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The history of biotechnology–exploration into the future technologies, trends and growth of biotechnology markets

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He Choil Wang, Bill Tawil
Department of Biomedical Engineering, University of California Los Angeles, USA

Correspondence: Bill Tawil, Department of Biomedical Engineering, University of California Los Angeles, 420 Westwood Plaza, Room 5121 Engineering V. P.O. Box 951600, Los Angeles, CA 90095-1600, USA, Tel 805 558 4887, Fax (310) 794-5956, Email btawil@seas.ucla.edu

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Introduction

Biotechnology has been discovered by the humans of ancient civilizations. It has been reported that as early as 7,000 B.C.E, the Chinese discovered fermentation through beer-making.[1–6] Other common food products such as yogurt, cheese and bread are all biotechnology products that humans have been producing and consuming for centuries. One nemesis that has followed mankind through the passage of time is disease. As civilizations grew larger with more citizens living in close proximity to one another without sanitary conditions, disease became a prevalent problem. One feared enemy of the 18th century was smallpox. Repeated outbreaks occurred throughout the century, claiming the lives of millions- in the epidemic of 1721, the fatality was nearly 15% among those who contracted the malady [19). One of the most important medical milestones achieved in the late 18th century was by Edward Jenner, who inoculated live cowpox virus in order to vaccinate individuals against smallpox.[7–9] While he did not discover the scientific principles of vaccination, he was the first scientist to use the scientific approach to conduct scientific investigation.[9] Today, many individuals are now aware of the complexities and considerations that must be made when developing a new (or new type) of vaccine.[9] The vaccine was such a godsend that in fact, vaccinations became entrenched as a routine operation in local communities because of early governmental enthusiasm for and legislation around the practice.[9] Such discoveries led to one significant discovery after the other, scientists drawing inspiration from one another. Another hallmark milestone of the 19th century was the development of cholera and anthrax vaccines by Louis Pasteur in 1881.[9–12] He studied anthrax, with the goal of proving how anthrax was spread and how it made people or animals sick.[12] Later in 1885, he and Emile Roux developed and tested the first rabies vaccine on a 9-year-old boy named Joseph Meister.[11]

Early biotechnology history

While these discoveries capture the power and capabilities of biotechnology, the term itself had not been coined until 1919 by Karl Ereky, a Hungarian agricultural engineer.[12–37] His definition of 'biotechnology' did not endure, as scientists would eventually define it as "application of the principles of engineering and biological science to create new products from raw materials of biological origin, for example, vaccines or food."[37] In 1928, Alexander Fleming had discovered penicillin while sorting through his petri dishes containing colonies of Staphylococcus.[30] Another landmark discovery was made in the field of agriculture - the breeding of hybrid corn. In 1933, the first hybrid corn was commercialized by George Carter.[27] Entrepreneur Eugine Funk and his family started the Funk Brothers Seed Company, becoming one of the first seed companies at the beginning of the 20th century.[27] Beginning in the 1970s, the field of biotechnology begins to flourish and thrive - Stanley Cohen and Herbert Boyer perform the first successful recombinant DNA experiment using bacterial genes to artificially introduce a genome of another organism and then replicate the genome.[27] Their research and studies would later inspire a race for the development of synthetic insulin by large companies and institutions such as Genentech (the first American biotech company), Eli Lilly, Harvard, and UCSF. David Goeddel and Dennis Kleid were the first team of scientists from Genentech to successfully synthesize human insulin by creating the genes by chemically linking together snips of DNA sequences and then stitching those genes into plasmids.[16] Genentech licensed their technology to Eli Lilly so that they may scale up their manufacturing processes to bring Humulin onto the market in 1982.[16] Humulin was the first recombinant pharmaceutical approved by the United States Food and Drug Administration (FDA).[16] Several additional hallmark discoveries of biotechnology include the discovery of the Polymerase Chain Reaction (PCR) technique in 1983,[34] cloning of Dolly the Sheep from two adult sheep cells in 1997,[36] and completion of the Human Genome Project in 2000.[35]

Modern biotechnology applications

Biotechnology has evolved into many advanced industries that have become dominated by companies in the field of biotechnology-industry leaders have reached significant milestones in the fields of biosurgery, biomaterials, tissue engineering, and medical devices have been made by the scientists and engineers from these numerous companies. There are manufactured skin grafts by companies such as Integra Life Sciences, Organogenesis and Advanced Tissue Science. These companies produce skin graft products consisting of collagen scaffolds, synthetic materials, and fibroblasts to promote wound healing at the injury site.[31]

The biomaterials industry optimizes and discovers biomaterials that are used to construct products such as heart valve prosthetic

devices, hip replacement devices, dental implants, and more. When companies explore what type of biomaterials to consider for use in a device, it is very important to be mindful of the physical properties that may be required for the device to function properly. Implantable devices are composed of different quantities of these biomaterial polymers[31]- chemists, biomaterial specialists, and engineers must be cognizant of the chemical & immunological reactions that the polymers may undergo once it has been introduced into the human body. There are various types of tissue engineering such as bone tissue, vascular tissue, stem cells, and more.[31] The medical device industry is vastly different from the tissue engineering and biosurgery industry, as one company can create medical devices for many human ailments. For example, Abbott has 6 main product offerings in the following segments: cardiovascular, diabetes, diagnostics, neuromodulation, nutrition, and pharmaceuticals.[3] Confirm Rx™ is Abbott's insertable cardiac monitor.[1] By continuously monitoring heartbeats with a smartphone connection via Wi-Fi and Bluetooth, it is capable of accurately monitoring heartbeat irregularities.[3] The Gallant HF™ is a cardiac resynchronization therapy that monitors the heart for failure.[3] To help prevent heart failures, the SyncAVplus™ CRT technology offers dynamic AV timing to ensure proper electrical resynchronization.[1] The FreeStyle Libre™ is a disruptive technology of diabetes management. The Libre is a wireless, continuous glucose monitoring (CGM) therapy system that can monitor glucose levels via painless scans of the sensor.[2] This product has been labeled for use in diabetic patients from the ages of 4+.[2] The large diversity of medical devices, the rapid evolution of its technologies, and an aging human population will pave the way for tremendous growth in the years to come.

Biotechnology markets

Market trends

According to the Pew Research Center,[16] 50.3% of U.S. adults 55 and older said they were out of the labor force due to retirement. As the aging population continues to grow, so too, does the demand for the diverse offerings of medical devices such as pacemakers and neuromodulation devices. Pacemakers are small medical devices that are implanted into the chest or abdomen to monitor and control abnormal heart rhythms.[32] The electrodes are implanted in the ventricles and aorta to deliver electrical impulses to the heart.[32] They are connected to the pacemaker at the head port with conductive wires called leads.[32] Pacemakers are designed to help patients with bradycardia and heart block, as well as those who have cardiovascular disease (CVD), are taking beta blockers, or have had a medical procedure to treat arrhythmia.[32] In 2015, 1.3 million pacemakers were sold globally and 6 million in the United States, generating slightly more than $8 billion in global revenues.[32] In 2018, more than 2 million units were sold globally, generating global revenues of $12 billion.[32] Past market analysts have projected the 2014 - 2018 global cardiac pacemakers' market to be exhibiting accelerating growth rates at a compound annual growth rate (CAGR) of 13.89%.[17] The projections were accurate then and they still remain accurate now; the 2017 - 2021 global cardiac pacemakers' market is projected to grow at a CAGR of 13.00%.[18]

The market trends for the demand for pacemakers remain strong, not solely because of the growing aging population, but also because of the large number of patients with CVDs who may require heart valve procedures.[32] In fact, approximately 2,150 Americans die of heart disease every day;[24] CVDs are currently the leading global cause of death, accounting for 17.3 million deaths per year.[24] This number is projected to grow by more than 50% to 23.6 million by 2030.[24] It is estimated that about 86 million Americans are currently living with some form of CVD or the after-effects of a stroke.[24] There are several medical device companies that manufacture pacemakers, such as: Abbott, Medtronic, and Boston Scientific. Confirm Rx™ is Abbott's leadless, insertable cardiac monitor.[3] By continuously monitoring heartbeats with a smartphone connection via Wi-Fi and Bluetooth, it is capable of accurately monitoring heartbeat irregularities.[3] The Micra AV™ and VR™ is Medtronic's implantable leadless pacemaker.[22] With a very similar form factor to the Confirm Rx, this small implantable device is placed into patients' hearts with minimally invasive procedures. Boston Scientific also manufactures pacemakers, the ACCOLADE™ MRI and ESSENTIO™ MRI being their latest models.[7] Although these two pacemaker models are safe for MRI scanning environments of 1.5T (teslas) and 3T,[7] the form factor is still quite large and resembles those of the previous generations of pacemakers, requiring patients to undergo invasive surgeries for implantation.

A medical device market that has experienced rapid growth is neuromodulation devices. Neuromodulation devices focus on restoring function, relieving pain, and controlling symptoms by modulating the nervous systems' functions.[33] These devices provide electric stimulation treatments using methods such as deep brain stimulation (DBS), spinal cord stimulation (SCS), and other nerve stimulation methods.[33] One of the most developed methods of electrical stimulation is SCS. Spinal cord stimulators are medical devices very similar in functionality to pacemakers- there is a pulse generator that creates an electrical signal and delivers it through the leads.[33] The electrodes at the ends of the leads are connected to the patients' spinal cord at specific locations, anywhere from the low thoracic to the upper lumbar levels.[33] The SCS device market accounts for nearly 70% of all neuromodulation treatments.[33] There are approximately 34,000 patients every year who undergo spinal cord stimulator implants each year around the world.[33] The global SCS market was predicted to grow to $3 billion by the year 2022;[33] however, market analysts are projecting that there will be slowed growth, growing to only $4 billion by the year 2027.[14] The entire neuromodulation devices market was valued at $7.6 billion in 2019.[25] Market analysts are projecting the neuromodulation device market to grow to $16.3 billion by the year 2027, at a CAGR of 10.3% during the period 2019 – 2027.[25]

Market growth

The growth of this market can be attributed to several major factors: the growing prevalence of neurological disorders, incidence of chronic diseases, and a rising geriatric population.[21] According to researchers,[21] roughly 50 million adults in the United States are dealing with chronic pain - when considering the entire US population, it is estimated that 100 million individuals in the United States deal with chronic pain.[32] I believe that by the year 2030, we will see that value rise to 150 million individuals, as more individuals enter retirement, and the geriatric population grows. There are several companies that produce neuromodulation devices, such as: Abbott, Boston Scientific, Cyberonics, and Medtronic. The Proclaim™ XR is Abbot's implantable SCS system, while the St. Jude Medical Invisible Trial System™ is Abbott's trial device for new SCS patients.[1] Boston Scientific has their implantable Precision Montage™ MRI SCS system;[8] to my surprise, they do not offer a trial device for new patients. Cyberonics manufactures their VNS Therapy™ to combat epileptic seizures- it is currently used by over 100,000 patients, including 33,000 children globally.[12] Medtronic produced the implantable Vanta™ SCS neurostimulator, a device boasting long-lasting battery life up to 11 years.[23] The medical device industry giants are constantly being disrupted with new technologies from start-up

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companies developing their own devices to deliver unique value to the patients. Incumbents of the industry must either keep technological pace with the disruptors or create strategic partnerships with the new market entrants.

Future trends

Technology trends

Medical devices and the technologies driving these devices are continuously evolving, becoming smaller in size but having larger capabilities and functions. We have witnessed not only tremendous growth in the cardiovascular medical device industry, but the evolution of some of its most prominent devices such as the pacemaker. The first implantable cardiac pacemaker was invented in 1957 by Swedish inventor Rune Elmqvist,[29] under the guidance of Earl E. Bakken, one of the co-founders of Medtronic Inc.[4] Prior to the invention of an implantable pacemaker, pacemakers were extremely large and had to be pushed around like a shopping cart.[29] Presently, we now have an implantable leadless pacemaker the size of a large vitamin capsule.[22] It is anyone's guess as to how much smaller the medical device can become - this device has, in my opinion, reached the apex in terms of size and form factor; however, improvements such as longer-lasting battery life and accuracy of the detection of irregular heartbeats will always remain. How far the technology can be improved upon, it is impossible to say at the moment.

Neuromodulation devices have yet to see this evolution in form factor. Spinal cord stimulation (SCS) devices have a very similar design to the implantable, stainless-steel pacemaker - they have an antenna, built-in lithium-ion battery, and lead ports. The leads are implanted just above the spinal cord in an attempt to mimic the anatomy of the damaged nerves. I believe that within the next 5- 10 years, a company is going to launch the first leadless SCS device for chronic pain patients. A leadless SCS device would look similar in form to Medtronic's Micra pacemaker, except that a leadless SCS device would require a neural network of small, implantable devices that are capable of discharging powerful electrical impulses from a remote controller (preferably with Bluetooth Low Energy technology) or a mobile device. There is a laboratory called Artann Laboratories that has developed a technology that allows for a remote electric signal to be generated with their proprietary 'TRA ultrasound focusing system'.[5] A wireless neurostimulator device can be implanted near the pain site, where it then receives a wireless signal to discharge an electrical signal to the nerve. While we do not know the full limitations of this technology, some prevalent ones may include distance needed for the devices to communicate, form factor of the implanted neurostimulator, and the battery reliability / longevity. This lab's technology could certainly be implemented by larger medical device companies to get one step closer in developing their own leadless neurostimulators.

Drug delivery systems such as diabetes management devices are making huge progress towards improving the ease-of-use for their patients. One of the most disruptive insulin therapy systems on the market right now is Abbott's FreeStyle Libre. The FreeStyle Libre has forced Abbott's competitors to develop a similar product that delivers Bluetooth-enabled, glucose-sensing technology to their smartphones. There is another company called Senseonics that has developed an implantable, long-term use glucose sensor the size of a pill capsule.[28] The sensor is implanted just underneath the skin, constantly communicating with a smart transmitter that must be paired with a smart device via Bluetooth.[28] While this company does not have an insulin delivery device with this sensing technology, other industry incumbents may certainly try to acquire this technology, if not develop something similar in size and function, to make the next great leap in technological innovations. The current trend I am observing for more drug delivery devices is to focus on reducing the form factor and the burden on the patient - while I am not disregarding that the engineers of these medical devices are also focusing on improved device functions, reliability, and accuracy; these medical device companies focus mostly on the burden of use of a medical device for the patient.

Prospective future

As the design engineering aspects continue to improve, so too, do the advancements in the communication software that the devices rely upon. In recent years, many consumer devices such as wearables and apps have made tremendous progress in helping users to monitor their biometric data such as pulse, heart rate, blood oxygen, and blood pressure. I believe that when we establish the proper rules and regulations to overlook how patients' personal data will be stored and distributed, we will then be able to implement more advanced technologies such as artificial intelligence (AI) and machine learning into the software. Using the example of diabetic patients who are actively managing their diabetes with an insulin therapy system, I visualize the disruptor of drug delivery systems as a patch glucose sensor (usable for 30 days) that communicates with the patient's personal smartphone device and patch cannula with a built-in reservoir. The three devices are paired together and are continuously communicating with each other. Should the sensor detect abnormal glucose levels, patients would be alerted on their smartphones and prompted to authorize a delivery of bolus or suspend basal delivery by the patch cannula. Combining these features with machine learning, where the software can collect and analyze real-time data to determine trends in BG (level of glucose in blood), the device can automate itself to deliver the insulin, when necessary, based on data analytics. This smart, neural network of a medical device would truly exemplify what it means to alleviate pain, restore life, and extend life.

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Conflicts of interest

The authors state that there is no conflict of interest.

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