The commercialization of gene therapy concepts into products

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Abstract

Science and technology in the 21st century will require a stronger collaboration between the business and academic communities if medical products are to be invented faster, better and cheaper. The first government to facilitate this synergistic science/business partnership will dominate the health care industries and impact the world economies. Innovative science is the engine for creating these medical products. If the scientist/entrepreneur is to succeed in commercialization, they will need stronger mentoring and funding for transforming their technology into products. Governments in Europe, Asia and the United States are competing to create these synergies between their business community and their academic institutes for the successful technology commercialization. The leader of this scientific transformation will become the economic leader in treating an aging world population. The successful entrepreneur can expect greater support from the investment community and sheltering environment in a business incubator to transform their concepts into validated products for the pharmaceutical industry. Gene therapy and stem cell therapy have an opportunity to impact human health if these novel concepts are carefully mentored and incubated.
(Gene Therapy 2007; p000-000, 2007)

Keywords:

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Introduction

Therapeutic products using gene therapy and stem cells are the goals for treating human diseases in the 21st century. There has been successful demonstrations of both protein and cell therapies during the last century. These treatments in the form of blood transfusions, bone marrow transplantations have been both therapeutically and commercially successful as medical products. More recently, the use of protein therapies have been economic drivers for start up biotechnology companies. Epogen, a growth factor that can stimulate hematopoetic cell growth, has been developed over twenty years and has given Amgen a stable foundation in the biotechnology field. In contrast, gene therapy agents have yet to demonstrate either limited pharmacological activity in the clinical and a lack of financially successful products. Today stem cell research has promised similar results as gene therapy did fifteen years ago. The expectations must be managed more carefully if these innovative therapies will become effective products.

During the past twenty years, we have seen the introduction of novel technologies

that can knock down gene expression in cells. These agents can function as both gene target validation for human disease as well as have gene therapy applications. Antisense and ribozymes have successfully identified novel gene targets in human malignant tissue. However, there has been a failure of gene therapy to deliver pharmacological effective doses of these anti-cancer genes to the target tissue. This year again we see the Nobel Prize for a gene knockdown technology (small inhibitory RNA, siRNA). Twenty years earlier, the Nobel committee also sited the ribozyme technology for this prize. Will we make the same mistakes again commercializing this gene regulation technology? We have now demonstrated a broader array of genes that are up regulated or down regulated using high through put micro array screening. This gene screening technology has increased our ability to identify more changes in genes expression but have we improved our insight to understand the disease process? Hopefully, we will learn from our past mistakes and optimize the therapeutic targets and create more efficient gene knockout strategies. Then we can develop better gene therapy products with or with out stem cells. This will make commercializing these products more clinically relevant?

The scientific and technological innovations created by universities and research institutes have driven local, regional and global economies for the past fifty years. The United States Government has funded medical research at a comparable level to that of the industry sector. However, less than 5% of this government-funded research has created successful consumer products. Why have so many potential life science opportunities that could improve health care failed? The mixing of innovative science with good business strategies is a high-risk venture for most companies that make medical products. For the entrepreneur, it can be even more daunting especially doing this the first time. Validation of novel concepts into viable products is a time consuming and a costly experience. The pharmaceutical industry has pushed the validation of these drug candidates down to the biotechnology companies. The innovative science is the outcome of most the government funded academic research. The academic-entrepreneur must either license the technology or become more knowledgeable in commercializing their patented ideas. The entrepreneur must learn this drug development process either in an academic environment or through a mentorship program in the investment community. These life saving therapies will move from inception into medical products faster if there is a better synergy between science and business communities. This will be achieved by managing the drug development process: pre-clinical validation, clinical and regulatory progress and product marketing and launch. This process has defined criteria to pass before it can more to the next step: novel patented concepts, validation of the idea, funding development of the project, incubating the process, FDA approval and defined customers and market.

The pharmaceutical industry

After the Second World War, the US government comprehended the medical and commercial impact of antibiotics on the management of human infectious diseases. They wisely funded the development of our current medical infrastructure for the second half of the 20th century. America became the center for medical education and scientific advances. English became the language of international science. The government began initiating funding of academic research on cancer in the 1970's, AIDS research in the 1980's and the Human Genome Project in the 1990's.

The hope was to repeat the successful impact of antibiotics on infectious diseases with new therapies to treat other catastrophic human diseases. What was not achieved was a better understanding of why antibiotics were so selective against infectious diseases and why there was such a lack of selective between cancer cells vs. normal cells. The animal cancer models, containing homogenous population of cells were eventually shown to be a poor predictor for drug selectivity in human cancer.

The pharmaceutical industry developed a codependence on the academics for innovative science funded by the government. This government funding assisted both the academics as well as the drug industry. This industry, however, focused on the development of small molecules that were orally available and chemically synthesized. This is how drugs were made for the past hundred years. After Dr. Holloway patented the pill-forming machine in England in the 19th century, the drug industry had a uniform product that was orally available for the masses. Drug companies continued to direct their research on the technology advances for small molecular entities. Developments in combinatorial chemistry allowed for a magnitude increase in the synthesis of candidate analogues, high through put screening allowed for more of these candidates to be tested and screened. However, there was a lack of critical disease specific targets and validated assays systems. Most of these screened drugs were eventually left on the shelf until an appropriate target was identified because they lacked selectivity, were toxic or were not soluble.

This method of making drugs had not changed from the 1880's to the 1980's but the technology advanced. This process of discovery was serendipitous and required chemical synthesis. This all changed when molecular biology techniques were introduced to the academic laboratories and human genes could be isolated and cloned. It was now possible to synthesis these critical proteins in cells, then purify the therapeutic proteins and treat patients with chronic diseases. The pharmaceutical industry was not prepared for protein therapeutics.

Young European and Asian scientists moved to America because of this significant government funding of medical research after the world war. The German and British scientists brought with them different attitudes of on the role of science: commercialize science or do not commercialize science. This would play out in the beginning of the biotechnology era and continues today in many academic institutions. So why San Francisco was the place where molecular was commercialized?

The biotechnology industry

How did California spawn the biotechnology revolution in the 1970's? It was the science of molecular biology met business: investment banking. The government had funded research most cities in the United States. There were major investment banks in all the large cities across America as well as Europe and Asia. One scientist in San Francisco and one businessman were able to successfully communicate with each other and outline a common goal: the commercialization of a medical product: insulin. The cloning of the insulin gene laid the foundation for the development of the biotech industry worldwide. The expatriated scientists from Europe and Asia helped drive the next wave of medical advances into commercialized products by the 1980's. Insulin was the first major commercialized medical product. Insulin set the bar on expectations for successful medical products but not all scientists

were interested in this type of drug development. Today most governments in Europe, Asia and many states are trying to repeat the success of California.

Why was Insulin and Genentech successful? They had created a breakthrough technology that was better at producing insulin (faster, better and cheaper) than the slaughter of hogs for purification of insulin, which was not keeping pace with the demands for diabetic patients. They had a critical product for a high growth market and built alliances with the major pharmaceutical company in this field, Lilly. Genentech had a fast revenue growth and a high return on investment for their shareholders. The pharmaceutical industry had built a industry around the chemistry of small molecules for disease treatment and a sales/marketing force to distribute these agents. The biotechnology sector became the center for discovery and manufacture of biological therapies. Today there are several successful synergies between pharmaceutical and biotechnology sector to lower the risk of products failing and playing to the strength of each sector. The unknown question to be answered is how will the human genome project impact drug development in the future.

Today, the American trained international scientists have started to return to Europe and Asia. These scientists and their governments are very aware of the commercial potential of biotechnology. Those governments are now more prepared to play an active role this new science. China, Singapore, Taiwan, Japan, Hong Kong, New Zealand, Ireland, Britain and Israel are such examples of these governments that support biotechnology in their country. Will medicine in America continue to dominate science or will new scientific innovations appear in Europe or Asia?

Entrepreneurs and startups

The successful early stage companies, as we have seen with Genentech, have innovative or breakthrough technology. The unique product offers a value proposition for successful commercialization. The product is faster, better and cheaper than the competition. The scale up of the product has been evaluated by manufacturing. There is early marquee customer adoption and a large growth market. There is an opportunity to build an alliance with major companies, as Genentech did with Lilly.

One of the most important advantages in the business culture in America and especially in California is confidence or a lack of fear in failing. In some industries, the manager that ahs failed will bring more experience to the next company and their failure may bring success the next time. This business personality trait is both strength as well as a weakness. Many academic entrepreneurs lack an understanding of the process of commercializing their ideas, and the basic skill set to make it happen. The scientist is skilled in publishing his research and get government funding. The process of commercializing your science requires similar discipline. The concepts need to be validated and models tested. The more validation, the risk of investing decreases. Government funding for commercialization also encourages investors. The process for obtaining funding from the investment community is in principle getting research funding from the government research agencies. How to attract the investment community to mentor and support your idea is the next step in the commercialization.

The investment community

When investors are evaluating a business idea, they are asking three important questions:

1. Is the technology novel and unique and patented?
2. Does the scientist listen and take advice well?
3. Is there a first mover customer and a sizable market that will give a good return on investment?

Success in science and success in business require two very different skill sets. The successful scientist has a very powerful, very narrow focus area of their research. A businessperson needs to take a broader view and look at the science from a practical point of view. The pre-venture capital community (angel investor) provides opportunities for entrepreneurs to be mentored and funded. These investors have played an important role in the deal flow of bringing technology concepts forward into products. The angel investors can enhance the rate of success by supplying funding for testing these concepts, determining the feasibility of manufacturing the product and carefully defining the customer/market. These Angels communities (~200 in the United States) have demonstrated their success by helping limit the number of common business mistakes by the entrepreneurs. The venture capital community then has the ability to partner with these start-up companies to effectively launch the product into the market. The business process of creating a profitable enterprise will thus benefit all the participants involved. How can we make this process more efficient? The next generation of entrepreneurs must be educated in the understanding of these new dynamics of commercialization. In fact, the major universities in Europe, Asia and the North America are playing vital roles in educating and supporting their entrepreneurs. The Tech Coast Angels of Southern California are one of the largest organizations in the United States and most imitated models for supporting start-up companies. Their track record for profitably launching start-up companies and reducing the risk of transforming novel concepts into commercial products is copied globally.

Business incubators

The goal of incubators is to create business by providing a supportive atmosphere for the entrepreneur. The majority of startup businesses fail but the majority of businesses located in incubators succeed. These centers are the cradle for concepts to be mentored and funded by the investment community. It is an environment for early stage companies to be in a safe and disciplined community. The ability to attract startup companies and surround them with mentoring, resources and funding leads to a more successful outcome for their businesses.

Conclusions

The challenges for commercialization of science are the following: a competitive science education program; improved processes for transforming technology into products and a synergistic science and business culture. If the academics, the business community and government have a working collaboration these goals will be achieved with better and cheaper therapeutics. The American educational institutions have a clash of two scientific cultures: commercialization of science or science for the purely an academic endeavor. This conflict continues today on academic campuses even after the government has passed laws in the 1980's for government-funded research to be commercialized. If there will be an improvement in the rate of commercialization for gene therapy products there are several cultural changes that will be

necessary in science and business. The researchers in the universities will need to become more open to the potential of applying their science to practical problems in the life sciences. The government will need to create incentives for the research community to applying their research. The university technology offices will need to bridge the science and business communities more successfully. Investment communities will need to learn the language and culture of the science community. The pharmaceutical industry will need to support and enhance the success of validating and marketing these medical products. Incubators, government or industry sponsored, will be required better collaboration between these disparate groups and have them work together under one roof.

The opportunities for business are the following: there is a strong business culture with a can do spirit; a culture that is not risk adverse and there is an established mentoring program by the investment/entrepreneurial community. The investment community in Southern California (Tech Coast Angels, www.techcoastangels.com) has one of the best working models to date but there can always be improvements. Their website offers may tools for the startup company to be successful and ask the important questions.

We live in a digital world of instant information exchange; there is no longer a time lag to acquire the latest scientific information or obtain access to a current web cast of scientific medical conference. Thus, a collaborative network between the university, government and the investment community is vital for supporting entrepreneurs and a strong economy. The transformation of a scientific concept into a medical product is a multistage process requiring both excellent science as well as good management. Who will make the next advances in gene therapy treatments of cancer? These new and novel gene products may have a similar impact on the global health system and national economy, as antibiotics did on infectious diseases in the 1950's.

Gene therapy and stem cell therapy offer a potential impact the treatment of catastrophic human diseases but unless were understand the pathology of the disease process and their therapeutic intervention sites we will not achieve the medical impact of antibiotics on infectious diseases.