively cold.

There is a class of autologous cell therapy products e.g. I take some cells from your body and use them elsewhere. Cartilage is a classical example. There was a time when FDA said they were not going to regulate autologous products. When the first of those products were ready to hit the market place FDA announced that they were going to regulate those as well and "here's the deadline". That caught a lot of people by surprise. These were things surgeons were doing all the time; they would take a cartilage from the ear and turn it into something. The only thing people were doing differently is taking a bunch of chondrocytes, place them in a scaffold and put them back in. Even autologous transplantation got to a point where you had to do a lot of testing. In autologous grafts you can at least make a 100 and test 10, and do all this testing that is pretty prohibitive. So, it has to be a situation where there is no other option.

5. **Did the product fail because implanting it in the patient's brain involved multiple surgeries?**

Life Scientist: The surgery was pretty straight forward. The procedure for inserting a device in the intrathecal space was comparable to 15-20 minutes of doing a spinal, which is a pretty simple procedure. Procedures for implantation to the brain would not have been unusual either, a standard neurosurgical procedure.

We thought that it was an advantage to remove the implant either if something went wrong or needed replenishment. It was easy with the ventricle but not when it was embedded in tissue. Looking back it is very hard to imagine that we were going to deliver Dopamine to the striatum by a single diffusion process in the brain. It had to be 3, 5, 10, 15 implants. It would be extremely costly. Every time, you penetrate the brain you have a 2-3% chance of a bleeding episode. It was difficult to do surgically as well.

Technical Head/Management: Clearly fewer implants the better. As for available treatments of PD particularly at that time, everybody would like to take a pill that would fix it, yet the benefits of surgery were tolerable. Basically you could justify a fairly expensive and complicated surgery because there was no alternative treatment. It all comes down to risk versus benefit and cost versus benefit.

Technical Head/Management: The neurosurgeons are already used to putting things in the brain. They are putting massive reservoirs in the brain to deliver chemotherapy and now electrodes in the brain to treat Parkinson's, with deep brain stimulation. These guys are used to all this. We did some nifty things like developing an interesting catheter, and even patented a kit for doing implantation. None of that was ground breaking per se, because that was more like standard device work. There were also safety issues. There's a small chance that you might hit a blood vessel and kill somebody.

5. **How much of reimbursement would a patient need to look for, for such a treatment?**

Life Scientist: A lot! There are limited numbers of neurosurgical centers in the State. It would depend on the number of devices that had to be implanted. If we had to manufacture multiple devices for a single person, it would have been extremely difficult to make any money. That was a significant issue but it wasn't a big deal. The issue was getting the product out. The very needy patients are going to be the ones you conduct safety trials on anyway. I think if you can get to that point, as you gather more and more encouraging data that is efficacious, I don't think you will have any problem enrolling patients regardless of what phase of the disease they were on.

Technical Head/Management: They never got to the stage of reimbursement because they never really got the FDA approval. You are just going to make sure that they are not going to be show stoppers. The assumption was always that if they got a product that was going to keep a PD patient out of the hospital, there weren't going to be any reimbursement issues. It was perhaps naïve of the people to assume that and

it might have been a problem but they never got there. What you have to show is that the cost/benefit ratio is justifiable and that we can make the chase for the reimbursement of our product because though the costs maybe high, the benefits are certainly worth the cost.

6. **If CTI did not market a product why do you say the technology worked when there was no product?**

Technical Head/Management: When I left CTI had finished construction on its clinical manufacturing plant, but CTI was still manufacturing products for animal studies. I think most of the assessment said that had there been enough time and money for development, it would have been a successful product. There were scientific challenges that could have been worked through. Development of such a product is a complicated undertaking that ranges from everything from consistency, to understanding mechanism of action, to very general things.

III. Technology strategy

Snapshot of comments:

Life Scientist: "You can always look back and pull out some data that was encouraging there. But pain was chosen because there was a corporate partner. Somebody was willing to foot the bill, as simple as that! ..... Nobody wanted to sponsor PD!" "Pain was attractive because it was a single device."

Technical Head/Management: "The pain Phase II trial was not powered enough. It was too small. It was conducted by our partner. ..... It is not clear if the technology would have ever worked in Pain given the amount of drug we would need to deliver. But there could have been one or two indications where we would have been able to deliver. May be that would have been ALS."

Technical Head/Management: "They thought, all things being equal, the complexity of the product, the risk-benefit ratios that the pain device would the easiest to get to the market. And that probably was a sensible strategy."

1. **Why was CTI changing directions from pursuing a solution for PD to Chronic Pain and then to Stem Cells Inc.?**

Life Scientist: It is a very long story. In the beginning two indications were chosen: diabetes and PD. Insulin and dopamine were molecules you knew would work if you could figure out a way to deliver them easily. Encapsulated islet cells from pigs turned out to be an engineering problem which was very difficult to overcome at the time. Delivering dopamine to the Striatum for PD sort of got lost because the company became enamored with delivering growth factors for virtually any indication. The strategic decision the company made in those days, while not having any access to NGF, GDNF, BDNF or CNTF, was pursuing programs of delivering those molecules. We ended up in a situation where you are trying to deliver molecules with unknown efficacy using unproven delivery sources and you had neither intellectual property nor access to the growth factors. That is why the relationship with Genentech was so critical, because we could at least get access to one of those factors.

Was the company a growth factor company? Was it a drug delivery company? Was it a CNS company? Was it a gene therapy company? We could never really define ourselves particularly well and we continued to lose focus because of it. Very early on the company was unable to define itself. You get into a situation when you have make a lot of promises of clinical trials, yet with a lack of scientific horsepower to address the fundamental questions that need to be addressed and you just sort of keep spiraling downwards until it falls apart.

I think choosing chronic pain as an indication was fundamentally a mistake. If you look at the indication, clinical trials are very difficult to do because there is an extremely high placebo effect. The clinical trials consist of a very large number of people, and are very, very expensive to do. If you do a literature search, you will never find a single piece of data that the chromaffin cells implanted in an intrathecal space are efficacious. In fact you will find the opposite. Over the last several years, individuals have published a lot of data showing that, in fact, they don't work. The real question was whether or not the product was efficacious or not to begin with. Coupled with that was a difficult clinical trial and the merger of CTI with Stem Cells Inc. With the resulting neglect of the encapsulation program by the senior management, the project was doomed; it never had a chance.

The target was chronic pain which by definition is a very heterogeneous population. It is a very needy population and so it is very difficult. You can always look back and convince yourself of some data, but pain was chosen because there was a corporate partner. Somebody was willing to foot the bill, as simple as that. When we were implanting cells with NGF as a treatment for Alzheimer's, that was because there was a partnership with Genentech. It wasn't nearly as profitable as the relationship with Astra but the choice of choosing pain was based on having a corporate partner. It was simply a corporate deal. It does shift the focus of the scientists.

Nobody wanted to sponsor PD! Amgen at the time owned GDNF; they believed at the time they could use a pump to deliver it into the ventricles. The deal with Genentech was good for Genentech but not for CTI, partly for the senior management support from Genentech. CTI couldn't get sufficient large animal data because of lack of support. It required significant effort. We had never developed a device that would be suitable to implant into brain tissue. We could at least have found out whether the technology was workable or not. Unfortunately small companies run out of business, not because technology gets them but because they run out of time; investors become impatient. The clinical program is way too long.

Pain was attractive because it was a single device. It is very hard to imagine that you are going to deliver Dopamine to the striatum by a single diffusion process in the brain. It had to be 3, 5, 10, 15. It would be extremely costly. Every time you penetrate the brain you have a 2-3% chance of a bleeding episode. It was difficult to do surgically as well.

Engineer: A lot of decisions between pain and PD were driven by the CEO. I think he was somewhat autonomous in the way he chose these things. With PD, we initially had a lot of success and then we stuttered and stalled a bit. The story with pain was that the CEO had read a paper of Jackie Saegan and asked her to come and reproduce her work. He was impressed by it and saw huge opportunity there. That is just my perspective and I'm not sure if I saw it all right. We did the same experiment but we did not come to the same conclusions. So it was dead before it began. A lot of people in the company believed it. As an engineer, I didn't understand; I left it to the scientists.

Technical Head/Management: Ultimately the first product they brought to clinical trial was the pain control product. I believe they chose that because it was not implanted in the brain but in the CNS, a less complicated surgery, in the subdural cavity in the spine. They went into FDA trial with 100 patients; they obtained clear signs of benefit. But they didn't reach statistical significance in the first trial and they didn't have money for the second trial. Money is always the limiting factor in development. But in this case for a randomized double blinded control study for an implant in the CNS, you needed a large number of patients if you wanted to see something come out of it and they never had the resources for that. For a drug to come to market it would typically be evaluated in 2000 - 4000 patients, getting that many patients for implants of a device. The cost of which could be at least a million dollars per person and the company didn't have that kind of money.

Nobody is going to fund the platform technology in the clinic. You have to pick one particular disease, and one particular application. The technology for the PD and pain implant was quite similar. They chose

pain because they thought it would be easier to get to the market first and then it would be easier to fund the second one. And that probably was a sensible strategy. If you didn't have money to do a clinical trial on one, you won't have money for more than one.

PD is a disease that is totally characterized. It is a disease very difficult to show improvement because the patients have good days and bad days. Besides, the patient population is not a pure PD population. They have already been on L-dopa. If you see the literature on cell transplantation encapsulated or unencapsulated, dopaminergic CNS cells, whether they came from embryonic or wherever, there was an awful lot of placebo effect and confusion. It was only when people ran very large scale randomized clinical trials that they were able to sort out that these things weren't really improving patients, indicating there's a large placebo effect in these kinds of trials. If your product works ¾ of the time, you have to run a very big trial to demonstrate effectiveness. That might basically have argued against the choice of PD for a platform technology.

2. **And then CTI became Stem Cells?**

Technical Head/Management: We had a number of corporate arrangements. Astra Pain control was a subsidiary of big Astra. At that time Astra had the world's best selling drug. They made a lot of money from lidocaine, which was off patent. This was before the merger with Zeneca. They were really high-fliers. The guys who were running Astra Pain control, which was 7-8 companies, were stem cells guys, who really liked stem cell work and stem cell engineering. They were already pre-disposed to like something like this. They were looking for something off the beaten path and sexy and that treat end-stage cancer patients as well. It was mostly those guys who were thinking at some point they would make a company. You had a confluence of events with CTI as a leader in the development part: product development, manufacturing and QC. No one else was close to have filed an IND and had clinical data. And, you had Astra, who really wanted to do cell engineering, cell therapy, and was interested in pain and

looking for the next big thing. The right place at the right time, together. There was another partner interested in the product which helps these issues. Real alignment of the stars....

There was a lot going on in the company. There were certainly people in the company who wanted to make it a stem cell company, thinking that was the future. I left before the merger with Stem Cells Inc. They did this merger with Stem Cells Inc. pretty much after that the pain data showed no efficacy and Astra pulled out. And you could see that happening a mile away. They didn't empower the trial enough. And the people in the company were all people from Stem Cells. A company is basically 100% people. They are doing a clinical trial on pain; they are hemorrhaging people because people are leaving; and Astra pulls out. So they lose that part of the project. The CEO of the company is now the CEO of Stem Cells Inc. What does he do? The partner for encapsulated pain has pulled out; so this doesn't work. So he fired everybody that was in the original CTI and contracted CTI out to just Stem Cells. The metamorphosis was complete. Fortunately I was gone by the time that happened.

3. **Was targeting too many disease areas a mistake that CTI made? Should the company have been more focused?**

Snapshot of comments:

Life Scientist: "The sex appeal of delivering GDNF, the brand new growth factor, versus the mundane delivery of catecholamines....."

"Was the company a growth factor company? Was it a drug delivery company? Was it a CNS company? Was it a gene therapy company? We could never really define ourselves particularly well and we continued to lose focus because of it. Very early on the company was unable to define itself."

"If CTI focused on a single disease such as PD or HD they would have pushed the science further and generated a lot of value in terms of the science. ... In terms of raising money it would have been harder for us to raise money with a few areas of focus."

Technical Head/Management: "How many is many? In a company that is not making any money you have to ask what is going to drive value to the investors. And that is progression in the clinic. You have to have more than one. I think we had 2 clinical projects and 15 pre-clinical projects. We held on to too many pre-clinical projects."

Management: "Our approach was the correct approach... Great technology can easily be destroyed by ineffective senior management."

Life Scientist: We never spent a lot of time playing around PC12 cells; only the first couple of years in the 1990s. Next, we had some people come on board who wanted to make the growth factor work. It was too much. We were so unfocused. We were delivering drug factors and we had this neural stem cells stuff on the side. If we had just hunkered down and said we are going to figure out a way of delivering dopamine to the striatum of Parkinson's patients, we could have gotten a product out there I think. But we became scattered. And when that happens you have factions develop within a company and it becomes a very unfortunate environment. The sex appeal of delivering GDNF, the brand new growth factor, versus, the mundane delivery of catecholamines....

Technical Head/Management: There were probably too many projects overall. And not enough attention and resources were being paid to the development of these projects. How many is many? In a company that is not making any money you have to ask what is going to drive value to the investors. And that is progression in the clinic. You have to have more than one. I think we had two clinical projects and fifteen pre-clinical projects. We held on to too many pre-clinical projects. We did licensing some out. But

then when your clinical shows lack of efficacy, you are pretty much dead. And that's what happened with the company.

In today's world it's products, products, and products. People are very products focused. Fifteen years ago there was not so much product focus. CTI had a lot of good people, some of whom had come because they wanted to work on Alzheimer's disease. They wanted to do pain, depression, stem cells, a lot of things. People who did research in the company liked to do a lot of projects. There were some people who wanted to make encapsulated products in the very early days. When I got there, there were few people and the company was going to make an encapsulated device for Parkinson's and an encapsulated device for diabetes and that was it. By the time I left, diabetes was gone, PD was not the main product, pain was. ALS was probably the 2nd biggest product and the company was focusing more on delivering growth products. These were technological feasibility driven decisions. ALS was a great project because it would have been an orphan drug. The only problem with working with growth factors was that you didn't own them. Somebody else owns them. Regeneron owns them, or Genentech owns them. That was a hurdle to business development. You had to do a license deal which got expensive. And so, the knock on the technology was we didn't have the license to practice. We finally crafted a deal with Genentech where we got the rights to use some of their growth factors for encapsulated cell therapy. In the early days of CTI people took the attitude that if you have the capability to deliver these agents that people will line up outside to want to do a deal with you, which never happened.

Management: Our approach was the correct approach. The approach that you take is that you go in with a base platform technology and you focus on a single or a couple of applications. Sometimes you have more than a couple of applications because there are surprises that come along. And in a venturing environment, you need to be able to understand that position to be able to show progress in the company. You have to make sure there is enough symbiosis in the programs and that they do not cannibalize each other's resources. So you go after a couple of disease states: one which is acute, one which is chronic, one

for which the cell type is absolutely well known, and another one for whom the regulatory pathway is very, very short, because it is a horrible debilitating disease. You need to have multiple programs but not too many. The other thing you need to do in the early days is to set up a series of principle exploratory experiments. And then you sit down and take about 10%, maybe a little less, and you say we need to build an intellectual property portfolio. Your IP is what you live and die by. You may well offer licenses.

We focused on diabetes and PD. I needed a quick near term program to give me some very spectacular clinical results. So I went to Illinois and licensed technology for pre-product pain, as a spinal implant. The program had a lot of excitement and preclinical results that helped raise money. That was the first to go through pre-clinical and then went through phase II clinical studies. Eventually we took out the program, because the placebo effect of pain required a very large clinical study. They needed a corporate partner to make decisions. The partner decided that they weren't interested any more since the number of patients was small. The managing partner had an inclination towards stem cells and the metamorphosed the company. Great technology can easily be destroyed by ineffective senior management.

4. **When did they realize that it was too early to commercialize an encapsulated cell therapy product?**

Snapshots of comments:

Management: "Some of them never felt that the technology was too early to be commercialized. The problem was that the results were spectacular, and promising in rat models and primates. ..... They published in Science, Nature and PNAS."

"The Capital market was interested in investing in promising science. So we raised a lot of money based on excellent science. A commercially viable product was very bleak."

"If the product was given to Pfizer with all the resources Pfizer has, I don't believe that Pfizer would have succeeded either."

Management: Some of them never felt that the technology was too early to be commercialized. The problem was that the results were spectacular, and promising in rat models and primates. An immortalized beta cell that doesn't get transformed and lived for 4-5 years presented a huge market with favorable reimbursement. Shimone Esrai had the beta cells, though their output would decline after 6-7 months, but it could be improved upon. The CTI scientists would meet with pharmacologists from pharmaceutical companies and show them brain sections from great animal models, showing sprouting of neurons. They also had terrific monkey behavioral data, even though they were relatively few in number, as happens in primate study. The results were published in Science, Nature and PNAS.

Commercial viability of making the membrane technology work (250-500 upper and lower control limit on the manufacturability of the membrane was a technical challenge), the cell technology work, and the pharmacology work in sync, was very, very challenging. The total plasmid experience world wide was less than 6 months. Gene promoter systems used the herpes simplex tyrosine kinase vector system, which was extremely new. To know the long term consistency of production we had to measure the output in vitro, in vivo and in the ventricle. From the ventricle you could go in very different directions. How many centimeters further from the site of the device would you measure impact? The answers required an enormous number of experiments that CTI wasn't equipped to do at the time.

The Capital market was interested in investing in promising science. So we raised a lot of money based on excellent science. A commercially viable product was very bleak. Every experiment teaches you a lot. For those who were working on it every day, it raised a lot of questions but also eliminated questions, and it encouraged the scientists to feel that they were getting closer and closer to a commercially viable

product. If the product was given to Pfizer with all the resources Pfizer has, I don't believe that Pfizer would have succeeded either. The technology was too immature to have made it a commercial success; the technological challenges were too daunting; too many pieces needed to be developed too quickly to make it work.

5. **CTI spun off Modex, Neurotech, and a number of companies. Were the spin-offs done so that the company could focus?**

Snapshot of comments:

Life Scientist: "CTI's immuno-isolation was all about capsules. If capsules could not be made to work, and if immuno-isolation was not a critically important issue, then CTI's competitive edge would be eroded. Strategies for solving problems by divesting diabetes and then subsequently for acquiring other "partners" sounds like a good strategy -- if the time line, the research creativity, and the investor confidence is there."

Life Scientist: No. The clinical research needed to be conducted in Switzerland and so the European Chapter was started. The diabetes division was spun out as Diacrine stationed in California. Stem cells were seen as a smart way to get around the concerns and costs of working with tumor cell lines and with primary cell cultures. Validation of cells and of cell lines is costly. QC/QA is costly, and if the cycle time for the required tests is rapid, then this adds a burden within the manufacturing place and through the distribution channel.

Engineer: It was done for complicated reasons. Patrick Aebischer ended up quitting the board. It is never a good thing when the founding scientist ends up quitting the board. Aebischer moved back to Switzerland. He took intellectual property and licenses around the encapsulation technology and

therapeutics from CTI and spun it off as Modex. Eventually it got bought out. There were two principal areas of focus: Type II Diabetes and an artificial skin product. They are currently selling the latter while the former never became a successful commercial project. Stem Cells wasn't a spin-off, it was something that Cyto morphed into before it took off to California. We had a diabetologist, Orion Hegre, who was spun off with Neurocrine. It wasn't a strategic spin off for the company but an individual decision.

IV. Did the investors have an impact on the firm's decisions?

Snapshot of comments:

Management: "In order to get more money you always have to demonstrate commercial viability and scientific promise. That was true in CTI."

"If CTI focused on a single disease such as PD or HD they would have pushed the science further and generated a lot of value in terms of the science. ..... In terms of raising money it would have been harder for us to raise money with a few areas of focus."

Management: "The VCs as an investment base tend to be basically impatient people. They want a home run and it is in disconnect with what is necessary to develop the product."

1. **Were there any pressures from the investors which forced frequent changes in technology strategy?**

Management: A big part of working in a biotech company is and was to deliver results that will justify further investment. That's true in any organization. Even in a large pharmaceutical company if your experiments don't show progress you won't get funding. In public markets the quality of the people

evaluating the science is different. In order to get more money you always have to demonstrate commercial viability and scientific promise. That was true in CTI.

Terrific science! The fact that the public market were willing to invest, moved the knowledge forward but the commercial viability turned out to be not very high in hindsight. There are lots of equally risky technology that have been invested in that have paid off, and then there are those that haven't because the science is really difficult.

Drug development is really hard for pharmaceutical companies, and more so for smaller companies. The success ratio for biotech companies is much lower than it is for pharmaceutical companies, even though they have much more pressure to raise money on them. Biotech often had very a narrow therapeutic area of focus or had a very narrow technology focus, only then can you be deep enough to be successful. You pick a very narrow area and then you really exploit it. Then you have to be really lucky. Even if you do all that, the chances of success are really low.

If CTI focused on a single disease such as PD or HD they would have pushed the science further and generated a lot of value in terms of the science. With a limited amount of resources you can't do a lot of things as well as you can do one thing. In terms of raising money, it would have been harder for us to raise money with a few areas of focus[76].

From the investor side it is very risky. Total returns on biotech aren't that good. A lot of people probably haven't made a lot of money. From a societal perspective, the science is very valuable and it is great when the public market is willing to back the science. Quality of work is in a commercial R&D laboratory is pretty high, and is very efficient compared to investment you get at NIH, for example. From a societal

[76] Repeated for context

perspective it is valuable but from an individual investor's perspective the returns aren't great. Collectively, the world's a better place with these investments.

Management: One curse of cell therapy is that the milestones that were necessary to get a product to a market were significant. But the benefit to medical science and to the company for cracking a cell therapy will be extraordinary because it will be revolutionary. The VCs as an investment base tend to be basically impatient people; they want 10X in 3 years. They want a home run and it is in disconnect with what is necessary to develop the product. So, what we are implementing now is a series of tools and methods where we try and to bring the needs for technology development closer to our sources of funding and our methods of obtaining resources. You have to be creative. There is a broad spectrum of VCs. There are other methodologies of obtaining funds. There is some near term product that you can pull off. And when you choose a senior manager that person has to be able to do this.

2. **Is there a solution to keeping investors happy and giving the science the time to develop?**

Technical Head/Management: It is your clinical progress and clinical efficacy. The focus was very wide. If you wanted to have a development company, we could have had a development company and had 3 things in the clinic. Certainly there was an element in the company that was focused on publications. Part of the management of the company wanted their publications too, to get their name out. And pre-clinical publications are not unimportant. They are important. To keep the investors interested you have to show you are developing a product and that has more value than basic research and you are making clinical progress and show efficacy in the clinic. If we could show efficacy in the clinic the investors would have been really happy. But you have to have enough money to get there. The company went public on pre-clinical data both in PD and diabetes, which is unheard off right now. It was much more common when the company went public. If you demonstrate you have the corporate partner and you have clinical efficacy, then your stock price rises. Then you can do a number of subsequent offerings

there to get money into the company, by selling stock of the company. Also when you show efficacy on phase I/II clinical trial, you are going to attract a partner and they are going to pay. That's exactly what happened. In pain we committed to making a full blown development program out of pain. We took a chunk of company resources and turned them into development people. We did this. We filed an IND and we had first rate regulatory, first rate clinical, and we got into a phase I trial in the US in end-stage cancer patients and that attracted Astra. Nothing in the pre-clinical pipeline attracted Astra. And people who wanted to do cell therapy saw that here is one partner that could develop a cell therapy product. And in my mind you generate value with clinical development. Either you generate share price, or partner interest, or both.

Management: I don't have the answer. What better companies do is that they are more patient. They realize that when you are doing science that has not been done before it is unpredictable. So, while they are patient they also make fewer investments. Some companies are better than others.

Management: As we got ready to go public, we made the decision to bring in individuals who had brass ring reputation and some of those individuals were unable to make this transition (from big company to small company). They had not been in those roles. At that time in history, very senior people, who had been in Wall Street and had the reputation of a white knight, often did not have the ability to run a small company.

There are a handful of people now who have taken cell therapy companies from start to finish. When we go in front of Wall Street, when we go in front of VCs, our pedigree tells them that we know all the tricks and all the steps necessary to put together an interdisciplinary organization. It also suggests that we make our mistakes on someone else's nickel. We all make mistakes and we learn from our mistakes. There are only 15 or 20 good cell therapy/hybrid device guys in the States.

3. **If everybody perceived the need to remain focused in the face of challenges, then why was it so hard?**

Technical Head/Management: I can tell you what doesn't work. What doesn't work is trying to please everybody in a company like that. People want to do stem cells, people want to do molecular biology, pain, ophthalmic, PD and the scientific founder here wants to do that, the scientific founder there wants to do that. You can't please all these people. At the end of the day it is the CEO who has to make the tough decisions. He has to say that this is the development company. We are going to work on two development projects and we are going to have this amount of money to do everything else. And if he makes the wrong decision, he loses his job. So the board prevents him from doing so. The CEO dictates what gets done, and what doesn't get done and the CEO dictates the culture of the company. And culture is 99% dictated by the CEO and CTI was no exception. The CEO has to be more or less a maniac to be successful and hold people's feet to the fire on development timelines and nothing else. It is not the norm that CEOs change all the time, sometimes it happens. CTI was not on its founding CEO when it went public. Different VCs have different views on that. The founding funding VC for CTI was Mayfield, who strongly believed that the CEO of a biotech company should be a Doc. This was their model. There are others who believe the CEO should be a business guy. Now who is right there, who knows? Every time you change the CEO you are putting the firm at a great risk, because it is going to be a different company. CTI was a different company when Mark Levine was the CEO than when Seth Rudnick was the CEO. That was a fact. They are both good guys but it was a very different company between the two of them.

V. Lessons Learnt from CTI

Snapshot of comments:

Life Scientist: "Maybe at the end of the day, you found out that the technology could not be made to work, but that's preferable to the company going out of business for all the wrong reasons."

Life Scientist: "If you adopt a strategy not to cure everybody with a xenogenic product, you could still go back to the interim step and could probably make something out of it."

Technical Head/Management: "I think the company was a very good place to develop the technology. Cyto did have a lot of successes. They went from a company with nothing, to over 150 employees and had raised over 150 million dollars. It wasn't tremendously successful but it wasn't really that bad. ... They failed but they were awfully close to victory. There just are no guarantees between the technical risk, the managerial risk, and the money risk."

Technical Head/Management: "There are a lot of players in the field and we did a better job than any of them, as far as getting to the clinic and having a development program. We had better pre-clinical data than any of them. And we were the last to get started."

1. **What lessons did you learn from CTI's failure?**

Life Scientist: You needed to sit down with yourself and be honest with yourself. Look at the data and make an intelligent decision about how you are going to move forward and you needed to know what the questions were that needed to be answered and you needed to answer them. Maybe at the end of the day,

you found out that the technology could not be made to work, but that's preferable to the company going out of business for all the wrong reasons.

Technical Head/Management: Who has seen it? It's not clear to me that 10 years would have made a difference and if you wait until somebody else has paved the way it is probably too late. The company did many things right! When developing a company, there is always a great deal of risk involved. CTI got pretty far on what they had. They made an appropriate choice to go for a clinical trial, knowing that if they failed that would be the end. And they failed. But they were awfully close to victory. There are just no guarantees between the technical risk, the managerial risk and the money risk. I don't think you can ever say we have a product and it is going to work.

I think the company was a very good place to develop the technology. Cyto did have a lot of successes; they basically went from a company with nothing to over 150 employees and had raised over 150 million dollars. After their clinical trial they divided the company in three parts and all 3 parts are still viable and, in fact, one of them is taking another product to the clinic right now. It wasn't tremendously successful but it wasn't really that bad. It is totally judgment to know when to take the company off, that it is not going anywhere.

Technical Head/Management: A lot of things went right! We went to the clinic with 3 things; there was also a small trial on HD disease. You were able to manufacture a product and test it. That went right. And you had a GMP facility that worked; you had a process that worked. You had people who were very creative that were creating such a process. We routinely said this was the hardest thing to do in drug development. You had gifted device guys that were making a lot of interesting gizmos and devices. This was challenging and a lot of things worked on the pre-clinical side, with lots of publications in Science, Nature and Nature Biotechnology. Lots of good stuff.

But in spite of everything, the price of the product was still very high. There were a number of companies trying to do cell therapy at that time: Biohybrid Technologies (which later spun into W. R. Grace), Hanna Biologics and Baxter (which was involved in the Diabetes Factor A program). Compared to a lot of players in the field and we did a better job, as far as getting to the clinic and having a development program was concerned. We had better pre-clinical data than any of them and we were the last to get started. I'd love to see one of these things work again!

2. Is now a better time for encapsulated cell therapy?

Snapshot of comments:

Life Scientist: "It would be difficult to convince investors because CTI did fail."

Engineer: "Cell therapy doesn't lend itself to economies of scale."

Technical Head/Management: "Where I see a better take up of cell therapy is where there is no other choice."

Life Scientist: I still think it was a great idea. It's funny the world hasn't changed that much. It would still be possible to get the technology to work. But it would be difficult to convince investors because CTI did fail.

Engineer: There was a window of time for cellular therapeutics where it could really work and then other technology would take over. I am starting to believe the window is starting to close. Thus, it would be a riskier venture now than ever. I remember Pierre Galleti telling me once about that. He was one of the founding scientists of Cyto. He subsequently died. The window may be less open than now. Therefore, I

believe it will be a riskier venture. Cell therapy doesn't lend itself to economies of scale. It doesn't fit into any conventional model. More advanced technologies would come along as people better understand AD and pain. Alternate therapies would come along and this is too circuitous a route.

Technical Head/Management: Where I see a better take up of cell therapy is where there is no other choice. Or where you will put some cells in, and they are going to generate a tissue of some kind such as liver, kidney or a bunch of neurons, which they will be able to do in a reproducible way. That's pretty far away. There is a long way to go before regenerative medicine takes off.

Conclusions:

The interviews revealed that while many of the problems were truly circumstantial, many other problems were created by management errors that accumulated over time. A more detailed discussion follows in the next chapter. Amidst all the controversy between pursuing pain versus PD, it is perhaps best to complete the interview with a quote from Neural Transplantation, by William J. Freed.

"The effects of the implants in this study were examined over a relatively short duration, mostly between 41 and 85 days..... There were substantial, although variable, reductions in self-rated pain scores and morphine dosages. Three of the seven patients had reduction of self-rated pain scores of at least 80 percent, on at least one of two rating systems. Two patients had no reductions in pain scores. The three patients showing very large decreases (>80 percent) in pain scores were not receiving morphine and were studied between 43 and 85 days. One patient survived for an extended period after the device was removed and did not show a significant worsening of pain during that interval. Overall, the beneficial effects of the transplants were somewhat variable and the study was quite short in duration; nevertheless, the results were quite promising."

".... Reason that pain is an attractive application of neural transplantation technology is the potential usefulness of the method. For pain treatment, what is required of neural transplants is quite simple, yet what can potentially be accomplished may be quite useful. Few would argue that alleviation of the suffering of cancer patients is not a worthwhile or compelling goal. In the long run, there are additional pain syndromes that present treatment difficulties and might be amenable to treatment through this or similar techniques. Phantom limb pain, neuromas, and pain due to nerve injury are example. Many such syndromes cannot be treated effectively by conventional techniques and might ultimately be amenable to treatment using cell transplants. Thus, it would not be surprising to see the use of neural transplants in this area to become explored very extensively, and perhaps become a very significant clinical application over the next ten years."

Chapter 5: Lessons for Neurobiochip Devices

In trying to decide how to commercialise Neurobiochip Devices, I will start by analyzing the problems encountered by CTI and discussing potential solutions. Then I will apply the lessons to commercializing Neurobiochip devices in the context of the industry as it stands today.

(1) Problems faced by CTI

CTI tried to commercialize a technology that was still in the very early stages of its development. The industry was only warming up to the existence of stem cells. Issues with the FDA were clearly circumstantial and contributed to the problems of CTI. However, there were management errors that accumulated and manifested with time. The case study on CTI revealed that any entrepreneurial endeavor is risky, but a start-up in cell therapy is exposed to much greater risk compared to other biotech start-ups.

The problems encountered by CTI can be listed as follows:

(1) Project Management
(2) Strategic Partnerships
(3) Lack of Focus
(4) Managing Transitions during Growth
(5) Communication Errors
(6) Managing the Work Force
    (a) Scientists versus Engineers
    (b) Discovery versus Manufacturing
    (c) Passion versus Objectivity
(7) Hiring, Culture and Organisational Context
(8) Choice of Leadership
(9) Pulling it all together by taking a Systems Approach

In my opinion, among the challenges listed above, the most important problems that led to the dissolution of CTI were issues with project management, mis-management of cross-functional teams and finally the uncertainty in the technology itself coupled with the fledgling status of the industry for cellular therapy.

(1) Project Management

Perhaps the single most common reason why start-ups fail is a shortage of funds. Albert Chin, Director, Neurotechnologies, Codman, a Johnson and Johnson Company, described how many start-ups get focused on technology development and overlook the importance of product development. He could not stress more the need to identify risks and mitigate them by creating regulatory and clinical strategies as early as possible.

In cell transplantation at the time of CTI, nobody knew in which indications the therapy would prove most effective. Therefore, CTI chose to explore sites that where most immune privileged such as the brain, as well as, diabetes because it seemed relatively straightforward (requiring a continuous delivery of insulin with a feedback loop to regulate the blood insulin levels). Thus CTI chose to target a range of disease states with slight variations in its core encapsulation technology. For CTI, within its portfolio of relatively short-term and long-term options, the short-term projects took much longer than anticipated. Lack of "quick cash" projects, drove the firm into strategically unfavorable alliances. Most pharmaceutical companies were unwilling to partner with cell therapy start-ups at the time. Their unwillingness in turn caused VCs to become wary about the commercial potential of cell therapy, in turn, making them unwilling to invest further money during subsequent rounds of funding. This might have compelled CTI to seek an IPO. In trying to pursue potential revenue streams, CTI burnt cash which could have come helpful during the insufficiently funded, decisive clinical trial.

So, how does a start-up decide how many projects to fund at any given time, and which projects they should fund? The number of projects and the nature of the projects depend on the nature of the technology at hand. Is the technology well developed already in its applications? The decision around projects naturally is dependent on the amount of money available as well as the amount of money that needs to be raised in future. It is very important to synchronise critical milestones on projects with important fund raising activities and to ensure that the milestones are powerful enough to attract funds as well as partnerships. Funding multiple, low risk, low return projects will not create additional value in the firm. The aim is to run up the value creation curve. Each milestone has to be thought around dollars, value creations and likelihood of success, and ultimately tied with the goal of going public. Projects are never independent in themselves. Project management is about creating and achieving milestones which will attract partners, which in turn will impress venture capitalists to invest further in the business.

The Neurobiochip Devices is at an advantage in this respect, because the scaffold in itself (without the neurons) can be used as "bridges" to treat cases of spinal cord injury and can also find application in retinal implants. The neuronal replacement for PD could be midterm, given the long history of attempts at treating PD by grafts, while application of neuronal replacement to HD could be treated as a long term project, given so little is presently known about disease pathology. By using the scaffold to treat spinal injuries the company can create a finite cash flow early on, and keep itself from being driven into a situation where it is in strategically poor partnerships for the sake of funding. This "three horizon" approach[77]: short term, midterm and long term, in theory, allows managers to focus better, allocate resources judiciously and their actions send a positive and clear message to investors and employees alike. This tool allows managers to identify loop-holes in the pipeline and plan accordingly. Finding the balanced portfolio suitable for the "three horizon" growth approach is not a function of the number of initiatives per horizon but a dependant variable of industry evolution, firm's financial and functional capabilities and other environmental and circumstantial factors. Of course this tool is only as good as the person behind it. It does not guarantee success but substantially increases the chances.

However, as Mark Levin, founding CEO of CTI and current CEO of Millennium Pharmaceuticals, pointed out, "Though, Project leadership skills are really important, very few great project managers are going to leave a secure job at Merck to join a start-up to do something unproven. The first year or two, the project management skills of the CEO or head of R&D should suffice. After that project management expertise would become necessary in the firm. There is also a flip side to having such expertise in house. The people who are naturally talented at project management aren't necessarily as creative. They start to lay down timelines which begin to stifle the entrepreneurial passion, sometimes too early. All of a sudden one person doesn't get to execute that brilliant idea which might have added value to the company. There has to be a balance."

(2) <u>Strategic Partnerships</u>

Since cell therapy is a cash intensive business, entering into partnerships along with raising venture capital is crucial for the survival of the firm. Partnerships should not merely serve a source of extensive funding or name brand. They should be right in the light of what the firm seeks to achieve in its three horizons: very short term, midterm and long term. Partnerships that are not in alignment with the firm's strategy at the very outset, almost never "evolve" into good partnerships over time. If a firm accepts a partnership because it appears lucrative or enables the firm to keep many options open, then indeed the

[77] The Alchemy of Growth

start-up is diluting its own corporate strategy and wasting its limited resources. It is setting itself up for failure. A desire to keep many options open is equivalent to not making a decision and generating confusion. In order that the firm is not forced into forming less than optimal partnerships for financial reasons, the firm should design a way to generate cash flow even in the near term, while pursuing its more glorious goals for the future. Partnerships that "blend" into the context of the organization are undoubtedly hard to come by. But such partnerships contribute to the firm's competitive advantage and long term success. Even with the options available, the firm might still run into a future that catches it entirely unprepared and without money.

(3) Lack of Focus

There is a fine balance between exploring multiple options and losing focus. Too many firms make the mistake of assigning five or six projects to their creative people spanning a couple of divisions. From the interviews, it appears that CTI took a long time to focus on a specific development path. The interviewees mentioned a clear sense of direction early on, but afterwards the firm's strategy frequently changed from preparing cell therapy to cure PD, to developing a platform technology for delivering growth factors and eventually to ameliorating pain. While this meandering could have been in response to economic constraints, it caused CTI to invest too much money, too frequently, into early stage products in various therapeutic areas, contributing to confusion within the firm. While it is important for the start-up team to remain flexible, it is crucial to commit to a path beyond a certain point and focus on its implementation. Under ideal circumstances there would have been a few early and late stage projects with a cluster of projects at the middle stage of development, to provide strong support as back-up pipeline projects should the clinical trials fail. Commitment gives employees a framework within which they can act. It brings into perspective the value chain they need to put in place, it allows them to decide on capabilities to build in-house and which ones to outsource. The firm can then build skills and capabilities to grow in a deliberate sequential manner.

(3) Managing transitions during growth

CTI made a brilliant start in terms of employee morale, culture and accompanying progress. Like most start-ups, CTI stuttered as they transitioned from a less than 100 employee stage to more than 100 employees stage. The culture rapidly disintegrated as constructive dynamic tension degenerated into misunderstanding and rivalry. Career advancement became uneven. Some employees even complained of being promoted so rapidly that they themselves felt unsure of their ability to handle the new

responsibilities. The engineers at CTI felt the company was into quality control even before the manufacturing had been sorted out. Another interviewee said: "I ran quality control operations from within a Central Analytical Laboratory as the company grew from 30 to 90 staff. Other units also had quality control tasks (polymer, cells, etc). Quality control was system-wide, but it was run by an external hire – with the effects that the core groups felt that the controls were being imposed upon them." The interviews abound with evidences of fractured employee morale.

Having sufficient funds to grow, does not justify growth. The company has to be ready for growth or as the book Alchemy of Growth calls it, "earn the right to grow". Managing growth is a multi-step process and special care has to be given to each step of the process. Before implementing growth, management needs to thoroughly review whether growth is indeed well-timed for their firm. They need to ask themselves whether the operating performance has reached the required stability to provide the firm with a strong foundation to build upon. CTI became a story of "growth in place of operational excellence" instead of "growth and operational excellence". A company simply can never grow out of trouble. Therefore, often times instead of aiming for high growth, start-ups should manage controlled growth. The firm should grow at a pace their managers are able to keep pace with. This helps sustain the cultural consistency the firm has built and allows the firm to continue to operate as a systemic whole instead of a congregation of functionalities.

Having earned the right to grow, the firm should remember that the processes of communication, hiring and increasing productivity that work very well at 20-employee start-up stage, are not always scalable to a 150 employee stage. At that employee strength and if the firm is already public, the firm needs to put into place different processes to achieve the goals of reformulating and maintaining culture, retaining or increasing productivity and continuing communication. The company needs to plan its transitions. It is just as vital to hire the right people as it is important to let go of employees whose skill sets and attitudes no longer fit with the firm's evolving culture, values and needs. This needs to be done in a proactive fashion instead of spurring an employee exodus from the firm. This involves changing the firm's employee evaluation and incentive structure, to promote behavior conducive to the transformation of the firm from a discovery phase to a development phase of its life cycle, and reprimand counteractive actions.

To quote Mardis, Aibel and Associates, a Biotech Management Consulting firm: "Failure to evolve organizational and operational practices consistent with the status of products (e.g. discovery, development, or commercialization), the overall size of the firm, and the extent of functionality almost guarantees failure. In addition to failing to plan adequately and deploy the resources that a major

transformation requires, inadequacies in communication, a lack of proactively addressing cultural resistance, and an inability to deal effectively with staffing issues are critical impediments to making a successful transformation."

(4) Communication errors

Managing expert information exchange and organizational learning across product development programs is a challenge in itself. Added to this, growth changes the entire corporate culture as does change in management. In its initial stages, the CTI culture was marked with frequent meetings and open exchange of ideas. However, as the company grew to 150-200 employees, the management clearly failed to communicate change and decisions to the rest of the firm. Interviews on hiring and choosing between pain and PD reveal apparent communication errors within the firm. There seem to be many contradictory views on why pain was selected as the ultimate market for clinical trial.

An ex-CTI Life Scientist commented that, "The CEO once remarked that getting the entire staff together for a pizza lunch actually cost the company something like $60,000 an hour. Consider the burn rate of the company!!" CTI did implement a "five-fifteen" weekly Intranet reporting system during the early days. The goal was to report on key successes or challenges individually each week. This could have become a powerful way to synchronize different workgroups around development issues. However, it never achieved its full potential partly because the company didn't have an appropriate individual to assemble and manage the input so that the development teams would see value from a shared knowledge management system. Unfortunately, for CTI in those days, there wasn't as much expertise available who knew how to use IT to integrate knowledge within a firm.

This is not about IT. It is about managing cross-functional teams in a matrix organisation. Cross-functional teams include a representative from each of the core functionalities. They handle cross-functional integration and deal with problems very effectively. It is however, very challenging to run a matrix management organization. Individuals have multiple bosses they report to. Decision making can easily become prolonged and cross-functional team members can become mere messengers between teams. However, in making a hybrid device such as the Neurobiochip, a matrix organization is mandatory. In the words of Mark Levin, CEO, Millennium Pharmaceuticals, "In general matrix organization is very important very early on and in any company. How early depends on the company and what you are doing. Unless you bring all these people on a project team with an overall leader who is integrating what they are trying to do, they will all be doing their own thing. When the company had

moved downstream and has molecules in the clinic and on the market, then you need project teams not only for partnerships, but you also need project teams for the molecule, involving commercial people, regulatory, clinical, pharmacology, discovery, manufacturing,... the list goes on and on. If there are 10 departments, their goals have to be integrated and those goals always change and have to be integrated on a regular basis. You need to build a business plan or a project plan around the project and the group has to act almost like they are a company. In cross-functional activities where you need to bring people together to make something happen, for some long period of time, where there is a common goal and where things will change, you will need a matrix organization."

(5) Managing the work force

In a cell therapy start-up, the diversity in the work force is not restricted merely to two categories of people, namely, scientists and business people. In this industry the research staff in itself, is composed of engineers, polymer chemists and biologists from a variety of disciplines. Each subset of this population has its unique characteristics, problems and things that motivate them.

(a) Scientists versus Engineers

The interviews reveal that the engineers could not comprehend the biologists' issues making the biologists felt unappreciated and undermined. The underlying reason for dispute is a fundamental difference in "clock speeds" of the engineering and biological products. In polymer engineering problem solving in the wake of an experimental failure, is relatively structured with definite answers. Biological systems being intrinsically more complex and with largely unknown signaling pathways, when experiments don't work, Life Scientists are often helpless in providing answers. In a firm culture driven by polymer chemists and engineers, the biologists by the very nature of their experiments, appeared slow. Therefore, barriers came up between the engineers and the biologists very early on. It would be the responsibility of the management to communication systems between the groups in place, however, the individual group leaders for polymer chemistry and the biologics were not equivalent in their personality contributing further to the divide.

(b) Discovery versus Manufacturing

Technology is product driven relative to basic science. However a "publication mill" culture seemed to prevail at CTI, with scientists very focused on publishing. This could have been either for reasons of

personal career growth or lack of expertise in the firm. A previous employee of CTI explained that, "The development culture was there since day 1, but the rising level of QA/QC reporting was not managed using the same individuals who had been with the early discovery group. Much of the friction could have been reduced if the QA/QC staff had a really deep and personal experiential understanding of the nature of the discovery work and the challenges of the development process. " Regardless of the cause, the firm as a whole failed to transition from a start-up discovery phase into the development phase

(c) Passion versus Objectivity

One often hears entrepreneurs say, "Deliver a break-through and they will come." CTI did not seem to concern itself with issues like reimbursement early on, seeking to tackle them once the clinical performance had established a cost-benefit advantage. Everybody at CTI, including the venture capitalists was extremely excited about the promise of the technology. Perhaps because they were so very passionate they lost perspective of the business potential of the encapsulated cell therapy.

In the course of the interview, one of the ex-management of CTI said that CTI was successful because of the funds that had been raised and the increase in the employee strength the firm. Unfortunately, both of these factors are poor yardsticks of the firm's strategic health. They are a measure of the firm's past performance. For CTI, those numbers certified a great start, but not necessarily healthy growth nor a promising future. This particular employee had overlooked the fact that employee morale was sagging at CTI. It was not possible to win the war with unhappy soldiers. It is quite possible, that the brilliant start CTI made gave the management a complacency, which caused them to overlook communication and hiring as the firm grew. However, even after having sensed trouble and having identified the source of the trouble, it is not easy to put the corrective measures in place, especially within the short time span available to rapidly growing start-ups.

(5) <u>Hiring, Culture and Organisational Context</u>

"Start-up companies are typically not started with people with lots of perfect experiences. The likelihood of getting all the right skills in 20-30 people in the first year is unlikely. A start-up is usually formed of very smart scientists and/or strong entrepreneurs. These are advantages but it has its limitations." Mark Levin, founding CEO of CTI. As a firm evolves, it is important that its employees have the skill to match the requirements of the firm at its particular stage of its life cycle. Detailed enquiry into the unusually rapid promotion revealed that because the company was growing too fast or it became more difficult to

attract talented individuals and what followed was a "grab-and-fill tactic". When the company was growing at a very rapid pace, scientists found themselves in business development roles, calling for skills not within their domains of expertise and familiarity, and not finding the resources within the firm to develop those skills. Such delegation of responsibility without prior training and support can only be expected to backfire. This did not characterize the early phases of the company's hiring and promotion practices. Improper or ineffectual hiring can fuel misunderstanding already existing between the various groups and adversely affect innovation. Problems might have been caused because many individuals were from purely academic backgrounds and had no industry experience. Since cell therapy was still an emerging industry it was very difficult to find the necessary talent.

Without a product in hand, the most important asset for a start-up is its intellectual capital, its people. Without emotional commitment from the staff, even the best strategies are bound to fail. The management needs to create the environment which will elicit and support the desired behavior from the employees. This is more than getting employees to buy-in to their decisions. Employees behave in a certain way, either because it is the only way to survive in that environment or their actions are in step with their performance measures. Agreeing to do something is not a confirmation of the employee's passion and enthusiasm to the new cause, and both these elements are crucial to the success of any start-up. The management has to proactively ensure that the firm's structure and organization support the decision its making. Decisions are made "in context" of the firm's capabilities and goals.

Like people, organizations also tend to develop "mental models" which are exhibited in their culture and in the unspoken norms and behaviours. Positively reinforcing mental models can catapult a firm into heights of success, but mental models can also cause passivity which can be detrimental as they create tremendous inertia in the firm culture which can impede growth and adaptability of the firm to the changing needs. Unless the management is aware of the existing mental models in the firm, it is not possible to replace them with positive reinforcing action. Just as much a firm's culture should be facilitated by norms and structures put into place, it should also be allowed to evolve on its own, with help from the employees. Like many abstract things in life, culture cannot be rushed or imposed.

It is difficult but imperative to create and maintain an environment that constantly questions the firm's decisions in terms of its strategy and financial health. A periodic critical review of development challenges is an essential task for responsible product development. In most cases, employees start to question when they see trouble, but by the time the organization is able to overcome its inertia and get

mobilized it is well midstream in crises. The worst time to bring about change in a firm is in the middle of a crisis.

(6) Leadership

One CTI employee said, "At the end of the day, a firm is 100% it's CEO." In addition, there was a lot of discontent with the CEO. The company is accused of "dressing for the investor" by some employees, while hiring senior members of the management, directors and vice presidents. A company is heavily dependent on its CEO, therefore it is mandatory that the CEO match the needs of the start-up and be accepted by the people. One ex-employee commented, "Bad management can kill good discovery/development culture." So, what should a start-up look for while hiring a new CEO?

"Every company is different but when we are looking for CEOs we were looking for someone who had clearly come out of the industry, was passionate about doing something that had not been done before, had been very successful in the past, had a strong capability in integrating science and clinical medicine and business, was a strong communicator, a strong leader, a strong organization builder, knew how to build products, had the ability to hire great people and the ability to create an environment where great people can do great things. There is a long list of things you are looking for and no particular person is perfect. And so you always have to make choices for one, and secondly depending on what stage the start-up is in, different people can be right at different stages.

As a CEO it is very important to get yourself understood by the rest of the company. So, having a very clear vision for the future of what you are trying to do, being really emotionally and passionately involved in it and being committed to it, so that the employees understand where the company is going; Being able to tell the vision as a story so that people can understand it, and to tie that story to specifics, to empower people to get those done and to hold people accountable in getting them done; And then, on a regular basis talk to groups of people and have the right forums to change the story, because the story always changes. Make sure you are listening to everybody on the team on how to make it better as you go forward. You can't involve everybody on each decision you make, but convey it as best as you can." Mark Levin, CEO, Millenium Pharmaceuticals and founding CEO of CTI.

(9) Pulling it together by taking a Systems Approach

A firm is best described as an ecosystem, where all the individual subsystems (divisions) though unique, work in harmony with each other. Strategy is not merely about defining the business, the consumer and the operations to get the product to the consumer. It is about devising a "system" in which the consumer and the product can come together in the best possible way, in keeping with the company's competencies. No matter how successful the subsystems are in themselves, they need to work cohesively with one another to make the firm a success. The top management has to continuously work to ensure the employees see the interdependency of the subsystems. It is only too easy for managers to focus on optimizing their own functionalities, mostly in response to the structure of performance evaluation, disregarding (or losing sight of) the big picture. Since the divisions work productively and efficiently within themselves, the unlinking created between different divisions becomes masked. By the time, the disintegration of linkages become visible, it is usually too late to repair.

The most innovative and companies in the world are born out of careful design. To quote Paul Cook, Raychem's founder and CEO:

- The most important thing we do is build an organization - a culture, if you'll pardon the word - that encourages teamwork, that encourages fun and excitement, that encourages everyone to do things differently and better and that acknowledges and rewards people who excel.
- You have to make sure your company has the brightest people in your core technologies, and you have to make sure those people talk to each other, that there is a regular and intensive interchange between all those disciplines. They have to work together, sweat, swear, and do whatever it takes to extract from the core technology every product that is possible.
- Size is the enemy of innovation. You can't get effective innovation in environments with more than a few hundred people. That's why as we continue to grow, we want Raychem to feel and function less like a giant corporation than a collection of small groups, each of which has its own technical people, marketing people, engineering people and manufacturing people.
- Innovation happens in pockets and the location of those pockets changes over time. So, we want to play musical chairs with people and make extensive use of skunk works and project teams.
- The most important factor that motivates people to focus on innovation is individual recognition – more important than salaries, bonuses and promotions. Most people, whether they are engineers, business managers or machine operators want to be creative. They want to identify with the success of their profession and their organization. They want to contribute to giving society more comfort,

better health more excitement. And their greatest regard is receiving acknowledgement that they did contribute to making something meaningful happen." [All the Right Moves, HBS Press.]

In Conclusion:

The opening chapters confirm the great need for neuronal replacement therapy but the case study on CytoTherapeutics simultaneously spells out how very difficult it is to commercialise such a hybrid technology. Cellular Therapy is very unique from businesses in pharmaceuticals and medical devices. The following is a comprehensive list of challenges that need to be kept in mind while commercializing the NeuroBioChip Devices:

1. The technical details of the polymer will soon be solved. It is the cellular side of the Neurobiochip which will lag behind. Different clockspeeds of different components of the same product will make product development within the same firm, very difficult.
2. Ensuring the sterility and stability of cellular products makes this business extremely cost intensive. Therefore, manufacturing and operations have to be uniquely designed for the purpose.
3. It is needless to say how very critical quality control will be in cases of delivering neurons on a chip for implantation in a patient's brain.
4. The FDA is yet to come up with a clear regulatory approval process for hybrid devices.
5. Cellular therapy aims at providing a new treatment methodology, which means changing physician behavior. This calls for a whole new approach to marketing and will involve extensive training of physicians, surgeons and care providers.
6. Speedy adoption of cellular therapy is dependent upon the burgeoning of complementary technologies such as the development of stem cells and even application of wireless technologies to medical devices.
7. The extensive funding and expertise that commercializing cellular therapy calls for, is available with the large biopharmaceutical companies. However, the value chain for cellular therapy falls outside of the value chain expertise of the giants in the pharmaceutical and medical device industries, making it virtually impossible for such start-ups to get multiple lucrative partnerships.
8. The inability to establish credible partnerships will make it more difficult to attract funds beyond initial rounds of funding, from either venture capitalists or public markets.
9. The cost of delivering cellular therapy is so high that the price of delivering the cure will be too high for reimbursement.

10. The lack of reimbursement coverage will make it very difficult to find the critical mass of patients to make this a commercial success. Other than the obvious financial consequences, not having enough patients to cure will also make it difficult for cellular therapy to prove its superiority over existing treatments.
11. The numerous barriers (as listed above) encountered by the fledging industry, will make it very difficult to attract the necessary talent to make such an endeavor, a success. This explains why the talent in the cellular therapy firms has thus far largely been scientific and academic, with lack of significant business training and exposure. This has compounded the problems faced by these start-ups, manifold, since they have been left to teach themselves how to transition from an academic powerhouse into a product and development driven commercial entity, in the absence of significant management expertise.
12. Managing any start-up is a challenge, but the intensely multidisciplinary nature of cellular therapy business makes human resource management an extreme challenge.
13. Adding to all the problems listed above, this field faces competition from the medical devices business with a cycle-time of 18 months. This means that the medical device industry has an inordinately high rate of innovation, even if incremental. On top of it, medical devices industry is very cost efficient, primarily because it is more engineering based. Owing to the incredible pace of improvement in electronics, devices are rapidly getting smaller and more efficient with feedback loops and even wireless monitoring. The advantage cellular therapy has over medical devices is that it offers a cure versus symptomatic relief. However, an elderly patient, with only a decade of life remaining, it more likely to settle for a compact and cheap device, than to undergo surgery for a cellular implant. Following its commercialization, cellular therapy will find very difficult to compete with the devices.

The long list of challenges listed above, paint a truly grim picture for the commercialization of neuronal replacement therapy. Perhaps, the electrically conducting 3-dimensional polymer matrices could be licensed to a host of companies involved in producing spinal implants, retinal implants and the like, and the incoming revenue stream could fund the development of the neural components. Unfortunately, it is not possible to build a business solely from licensing revenues. The only way to make the business work would be the ready and reliable availability of neural stem cells. The tissue engineering industry is roughly divided into: cellular therapy (that is, stem cell or therapeutic cloning and encapsulated cell therapy), metabolic (that is, bioartificial liver, kidney and pancreas) and finally structural (which includes, regenerated skin, heart valves and other musculoskeletal components). Presently there are 89 firms engaged in various aspects of tissue engineering, operating in more than 16 countries worldwide,

employing 2600 workers (Lysaght and Hazlehurst, 2004). Within this field of tissue engineering, significant funds, resources and attention is being funneled into stem cells research. Tables 1 and 2, indicate a growth in cellular therapy by 48%, most of which is around stem cells research and development. As mentioned earlier, a reliable source of neural stem cells being fundamental to the success of the Neurobiochip, funding of stem cell research and its commercialization, can only mean good news for the technology.

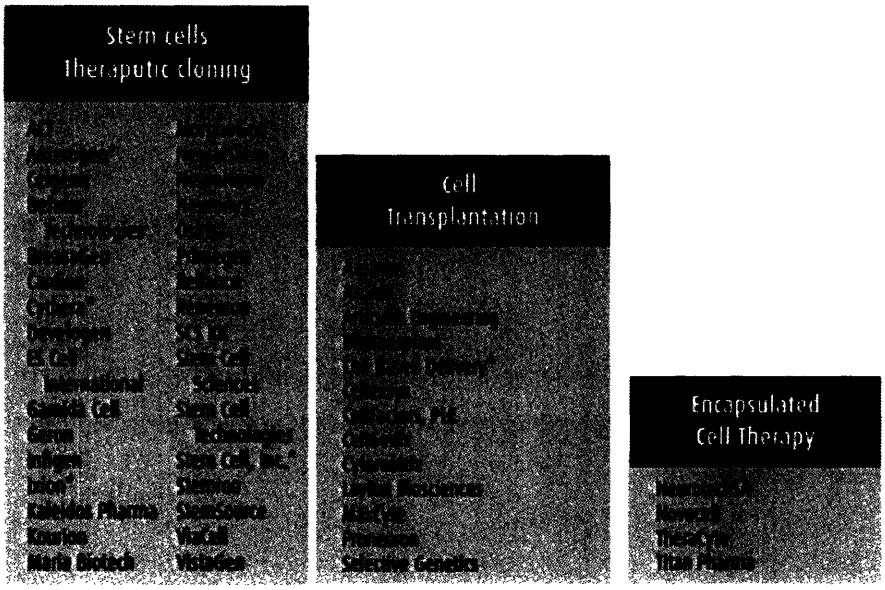
Cellular therapy is not simply about curing a large and diverse segment of the patient population suffering from neurodegenerative disorders. Unfortunately, the problem of commercializing cell therapy, is much larger. It calls for a whole new way of designing development and the delivery of treatment, from regulations, to reimbursement, to surgery, to post-operative care. To say "This is no easy task", will be putting it too mildly. As of today, its likelihood for success will be increased manifold if it is pursued within a larger company instead of a stand alone commercial entity. It is mention worthy that Medtronic has an alliance with the biotech company, Genzyme, involving cellular therapy.

Table 1: Analysis of Activity in different sectors of Tissue Engineering.

	Cellular	*Metabolic*	*Structural*
Number of FTEs	1225	381	975
Percentage of total	48%	15%	37%
2002 spending ($million)	$230	$72	$185
Growth since 2000 survey	+37%	−33%	−50%

[a]*Note:* Percentages may not total 100 because some firms were included in more than one group. FTE, full-time equivalent.

Table 2: Companies engaged in Cellular Therapy.



Tables 1 & 2: Courtesy: Lysaght, Hazlehurst, Tissue Engg., 2004.

To end on a note of optimism, it is important to remember that these challenges have been confronted by all novel medical technologies. What NeuroBioChip now needs is a breakthrough in neural stem cell technology. Thereafter, it is a matter of time that these challenges will be overcome and Neurobiochip will become a reality for patients suffering from debilitating neurodegenerative disorders.

Appendix: List of Interviewees

Interviewees related to CTI:

Dr. Dwaine Emerich was the Director, Preclinical Studies at CTI. He later joined Alkermes as a senior research scientist and is now VP Research at Sertoli Technologies Inc and continues to work closely with Dr. Moses Goddard, a senior scientist from CTI.

Dr. Tom Flanagan was the Group Leader of Analytical Chemistry at CTI. He subsequently became Founding Director of Diagnonlogy Inc., an international point-of-care diagnostic product company. Currently he is Managing Partner of the Massachusetts Strategic Envirotechnology Partnership (www.STEPsite.org), UMASS Boston.

Dr. Frank Gentile was the Director of Polymer Chemistry at CTI. He is now Vice President of Research at Hambrecht & Quist Capital Management LLC.

Mr. Mark Levin was the founding CEO who joined from Mayfield Fund in California which helped fund CTI. After the first year he continued as a Board Member on CTI. He is presently the CEO at Millenium Pharmaceuticals.

Dr. Mike Lysaght was recruited into CTI from Baxter for his experience in biomaterials relating to dialysis. He was the Vice President in charge of product development for CTI. Dr. Michael Lysaght is now at Brown University where he leads an academic group for the study of artificial organs and cellular therapy.

John Swen was the Director of Business Development and President of the European division for clinical application at CTI. John served as Executive Director for the Rhode Island Economic Development Corporation and is now Executive Director of Science Policy and Public Affairs at Pfizer. He was at CTI from 1992 to 1996 when he joined the spin off, Modex, as the CIO in Switzerland.

Al Vasconcelos: The founding business director of CTI, subsequently a founder of four additional cell therapy companies, he is currently the CEO at Sertoli Technologies Inc.

Nick Warner: He was hired as a model maker and worked at CTI for 8 years. "They hired me to make

semi-permeable hollow membranes. I am an engineer but at that time I was a machinist who built high altitude balloon experiments and parts of space shuttles. I designed and made all the manufacturing equipment. I designed a collapsible device for the diabetes program and the encapsulated islet that that you could inset into a catheter that would pop out in place. I worked very closely with the polymer chemists and with Patrick Aebischer's group at Brown University. He is now the head of a Swiss Engineering School, with a lab in the University of Lausanne. He's a wonderful guy. ..." Nick is now with Sontra Medical Corporation.

Interviewees unrelated to CTI:

Albert Chin, Director, Neurotechnologies, Codman, a Johnson and Johnson Company.

Paul George Matthew, graduate student in Prof. Robert Langer's laboratory in the Dept of Chemical Engineering at MIT.

Dr. Thorkild Norregaard, a neurosurgeon at Mt. Auburn Hospital who regularly operates on PD patients. He is also a professor at Harvard Medical School and has extensive research experience with polymer implants in spinal cord injuries.

Dr. Stephen N. Oesterle, Senior Vice President, Medicine and Technology, Medtronic. Previous to this he was a faculty at the Harvard Medical School.

Nathan Wilson, graduate student in Prof. Mriganka Sur's laboratory in the Dept of Brain and Cognitive Science at MIT.

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