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Biomedical Research and Healthcare: Opportunities, Expectations, and Limitations

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Abstract

The last fifty years have been the "golden era" of biomedical research and innovation. Major discoveries in genetics, genomics and various fields of "Omics", together with the technology revolution, has created unlimited opportunities for the development, and improvements in the way the healthcare is delivered. Not a single day goes by, without an announcement of a new sensor, new app, or a new and novel technology, that can be integrated with the wealth of knowledge in biomedical research and applications. To the extent, one of the largest insurance provider, John Hancock announced, that they no longer offer policies, that do not include digital tracking. They will sell only "interactive" policies that collect health data through wearable devices, such as smart watch. The breakthroughs in biomedicine, and advances in technologies, have been miraculous. This is especially true in the USA, which is the envy of other nations, when it comes to innovations in research and technology. The fact that all of these innovations are "news makers" creates great expectations from the care receivers. Having said that, patients, clinicians, and healthcare providers feel at times a letdown, or question the slow pace of advance, escalating cost, sometimes dubious clinical values and inappropriate exploitations. Policy makers and economists are debating, about the cost-effectiveness and the return on the investment in biomedical research, as it relates to improvements in health care. Researchers worldwide are debating about the availability of "Precision Medicine" and "Personalized Medicine." Despite the developments in biomedical research and emerging technologies, which have raised our expectations and created infinite opportunities, there seems to be some limitations in their applications. In this mini review, we will briefly discuss some of the developments in biomedical research and innovation. We will also express our views on the opportunities available and explain limitations. (**International Journal of Biomedicine. 2018;8(4):273-279.**)

Key Words: biomedical research • healthcare • technology innovations • genomics

Introduction

Measuring the contribution of biomedical education and research is more or less a guess than a true estimate. It has been estimated that 23-48% of the decline in mortality over the 1930-1978 is attributed to biomedical research efforts. It translates to a net return of 83 billion, illustrating the wisdom of investment in biomedical education and research.[1] For example, biomedical research in the U.S. is a over 100-billion-dollar enterprise, - 65% supported by the industry and 35% by the National Institutes of Health. The dilemma regarding the return on investment is compounded by the unpredictable nature of basic sciences and its applications.[2] In the "State of the Union" address, President Barack Obama on the 20th of January 2015 made the following announcement; "Tonight I am launching a new precision medicine initiative, to bring us closer to curing diseases like cancer and diabetes- and to give all of us, access to the personalized information we need to keep ourselves and our families healthier." Dr. Francis Collins, the director National Institutes of Health, USA announced an initiative called, "All of US", a billion-dollar program, which has two main components: a near-term focus on cancers and a longer-term aim to generate knowledge applicable to the whole range of health and disease.[3] The NIH researchers envisage to recruit a "cohort" of 1 million Americans, who will consent to give biologic specimens (cell populations,

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proteins, metabolites, RNA, DNA-including whole-genome sequencing and behavioral data, all linked to the electronic health records.

If you do a search on the top ten biomedical innovations, you hardly get any discussions on biomedical education, research or applications. Cleveland Clinic at their 15th annual medical innovation summit in October 2018 list the following: Artificial pancreas, pacemaker, gene therapy, reduction in LDL, new generation vaccines, breast cancer therapies etc. Since the discovery of the double helix nature of the DNA (1951-53), biology has evolved into a global industry promising miraculous biomedical applications and opening the door to precision and personalized medicine. The Human Genome Project launched a new area of "BIG Science," It was 13-year-long publicly funded project initiated in 1990, with two key principles; 1) welcomed all collaborators from any nation, 2) required all human genome sequence information should be freely, publicly, available. With the initial success in this project in 2002, first successful genome-wide association study (GWAS) was published for studying myocardial infarction.[4] With the advances in the knowledge of molecular cloning, gene transfer in the 1980s, molecular medicine emerged as a novel and revolutionary therapy.[5] After decades of ups and downs, according to an article in Science, "return of gene therapy" had a breakthrough in 2009. In brief, the gene therapy is quite simple; a functional copy of the defective gene is introduced to replace the missing function or a defective gene.[6] Two decades after the initiation of gene therapy trials with more than 1700 approved clinical studies, first therapy product (Glybera) approved by European Medical Association, is available for use in the European Union for the treatment of ADA deficiency.[7]

Cellular therapies and regenerative medicine, with great potential to improve the health of patients, represent a game changer in modern healthcare delivery, by focusing on the underlying causes of the disease by repairing, replacing, or regenerating damaged cells, organs and tissues. First allogenic hematopoietic stem cell transplant (HSCT) was done more than fifty years ago in a patient suffering from acute leukemia. Fifty years after this clinical breakthrough, HSCT remains the only stem cell therapy widely used in clinical practice.[8] Researchers, clinicians, and biotechnologists worldwide, are investigating ways and means to mitigate, the challenges and risks of stem cell therapy. Embryonic stem cells are promising, but there are challenges when it comes to controlling the cell growth. Several laboratories are testing mesenchymal stem cells (MSCs), as they can be isolated from any adult tissue, in addition to fetal tissue and cord blood. Due to the lack of a single marker to define MSCs derived from different sources, the regulatory bodies have adopted a criteria, regarding marker expression and differentiation potential.[9] In the area of regenerative medicine, the University of Minnesota researchers developed "Ghost Hearts" and claimed that a real beating bio-artificial heart will be ready in a few years.[10]

Doris Taylor and associates at the University of Minnesota, pumped detergents through rat hearts, and obtained a biological scaffold (ghost heart), for an artificial heart that comprised of collagen and other extra cellular matrix. They incubated it in a bioreactor and reseeded it, with heart cells from a newborn mouse. Results of this pioneering study were published in the Nature Medicine.[10] Although tissue engineered hearts are not yet available, the techniques developed have been of great use in cardiac repair.[11] Developments in the biological sciences, cannot really compete with the rapid progress that is taking place, in emerging technologies and biomedical innovations. Just a few years ago, it was unthinkable, that any body part can be printed with synthetic components. It has now become a reality. Researchers at the University of Minnesota have 3D printed a bionic eye. The device is an array of semiconductor photodetectors, made of polymers, printed on glass hemisphere.[12] Scientists in Switzerland have 3D printed a silicone heart, that works and pumps like a real human heart.[13] Researchers in Netherland have developed 3D-printed tooth that has antibacterial properties. Canadian researchers have used 3D printing, to develop skin that is tissue specific to patients for wound healing applications.

We mentioned that developments in basic science applications are unpredictable. White in his article on the history of Diabetes, mentions that management of diabetes during the past several thousand years, since time of Pharoh's (3500 ago) to the present, has changed considerably.[14] Despite these observed changes in the management of this metabolic disease, it continues to increase even at the time of this writing in unprecedented rate. Metabolic diseases such as, hypertension, excess weight, obesity, and diabetes (type 2) have reached epidemic proportions worldwide.[15-20] According to these experts, obesity has doubled (over a billion) and diabetes has increased four-fold worldwide in the last three decades. A multi-country review on the global prevalence of diabetes concluded, "Most people with diabetes live in low- and middle-income countries and these will experience, the greatest increase in diabetes for the next 22 years. Countries like India and China, with very large populations, have had an increase of two-fold to 17-fold in diabetes incidence in the last three decades. Framingham Heart Studies, initiated some 70 years ago in the USA, developed basic information on the modifiable risk factors for developing cardiovascular diseases (CVDs). In a Science editorial, Brown and associate speculated that, "Exploitation of recent breakthroughs-proof of the cholesterol hypothesis, discovery of effective drugs, and better definition of genetic susceptibility factors- may end coronary disease as major public health problem.[21] Two decades after this claim was made, cardiovascular disease remains the number one killer worldwide. In this mini review, we will discuss some biomedical innovations, research accomplishments, expectations, and limitations as well as express our viewpoints on these findings.

Discussion

According to the experts, genomics will most likely make its greatest contribution to health by revealing mechanisms of common, complex disease, such as hypertension, diabetes and asthma.[22-25] From the time the Human Genome Project was initiated, there is great expectation and excitement, about its possible contribution to improvements in healthcare. Having

said that, there seems to exist considerable confusion among health care professionals, educators, and public about the exact role of genetic information in medical practice. Dr Francis Collins in an article in N. Engl. J. Med. writes, "If genetics has been misunderstood, genomics is even more mysterious."[22] Genetics is the study of single genes and their effects. Genomics is the study not of single genes, but of the functions and interactions of all the genes in the genome. For instance, human gut microbiota contains tens of trillions of microorganisms, including at least 1000 species of known bacteria with more than 3 trillion genes, which influence human physiology, metabolism, nutrition, immune function, and disruption of normal metabolism. In the large genomic study, we described earlier as a part of the "All of Us' initiative, diabetes is one of the topics of interest. Metabolic alterations such as oxidative stress, chronic inflammation, hypertension, endothelial dysfunction, subclinical atherosclerosis, excess weight, and obesity contribute significantly to the pathogenesis of diabetes and its clinical complications. In a situation like this, we are looking at the individual's gene and its interactions as well as his/her microbiota genes and their combined contribution to the altered metabolic processes.

Several researchers have reported, that metabolic signature of plasma free branched chain and aromatic amino acids, strongly predict future diabetes development.[26-30] Based on this type of investigations, diabetes predictive amino acid score has been developed (DM-AA score). It has been shown, that a score of fasting plasma level of isoleucine, tyrosine, and phenylalanine, predict diabetes development, predicts CVD events during long-term-follow-up.[30] Fuzisaka and associates from Joslin Diabetes Center, Harvard Medical School, performed LC-MS based metabolomic analysis, of cecal contents and plasma metabolites. Of the over 1000 unidentified metabolites, eighteen correlated positively with host insulin resistance.[31] The researchers concluded that, "The changes at the level of gut and blood are dramatically influenced by diet, exposure to antibiotics, genetic background, and site of bacterial colonization. These and other such studies are challenging and hard to interpret, as we are dealing with thousands of gene interaction products and metabolites in the gut and their role in altered amino acid or fatty acid metabolism. Of course, it would be useful to fully understand the complex role of diet, gene expression of the host, the gut microbiota, and the modulating effect of various metabolites, in the initiation and progression of metabolic risks and metabolic diseases.[32]

Type 2 diabetes (T2D) has reached epidemic proportions, worldwide and as such there is lots of interest in genetic studies related to this metabolic disease. The Genome Wide Association Studies (GWAS) has confirmed epidemiological observations of genetic links, between lipid dysregulation and glycemia (FADS1, GCKR, HNF1A), circadian rhythmicity, metabolic derangements (MTNR1B, CRY2), low birth weight and subsequent T2D risk (ADC5). Type-2 diabetes GWAS have been successful in identifying specific loci, that contribute to the causation of the complex disease roughly in only 10% of the heritability suggesting, that much remains to be discovered.[33] Although there is a great hope and expectation that such studies, will provide opportunity for therapeutic interventions, and pharmacogenetic clinical trials, common genetic variants identified so far, are not yet useful in clinical prediction or therapy. In order to find the "missing heritability" researchers are pursuing fine-mapping around the associated regions, leveraging the 1000 genomes project, using next generation sequencing, analyzing the Metabochip, improved informatics for gene x gene and gene x environment interactions.[33]

Recent advances in regenerative medicine has generated great enthusiasm and expectations for various clinical applications and easy cure. Just like the new drug development, cell cultures require Good Manufacture Procedures (cGMP), but cell cultures are more complex and less controlled than small molecule research, common in drug discovery studies. In addition, many challenges exist in todays' highly regulated healthcare environment. There is no harmonization between different regulatory authorities. Stem cell research has a real potential, to have significant impact on human health. There is however great controversy, about the use of human embryos for this kind of work. Scientists have been circumventing this concern, by using a method that can turn adult stem cells into pluripotent stem cells, which can change into any cell type. Despite these advancements, there is still a lot more to be done before the researchers can create successful treatments through stem cell therapy. Stem cell therapies are not new. Clinicians have been performing bone marrow stem cell transplants for at least half a century. The very first successful bone marrow transplant was done in 1956 at Cooperstown New York, by Dr Donnall Thompson in identical twins. The first non-twin (allogenic) transplant was done at the University of Minnesota in 1968.

In early 80s our research group at the University of Minnesota, demonstrated that in drug- induced diabetes animal model, vascular prostaglandin synthesis is altered, to create an imbalance between the thromboxane produced by the platelets, and prostacyclin generated by the vessel wall.[34] The changes observed both in platelet and vascular tissue, were corrected by islet cell transplantation.[34] ViaCyte a company based in San Diego, California, has obtained FDA approval for their product PEC-Direct and has treated its first patient. Via Cyte's PEC-Direct device allows a patient's blood vessels to integrate and contact the transplanted beta cells. VC-01 or PEC-Encap, is an implantable device containing embryonic stem cells that develop into pancreatic progenitor cells. VC-02 or PEC-Direct also transplants progenitors but the device allows patient's blood vessels to integrate with these transplanted cells (direct vascularization). Has the regenerative medicine come of age? Currently there are number of funded clinical trials, studying everything from stroke, to spinal cord injury and HIV/AIDS. It is heartening to note, that FDA has approved Kymirah and Yescarta for chimeric antigen receptor therapy (CAR-T). A type of treatment in which patient's T cells are changed in the laboratory, so they will attack cancer cells when transfused back into the patient. There is lot more to do. Most of these studies are Phase 1, Phase 2 trials. There are just a relatively few Phase 3 clinical trials.

Advances in tissue engineering and regenerative

medicine technologies, created immense opportunities for the development of tissues, organs, and sophisticated grafts for therapeutic applications. Modern era of tissue engineering is relatively young and began only a couple of decades ago. In brief, tissue engineering involved the *ex vivo* engineering of replacement of tissues for subsequent *in vivo* implantation. Skin substitute represented the earliest attempts of engineered tissues. In the early 90s, the stem cell biology began a full-scale emergence, and dedicated Stem Cell Institute and Translational Science Institutes were developed to support these applied biomedical technologies. More than 4,000 people are on the waiting list for a heart transplant in the USA alone, at any given point of time. Doris Taylor, Bakken Professor and the director of the center of Cardiovascular Repair, University of Minnesota, outlined her results on "bioartificial hearts", prior to the publication of her research in 2008 at the "Understanding Aging, Biomedical and Bioengineering Approaches" conferences at UCLA. She seems to have claimed that recellularized human hearts may be weeks away. Popular science went wild with the announcement of new and emerging field of rejuvenation biotechnology. Just at the same time, I was participating in a Stem Cell conference in which, a young investigator was heralding, that in the near future body parts will be available on medical shelves, for replacement of the defective parts.

In brief, the process of developing a beating heart is a simple process. Infuse a strong detergent through a donor heart (rat, mouse or pig), obtain a "ghost heart" with the intact exoskeleton of the donor heart. The scaffolds obtained from donor hearts retain the macro- and micro architecture, vasculature, and biochemical cues for cellular adherence, proliferation and differentiation. Once you have the "ghost heart" from an animal or human source, infuse the donor heart skeleton with millions of blood or bone-marrow stem cells, from a person who needs a heart transplant, place it in a bioreactor- a container with artificial lungs and tubes that pump oxygen, blood or nutrient cocktails into it, wait as the ghost heart matures, and starts beating like human heart (Fig 1).

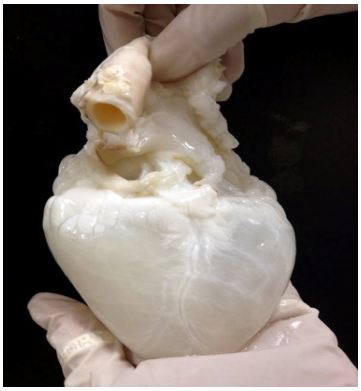

Fig. 1. *Bioartificial Heart (Dr. Taylor).*

According to the researchers at the Division of Cardiovascular Sciences, National Heart, Lung and Blood Institute of the National Institutes of Health (NIH), USA, despite widespread interest in the use of regenerative medicine to improve cardiac function, both in acute myocardial infarction and in chronic heart failure, the clinical benefit has been modest and variable between clinical trials, with some showing no benefits.[35] Just like the efforts to develop a bioartificial heart is facing challenges, 3D printing is also is in its infancy. Using imaging data and a thermoreversible support bath to bioprint an embryonic heart, researchers have developed a novel complex internal and external anatomical structure to mimic a human heart (Fig 2). However, these model hearts lacked the appropriate vasculature. Furthermore, all blood-contacting biomaterials and surfaces used in the development of these bioartificial organs, must be designed to be thrombo-and calcification-resistant in order to be successful post implant.

Fig. 2. *3D-Printed Bioartificial Heart (public: CNN).*

Long before the stem cell research and translational science platforms developed, the researchers at the university of Minnesota, were interested in developing bioartificial pancreas and bioartificial liver. As a young faculty of the Biomedical engineering, I was collaborating with the Center for Interfacial Engineering, a platform, which encouraged multidisciplinary research to encourage integration of emerging technologies. We also had established collaboration with the Medical Device Industries. One such company that we were collaborating at that time, was the Excorp Medical Corp Minneapolis, Minnesota. (http://www.excorp.com/html/product.html).

The product that they have been working on for quite some time is the Bioartificial Liver System. The system comprises of an extracorporeal (outside the body) loop that helps process continuously a patient's whole blood, maintaining temperature, oxygenating to arterial levels, adjusting pH to 7.2 and perfusing a hollow fiber bioreactor, charged with primary porcine hepatocytes, before returning the blood to the patient.[36] The bioreactor was patented (5,955,353) in the USA in 1999. The patent describes a platform technology of high-density cell culture, that can be extended beyond liver cells, to a wide variety of other cell types including, pancreatic islets (biocritical pancreas) and other endocrine cells. The company's bioartificial liver system has also been designated as an "Orphan Product" by the US/FDA, for the treatment of acute liver failure. Phase-1 testing of the system was done at the University of Pittsburgh (http://www.upmc.edu). A news release from the University of Pittsburgh Medical Center states, "Researchers at the University of Pittsburgh Medical Center (UPMC) have begun testing a new bioartificial liver

assist system designed by Excorp Medical, Inc., that uses healthy liver cells from pigs as a means to improve the liver function of critically ill patients with liver failure. The trial is intended to assess the safety of the system, but researchers also will be paying close attention to, whether it can improve a patient's condition until transplantation is feasible, or if it can obviate the need for transplantation altogether, if the failing liver recovers." Despite the success of the testing and the FDA approval as an orphan device, the system is still not available for commercial use.

We started this article with the news about the announcement of one of the largest "Genomic" study by the NIH. Despite the fact, that DNA sequence and analysis of metabolome has become easier and less expensive, interpretation of the data developed by such studies poses a great challenge. In a recent issue of JAMA (September 25, 2018), Burke discusses a case in point in which, "All protein-coding regions of the genome (an exome analysis) in 50726 individuals, found a median of more than 20,000 gene variants per person, most of them rare, and hundreds not previously identified." According to these researchers, the evidence for most variants is limited regarding pathogenicity. Just to illustrate this point further, I will discuss yet another study, which relates to the analysis of platelet lipidome. Researchers at Cardiff University, UK, found that resting platelets have over 5600 unique lipid species with only 50% being identified.[37] In reality, a only a handful of these lipid species have been shown to play a major role in platelet physiology and function. In a review article on this topic, Dr. Steve Watson and associates state that "applications of lipidomics to platelet biology is still in its infancy, seminal studies have shaped our knowledge of how lipids regulate key aspects of platelet aggregation, shape change, coagulation and degranulation, as well as how lipids generated by platelets influence other cells, such as vascular wall, and thus how they regulate hemostasis, vascular integrity, inflammation, thrombosis and atherosclerosis." Much of this information was available prior to any lipidomic studies. The thousands of lipid species discovered by lipidomics are like "orphan molecules" begging for explanation for their role, in the sequence of events described by these authors.[38]

To end this overview on medical innovations, we would like to include the top ten medical innovations for 2018, according to the prestigious Cleveland Clinic, USA. 1) Hybrid closed-loop insulin delivery system, 2) Neuromodulation to treat obstructive sleep apnea, 3) Gene therapy for inherited retinal diseases, 4) The unprecedented reduction of LDL cholesterol, 5) The emergence of distance health, 6) Next generation vaccines, 7) Arsenal of targeted breast cancer therapies, 8) Enhanced recovery after surgery, 9) Centralized monitoring of hospital patients, 10) Scalp cooling for reducing chemo therapy induced hair loss. In addition to these well recognized innovations, advances made in the area of polymer chemistry, material sciences, have provided us an important new class of mechanical and bioprosthesis heart valves. Five-year clinical studies have been completed, on self-expanding bioprosthesis. Rapid advances in human brain-computer interface technologies, have provided an electroencephalogram-based, brain-computer interface and lower-limb prosthesis control.[39] As is the case in all other innovative areas this new area of exploration, brain-computer-interface, has made impressive achievements over the past few-years.[39-42]

Conclusion

Advances in biomedical research, as well as technology innovations, offer new hopes and transformative opportunities, for improved healthcare. Since the early discoveries of DNA/RNA, micro RNAs, and beginnings of the Human Genome Project, there is a great expectation in the medical community, as well as patient population, that there will be rapid developments in the way the healthcare is delivered. There were lots of hopes and speculation, that we will find easy solutions, to address common chronic health issues. Rapid advances in the various genetic studies, elucidating the structures of DNA, RNA, and the total genome analysis, contributed significantly to our understanding of functional role of genes, gene expressions, gene x gene, gene-environment interactions, genomics, metabolomics, role of microbiota, use of CRISP technology, gene editing, gene therapy, cellular and molecular therapies. Medical technology innovations also have made rapid progress and complemented the advances in biomedical research and innovations.

The success of biomedical research in the early 50s of polio vaccination, antibiotics, antipsychotic drugs, and equally dramatic success in the applications of cardiopulmonary bypass, dialysis, and organ transplantations, prompted financing of research both by the industry as well as the government. In a review of this topic in the N Engl J Med. The authors make a very important observation, which summarizes the collective view of the expectant individuals, "Despite the justified scientific excitement about using knowledge of the genome as a fundamental exploratory tool, unrealistic expectations for a quick route to clinical applications have produced disappointment, especially among disease groups, and companies.[43] They further emphasize that with few exceptions, new scientific discoveries require 15 to 25 years for their clinical application. Advanced countries have sponsored and supported the research initiatives using a variety of models, encouraging alliances between the Academia and the Industries, multidisciplinary approaches, multicountry investigations, establishing specialized centers of excellence (Stem Cell Institute, Imaging Institutes, Genomic Centers), Clinical and Translational Institutes. Moses and associates reviewed 70 such alliances from the mid 1960s through 2000. In their opinion, these alliances have not accelerated the pace of either discovery or clinical application. According to these researchers, source of difficulty is idiosyncratic, but recurrent problems, or a failure at inception to agree on intellectual-property provisions, excessive secrecy, and disagreements over the overall research aims.[43]

Collaborators from the Johns Hopkins School of Medicine and the Harvard Medical School propose a seven point recommendation: 1) improve data on clinical value (develop more robust analytical techniques), 2) change the role of teaching hospitals (improve ability to do early-stage-clinical studies), 3) develop new models for collaboration and financing, establish biomedical innovation trusts (support

research on high-priority diseases), 4) create new class of bonds, use incentives to promote pluralism (preference in funding might be to new institutions and for new ideas), 5) defer patents to later in the discovery chain, renew professional commitments (remove personal bias and personal incentives), 6) focus on cost-effective targets, adopt realistic research goals (embrace new realism about the difficulty of the scientific process), 7) redefine the terms of conflict (not everyone believes biomedical research is essential). These suggestions are worth considering.[43] In this overview, we have discussed some of the major news worthy discoveries like, Framingham Heart Study (discovery of modifiable risk factors for heart disease), herald of the end or reduction in the CVD deaths, innovations in tissue and cellular engineering, development bioartificial heart and 3D printed hearts, and claims that a beating heart will be available in months or years for human transplantation, bio absorbable vascular grafts as substitutes for coronary stents, gene therapies, cancer antigen receptor therapies (CAR-T), and the progress made in bioprosthesis and computer-brain-organ-system interfaces. Despite rapid progress in biomedical research and emerging technologies, availability of new products for immediate clinical applications are limited. In spite of this observed slow pace, the overall contribution of the innovations in these areas to improved healthcare is phenomenal.

Conflicts of interest

No potential conflict of interest was reported by the author.

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