

Grand Challenges at the Interface of Engineering and Medicine

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Abstract—Over the past two decades Biomedical Engineering has emerged as a major discipline that bridges societal needs of human health care with the development of novel technologies. Every medical institution is now equipped at varying degrees of sophistication with the ability to monitor human health in both non-invasive and invasive modes. The multiple scales at which human physiology can be interrogated provide a profound perspective on health and disease. We are at the nexus of creating “avatars” (herein defined as an extension of “digital twins”) of human patho/physiology to serve as paradigms for interrogation and potential intervention. Motivated by the emergence of these new capabilities, the IEEE Engineering in Medicine and Biology Society, the Departments of Biomedical Engineering at Johns Hopkins University and Bioengineering at University of California at San Diego sponsored an interdisciplinary workshop to define the grand

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challenges that face biomedical engineering and the mechanisms to address these challenges. The Workshop identified five grand challenges with cross-cutting themes and provided a roadmap for new technologies, identified new training needs, and defined the types of interdisciplinary teams needed for addressing these challenges. The themes presented in this paper include: 1) accumulated medicine through creation of avatars of cells, tissues, organs and whole human; 2) development of smart and responsive devices for human function augmentation; 3) exocortical technologies to understand brain function and treat neuropathologies; 4) the development of approaches to harness the human immune system for health and wellness; and 5) new strategies to engineer genomes and cells.

Index Terms—Genome-engineering, human function augmentation, immuno-engineering, precision medicine, digital twins, neuroimaging, tissue engineering, organs-on-chip, patient on a chip, stem cells, biomaterials, bioreactors, models of disease, organ regeneration, drug testing, heart, lung, bone, brain, brain-computer interfaces, artificial intelligence, machine learning, neuromodulation, synthetic biology, gene therapy, cell therapy, biomanufacturing, disease resistance.

Impact Statement—The 21st century is witnessing a paradigm shift in human health and medicine. Engineering of entirely unforeseen devices, sensors and technologies has given rise to a deeper understanding of human physiology and pathophysiology. We are in the unprecedented position to translate the knowledge obtained from the multiscale myriad measurements into actionable outcomes and the Grand Challenges outlined here provide a roadmap for this future.

I. INTRODUCTION

THE engineering basis of human physiology has its origins in the first dissection of human cadavers by Herophilus and Erasistratus in the third century BC. Paulus of Aegina was recorded as the first to practice surgery when he operated on tonsils and lymphatic system of the lower cervical region and

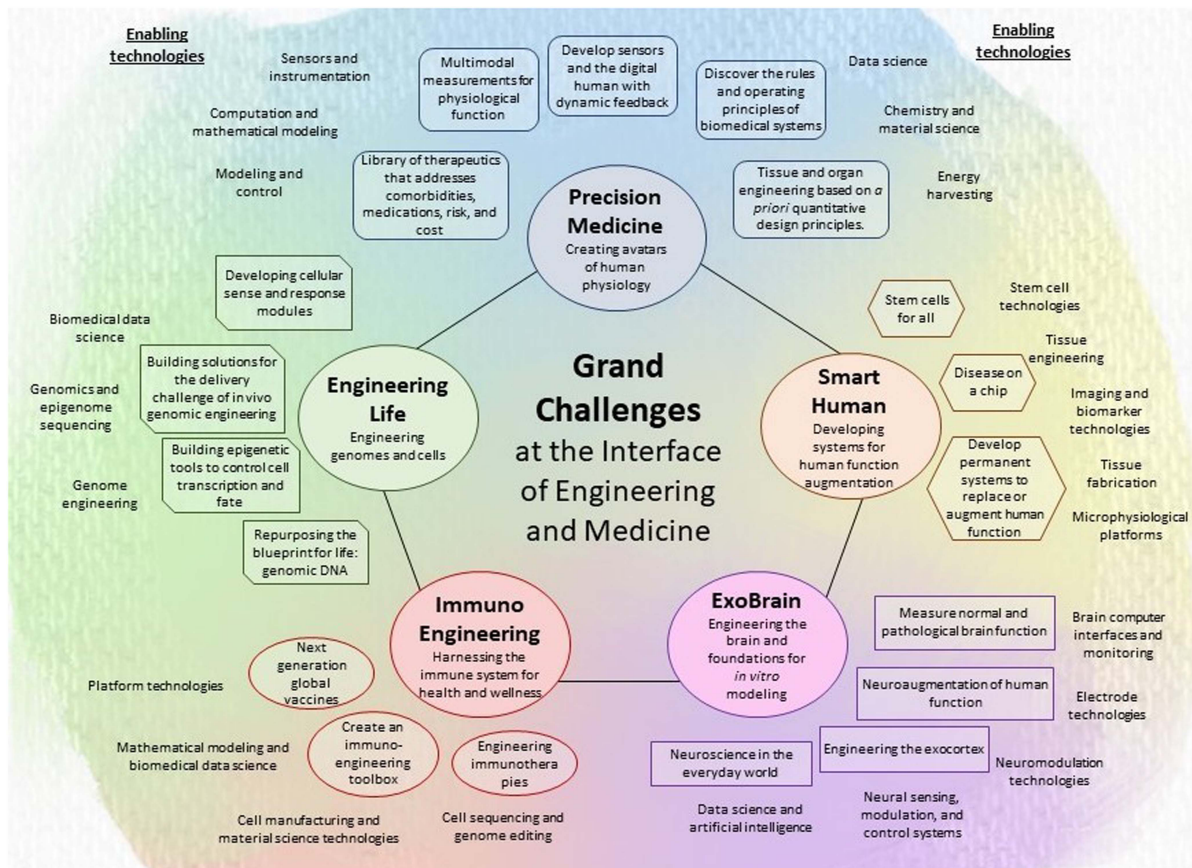


Fig. 1. Grand Challenges - A Schematic View.

cut the abdominal wall in 670 AD, although there is some evidence of human surgery carried out by ancient Egyptian and Mesoamerican civilizations. The first “engineering” annotations of the human body were made by Leonardo da Vinci in 1543 in his famous “De humani corporis fabrica”. The microscopic structure of the human brain, which made possible its engineering and functional analysis was presented by Santiago Ramon y Cajal. The first permanent implantation of an engineered heart was performed in 1982 at the University of Utah by Jarvik. Engineering has now become a *sine qua non* of medical practice, with myriad devices, implants, technologies and models.

We are witnessing tremendous advances in engineering and the blurring of the line between engineering and biology. We expected that this will result in the development of innovative medical diagnostic techniques and treatment approaches. To discuss the evolving role of engineering in the field of medicine, the IEEE Engineering in Medicine and Biology Society (EMBS), and the Departments of Biomedical Engineering at Johns Hopkins University (JHU) and Bioengineering at University of California San Diego (UCSD) organized the workshop titled “Grand Challenges at the Interface of Engineering and Medicine”. The event brought together international experts in the field of biomedical engineering for two days. This group of experts co-authored this position paper which is the result of in-depth discussions during the two days of the event and several months after the workshop. The group identified five

grand challenges as the research areas with the greatest potential of achieving tremendous impact on the field of medicine. These grand challenges are summarized in Fig. 1. The manuscript provides a roadmap of needed technologies and concepts as well as a discussion of the interdisciplinary training that will enable these challenges to be addressed. Our main objective is to inspire students and researchers to think of novel paradigms and bring new innovations and engineering ideas to human health and medicine.

While one of the great engineering challenges of the 20th century was innovative design of implantable and prosthetic devices, the new paradigm we describe here begins with the complete digital mapping of human health and disease. This mapping heralds the birth of precision medicine across all scales with the ultimate goal of creating an “avatar” for every human that can prognosticate the health and wellness of the human in a non-invasive manner. The avatar is not merely a digital twin but can be a physical manifestation of the human tissue or organ that can be explored *ex vivo*. The **creation of avatars of human physiology** is one of the current grand challenges at the interface of engineering and medicine. Implied in this concept is the design and construction of precise engineering models of human physiology from *in silico* models to actual realization.

One of the most intriguing concepts of this design is the notion of real time sensing and adaptation to all input by human physiology, -which is a dynamic control and optimization problem.

The engineering notion of avatar also rests on the idea that each component of the human avatar can be treated much like the individual tissues and organs designed independently to function in a synergistic manner with other components. These components can also be used as *smart and implantable devices to augment or in some cases replace their human counterparts*. This is a significant grand challenge at the interface of engineering and human physiology.

The last decade of the 20th century was declared as the decade of the human brain, albeit a little prematurely. The human brain arguably is the most complex engineered physiological component of the human. Understanding the brain and its myriad processes represents one of the major challenges of our time in terms of the treatment of both neurodevelopmental and neurodegenerative disease. At the same time in the age of artificial intelligence there remains no greater opportunity than to build artificially intelligent machines that resemble our innate and organic intelligence. In the vein of conceptualizing avatars, the greater challenge would be *the design and actuation of the human exocortex*, the design and mirroring of the functioning human brain outside of the human body. A realistic implementation of such a brain would revolutionize human existence ranging from improving perception to addressing neurodegeneration. The revolution in stem cell-based regenerative technologies offers the hope of realizing such a grand challenge.

Humans and microbes have coexisted since the origin of life on earth. The recent pandemic has strongly reinforced the notion that human physiology is strongly symbiotic with both living and non-living organisms, the latter carrying the blueprint for replication. Humans have faced these real challenges of infection since the dawn of history, characterized beautifully by Thucydides the 4th century BC historian describing the plague of Athens, perhaps the first conceptualization of the immune system. *Engineering the immune system* has immense consequences ranging from curing infection to cancer and in humans overcoming next generation infections. We have just recovered from one of the most challenging times of our century with the pandemic. The remarkable contribution of engineering in the design and manufacturing of RNA vaccines is a strong harbinger for the future of engineering in medicine.

At the highly granular level, the most revolutionary development in the past decades is the sequencing of the human genome and epigenome. The blueprint of human physiology only provides the most basic components for engineering design. Making the whole larger than the parts, designing and modifying living systems from engineering principles is not a utopian concept. *Designing and engineering genomes for repurposing organisms and introducing genomic perturbations that can alter pathophysiology* are already beginning to happen, albeit at a phenomenological level. Developing the engineering foundations for accomplishing this at a rational level has emerged as a grand challenge.

These themes formed the core ideas of the “Grand Challenges at the Interface of Engineering and Medicine Workshop” organized by the IEEE EMBS, JHU and UCSD. We present below a detailed discussion of these grand challenges framed as

Societal Needs, Challenges, Enabling Technologies, and Multi-disciplinary Teams and Core Competencies.

II. GRAND CHALLENGE 1: PRECISION MEDICINE – CREATING AVATARS OF HUMAN PHYSIOLOGY

A. Societal Need

The era of Classical Medicine, as practiced through the 18th century, was based on cataloging of patient symptoms for diagnosis and empirical selection of therapeutic approaches. Beginning in the 19th century, scientific advances such as the germ theory of Robert Koch contributed increasingly to our understanding of the mechanisms of disease, ushering in the era of Modern Medicine in which both the disease diagnosis and treatment are guided by knowledge of the mechanisms of disease. The second half of the 20th century has witnessed a molecular approach to understanding and treating pathologies, introducing the concept of molecular medicine. Despite these advances, misdiagnosis remains prevalent even for common conditions with potential morbidity and mortality. In addition, a number of diseases including cancer, cardiovascular and autoimmune disease show wide divergence to therapy in a highly individual manner, requiring patient-specific approaches. This need has led to calls for *Precision Medicine* in which the focus is on identifying approaches that will be effective for an individual patient based on comorbidities, and genetic, environmental, and lifestyle factors. We call this new approach *AccuMedicine*, a combination of precision engineering and precision medicine, and recognize that multiple layers of challenges are involved at the interface of engineering and medicine.

B. Challenges

1) Develop Accurate Models of Physiology That Integrates Multimodal Measurements and Physiological Function: Medicine will be “personalized” and will have “precision” if and only if we understand how to bridge individual patient data to diagnosis, risk prediction, and optimal treatment. We need new high-throughput assays that probe an individual’s biological function at the molecular, cellular and organ scales; validated modeling methods that harness these data across spatial and temporal scales, along with high-throughput genomic, transcriptomic, epigenetic, metabolomic and proteomic data, to diagnose, predict the risk of, and treat disease. We also must continue to develop patient-specific ex vivo tissue surrogates (e.g., organ-on-chip technologies) that could be used for biological discovery and screening. Our grand challenge is to improve the practice of medicine by making diagnosis, prognosis, and treatment of disease more accurate by using data-driven mechanistic and deep learning models, within AccuMedicine. Notably, the US congress has recently approved a bill allowing submission of physiological data obtained *in vitro* instead of preclinical animal data, for investigational drug applications.

2) Develop a Suite of Model-Derived Diagnostic and Therapeutic Choices to Choose one That Best Addresses Comorbidities, Concomitant Medications, Potential Risks and Costs: A large number of hospital deaths across the world

are driven by infections and poor hospital care. Developing models of patient state in many different disease settings that enable accurate alerting of physicians to their status has the potential to save millions of lives and reduce costs through improved care and efficient utilization of expensive resources. To do so, we need automated real time monitoring technologies, real time acquisition and processing of data, and real time analysis and modeling.

3) Develop Sensors and the Digital Human With Dynamic Feedback: The past two decades have witnessed the emergence of wearable sensors, both invasive and non-invasive, which measure physiological parameters in a digital manner. More recently, this has been supplemented by unobtrusive sensing often in the form of environmental monitors to infer health status, which has the advantage that they do not suffer from adherence issues if the user forgets or decides not to don a wearable device. Accurate diagnoses require an unambiguous assessment of physiological state and how that state has changed over time. Yearly check-ups do not have the temporal precision or physiological acuity to predict the likelihood of many diseases such as a stroke, heart attack or diabetes. Even regular monitoring of known health problems can be imprecise and inefficient, requiring frequent visits to a clinician. Ubiquitous technology would allow individuals and their providers to determine lifestyle patterns that are most beneficial for each individual, to predict disease exacerbations and intervene before the emergence of acute events, and to track the efficacy of interventions in real-time. A grand challenge is the integration of smart monitoring systems that continuously sense and interpret multiple physiological variables throughout the lifespan and their integration and analysis of their streaming physiological data in real time to deliver a secure longitudinal digital record of various aspects of human health. This dynamic feedback will facilitate self-care and enable healthy lifestyle changes that will help maintain a higher quality of life.

4) Engineering Digital Twins. Discovering the Rules and Operating Principles of Biomedical Systems: Rapid advances in digital simulation and artificial intelligence are leading to increasingly complex and realistic physiological models. To develop models of a biomedical system requires a detailed understanding of the system at multiple levels. The “digital twin” will enable clinicians and caregivers to measure, analyze and treat pathologies prior to their implementation in the “actual twin” and provide a deep perspective of the intricate mechanisms of functional physiology and pathophysiology. Take for example type 2 diabetes mellitus (T2DM), a chronic disease that affects 1 in 10 people around the world. Patients with T2DM suffer from hyperglycemia requiring the maintenance of a stable blood glucose level to decrease the risk of mortality and morbidity from cardiovascular diseases. The grand challenge is to develop tools that will lead to real-time prediction and decision-making for optimal diet and optimal insulin usage.

The opportunity to construct digital twin technologies for the major organ systems remains a grand challenge. Artificially intelligent engineered systems of health and disease require data-driven mechanistic and deep learning from the real twin. For instance, a digital twin of a T2DM patient can be developed

by integrating static data (e.g., comorbidities) with real-time data (metabolomics, glucose, insulin, diet, exercise) as well as with deterministic and stochastic rate models to develop a biology-informed learning virtual system as a backbone of the T2DM digital twin.

5) Tissue and Organ Engineering Based on a priori Quantitative Design Principles: Mathematical modeling, validated using experimental data, is increasingly being used to provide mechanistic insights into complex biological systems that have multiple interacting components, parallel pathways, and feedback loops. These modeling efforts can also provide insights into emergent properties that arise from inter-component interactions and guide design of experiments. In contrast, translational efforts in tissue and organ engineering have mostly relied on the experimental, trial-and-error approach that can be costly and time-consuming. The translation pipeline can be greatly accelerated by first performing *in silico* experiments to optimize protocols for manufacturing regenerative medicine products and treatment strategies, before embarking on the experimental work. Mathematical modelling-based optimization of protocols for growing bone tissue in a bioreactor is one example of the successful application of this approach. For widespread application of this *a priori* design-based approach to tissue and organ engineering, it would be critical to develop appropriate mathematical modeling infrastructure, rigorously validated mathematical models (mechanistic/phenomenological, discrete/continuum, statistical) of relevant biological systems that can integrate multiple data sources (e.g., molecular/cellular, biomechanical/biochemical, imaging), and large-scale biological databases.

C. Enabling Technologies

Several existing and future technologies will provide the basis for AccuMedicine.

Sensors and instrumentation: Human health promises to be transformed by real-time monitoring of the physical, chemical, and electrical signals in the human body. This will require major advances in miniaturization and biocompatibility that allow for sensors to operate unobtrusively within the body harvesting and conserving energy. Data from ambient and environmental sensors including imaging and activity sensors will provide additional modalities.

Data science: Multimodal sensing to monitor and regulate health generates vast amounts of data, which requires advances in biomedical data science to integrate real-time mechanistic and data-driven models of human biology into new kinds of hybrid, intelligent systems. Such data must be simultaneously available and secure (e.g., stored in ways that comply with regulatory requirements). The development of digital twins of tissues, organs and body processes including biology-informed neural networks will require major advances incorporating active and machine learning, innovative data visualization techniques including those relying on virtual and augmented reality.

Modeling and control: Automated systems to replace human function must respond intelligently to the body. Doing so will require advances in developing multiscale, dynamic models of

physiological processes and control algorithms that operate in the nonstationary, nonlinear environment of the human body.

Chemistry and materials science: Material biocompatibility is of primary concern for sensing technologies and materials for transducing physiological events. Significant advances in material design and fabrication of materials at the nanoscale are required to create the next generation of biocompatible sensors and delivery systems. For long-term biochemical sensing, reversible or sustainable material chemistry needs to be developed within the implantable biomaterials space. Improved fabrication technologies are needed that allow ex vivo modeling of physiological processes for biological discovery, screening, and patient-specific precision medicine. Key focus areas should include but not be limited to 3D printing/additive manufacturing, BioMEMS-based microphysiological systems (“organ on chip”), and three-dimensional polymer hydrogels.

Computational and mathematical modeling: A critical need exists for the continued development of quantitative tools for tissue and organ engineering, with inspiration from developmental and systems/synthetic biology. Mathematical modelling and data science are important, and new ideas and multi-scale approaches are needed.

Energy harvesting: Energy for sensing, computation, and actuation requires integration with wearable and implantable energy source technologies. This will require advances in energy harvesting technologies attached to the human body. In addition to traditional wireless systems, the conversion of mechanical or optical signals into electrical energy for sensors and actuators offers great potential to advance the field.

D. Multi-Disciplinary Teams and Core Competencies

A major goal of biomedical engineering education is to train the next generation of leaders who have a multidisciplinary background and can effectively integrate their expertise in a team to perform research, develop diagnostic and therapeutic tools, or design Precision Medicine treatments. The development of smart and responsive systems to augment human function will require a systems-level approach that considers fundamental principles from clinical medicine, biology, computer science, and engineering - precisely the domains of the biomedical engineer. The widespread adoption of smart and responsive systems will create a paradigm shift in how healthcare is delivered with implementation scientists facilitating the adoption of these new technologies and their integration into the healthcare system.

Critical core competencies for Precision Medicine include: engineering mathematics; data science and biostatistics; robust and resilient sensors and instrumentation to detect relevant biological signals and behaviors; biology, physiology and medicine to determine the appropriate responses; data science and machine learning frameworks to infer actions from internal and external signals; systems and controls to regulate the response locally or remotely; robotics to manipulate the human body on the micro- and macro-scale; biomaterials and bioelectronics to develop responsive devices and surrogate tissues that are biocompatible; systems interoperability to ensure seamless integration across platforms and formats; cybersecurity to protect

personal data; engineering to consider energy use and power delivery; human interface design to make devices and data accessible and to optimize the user experience; and medical ethics to consider the implications of augmented autonomous control.

III. GRAND CHALLENGE 2: SMARTHUMAN – DEVELOPING SMART AND RESPONSIVE SYSTEMS FOR HUMAN FUNCTION AUGMENTATION

A. Societal Need

The length and quality of our life critically depends on the functionality of our vital organs. As we live longer and better than ever before in the history of humankind, our aging population has an increasing need to repair or replace our tissues and organs lost to an injury, abnormality or disease. Organ transplantation remains limited by the number of available donor organs and the necessity for life-long immune suppression preventing organ rejection. The artificial devices, such as kidney dialysis machines or lung support devices, do not replace the entire organ function and are very difficult for the patient, especially over extended periods of time.

The field of tissue engineering was created in the late 1980s by the convergence of engineering with life sciences, in response to the need and opportunity to repair or replace our tissues and organs by their lab-grown biological substitutes. Originally, tissue engineering was defined as “the application of the principles and methods of engineering and life sciences toward the fundamental understanding of structure-function relationships in normal and pathologic mammalian tissue and the development of biological substitutes to restore, maintain, or improve function”. Interestingly, this definition of the field has not changed, and neither has the fundamental concept of “instructing” the cells to regenerate a specific tissue or organ by biologically inspired molecular, structural and physical regulatory signals.

The field has been transformed by the advent of human iPS cell technologies, gene editing and sophisticated tissue engineering tools (biomaterial scaffolds, bioreactors, sensors, nanotechnology), and “organs on a chip”, designed to recapitulate organ level or even system level human functions in health, injury, disease and regeneration and drive the development of new therapeutic modalities. Progress in the field has been driven by understanding the clinical needs, and the ability to provide patient-tailored treatments. Today, tissue engineering is ready to meet its grand challenge: engineering tissues and organs on-demand, to support human health and wellbeing. We propose four challenges in tissue engineering for human health, each being motivated by a major societal and medical need.

B. Challenges

1) Stem Cells for all: Our organs are maintained by the populations of resident stem/progenitor cells. However, the intrinsic regenerative ability of organs is limited, especially following injury, disease, or aging. Delivery of adult stem cells, matched to the patient or derived from the patient’s blood, provides the ability to achieve tissue/organ regeneration resulting in major

improvements in physiological function. In addition, adult stem cells or their derivatives, administered alone or with drugs, can be used to treat diseases or to activate the pool of endogenous cells and use their therapeutic capacity. Our grand challenge here is to develop approaches and technologies that will lead to stem cell-based therapy that is readily available and accessible to all. Appropriate gene editing has the potential to generate universal allogeneic cells that are immune acceptable, scalable and available off-the-shelf for therapies. Understanding the epigenomic control of cell identity and fate will enable more efficient derivation of desirable cell types by using genetic engineering and extracellular signals. The development of tunable and responsive biomaterials and the optimization of minimally invasive delivery methods will be critical to achieve effective therapies.

2) Development of Permanent Systems to Replace or Augment Human Function: The human body is the most elegant of control systems, continuously sensing and regulating its state to ensure homeostasis in different physical environments, during different activities, and in response to injury or disease. Artificial systems that replace critical parts of the human body control must be endowed with similar levels of sophistication. They should be able to sense a diversity of signals relevant to human health and select the most appropriate intervention from a range of available chemical, electrical, and mechanical stimuli. We envision that these systems could be permanently implanted or worn by the user to treat chronic diseases and the complications that arise from them. Exemplar systems include integrated prosthetic limbs, artificial heart, local drug-delivery devices, and brain-function devices driven by sense response and dynamical assessment of need to maintain normal function. A critical challenge here will be to integrate multi-modality/multi-fidelity signals in real time to make artificial organs respond in real time. We provide two exemplars below.

Engineering a limb: Limb injuries can have devastating consequences: from loss of joint mobility to extensive damage to soft tissue and severely affecting limb function, the loss of individual or multiple digits of the hand or foot, and the loss of an entire limb. Engineering a limb presents an important and far-reaching challenge for biomedical engineering. The societal needs are clear, and no regenerative treatments are currently available. Over 1.5 million individuals have experienced limb loss at this time, and this number is likely to increase over the next decade. America's wounded warriors have suffered limb loss through trauma. To accomplish limb regeneration, the convergence of several disciplines, termed regenerative engineering, will be important to explore. The approaches we need to develop include the use of materials that can sense and respond to their local environment, stem cells and bioreactor technologies, based on the lessons learned from developmental biology in organisms that regenerate limbs. In addition, effective use of new clinical models and clinical trials will be needed, making this grand challenge ideally suited for collaborative endeavors with clinicians.

Engineering a lung: The clinical impact of lung transplantation, the only cure for patients suffering from end-stage lung disease, remains limited by the shortage of functional donor

lungs, and the need to prevent the rejection of the transplanted lung by life-long immune suppression. Lung disease remains the third leading cause of death worldwide, with more than half a million hospitalizations and more than 130000 deaths every year, in the United States alone. Bioengineering lungs for transplant and intervening *in situ* to treat the targeted areas of damage would be transformative for the many patients in need. An additional challenge is to find biomarkers of early stages of currently incurable diseases (such as cystic fibrosis) that would allow curative measures before the damage has advanced too far. Finally, the approaches for bioengineering the lung could be extended to other blood perfused organs such as the liver, kidney and heart. The ability to engineer complex organs such as the lung – containing over 50 cell types and elaborate hierarchical networks of airway and vasculature, is a grand challenge that requires a team effort of bioengineers, clinicians, and experts in materials science, biomechanics, physiology, and cellular and developmental biology.

3) Disease on a Chip: When an individual develops a disease, many treatment options may exist for a given condition, and every individual tends to respond differently to any given treatment, due to that person's unique genetics and physiology. Moreover, every disease manifests itself differently in each patient due to the heterogeneity of the disease itself and differences in the presence of other medical conditions. Disease heterogeneity is a particular problem for treating complex diseases such as cancer and autoimmune diseases. In the absence of individualized approaches, treatment decisions are often made in a trial-and-error fashion, increasing morbidity and mortality, reducing quality of life, and adding cost to an already overburdened health care system. Our challenge is to meet the need for patient-specific models of diseases that can be used for diagnosis, prognosis and patient-specific drug screening. Ideally, such models should be built from the patient's own cells, such as blood-derived pluripotent stem cells and their progeny. "Organs-on-a-chip" platforms should ideally represent integrated systems with multiple organ units, and their success will be defined by the ability to accurately predict patient-specific responses and provide precise and personalized treatment plans with high efficacy and minimal side effects.

D. Enabling Technologies

Several existing and future technologies will provide the basis for Human Augmentation.

Stem cells: Developing technologies for economical production of large-scale, consistent, high-quality stem cells, including distributed manufacturing approaches, as well as shipping and storage methods that preserve cell viability, is a first step.

Tissue engineering: The first step in engineering a tissue is to isolate, expand, and differentiate patient-specific stem cells. To this end, we need to develop novel biomanufacturing and processing technologies that are scalable and affordable and with appropriate quality control.

Imaging and biomarker technologies: Imaging is necessary to assess the state of the cells and the quality of the engineered

tissues, along with the consequent remodeling/regeneration of the native tissue/organ function.

Tissue fabrication: For regeneration of whole organs and complex multi-tissue structures, engineering design and fabrication technologies are needed to co-culture or derive multiple cell types and organize them into appropriate tissue structures, with functional vascularization, innervation, and immune components. Development of advanced fabrication technologies including 3D bio/printing and bioreactor technologies warrant new engineering approaches.

Microphysiological platforms: Sophisticated technologies are also needed to establish microphysiological platforms consisting of micro-sized human tissues, linked to each other by vascular circulation.

E. Multi-Disciplinary Teams and Core Competencies

The design of smart and responsive systems that are integrated into human physiology will mandate the collaborative engagement of physicians, physiologists, biomedical engineers, biologists, electrical and device engineers, and computer scientists. Embedded sensors in human physiology need to be functional while not being adversely bioactive and this will warrant understanding design principles of interactions between synthetic and living matter. Similarly, designers of functional devices need to understand the physiology of the tissue/organ. Multidisciplinary teams created to address specific sensor-device design will be essential for this Challenge. Further, stem cell biology has matured significantly, although growing tissues continues to remain a challenge. Understanding the engineering principles of human physiology will aid in designing ex vivo biological systems.

Further, the scaling of tissue and organ engineering is a complex problem that will require industry engagement. In addition, regulatory and biomanufacturing principles play a key role in the translation. Research in several areas involving elucidating the design principles and rules of human tissue/organ form and function, stem cell engineering, and integration of sensing/feedback of implanted devices/tissues, will form the foundation for this Grand Challenge.

IV. GRAND CHALLENGE 3: ENGINEERING THE BRAIN AND FOUNDATIONS FOR THE EXOBRAIN

A. Societal Need

The human brain has been one of the few unconquered organs of human physiology; every decade, new initiatives are launched with the hope of making sufficient advances to understand and mimic brain function in its myriad complexity. Engineers have made dramatic advances over decades to capture information on brain structures and functions. Magnetic resonance imaging, magnetoencephalography, and electroencephalography are commonplace methods used in hospitals. Recent brain computer interface (BCI) wearable devices are becoming more and more accessible, and electrical activity produced by the brain (EEG) are being routinely monitored.

With the launch of the BRAIN initiative, there have been rapid advances in our ability to record and manipulate the brain. Even

with these advances in imaging, sensing and AI technologies, there remain huge gaps in our understanding of the functioning of the brain, and how to interface to it. This is so striking as our brain is so personal and individual, our brains are “who we are”. Turning to disease isn’t better with the causative origins of brain disorders often remaining undiagnosed until a stage that is too late for intervention or cure. Sadly, brain disease is not rare with the burden of neurological disorders being enormous, both in the US and worldwide. In the US alone, more than 60 million people suffer from chronic pain, and or depression, and 10’s of millions from neurodegenerative diseases. It is expected that by 2035, one in five Americans will suffer from dementia leading to Alzheimer’s disease (AD), for which there is no cure. We need new technologies for both early diagnosis and intervention. Avatars that can be studied for disease progression in brains can go a long way in improving the quality of life of aged population.

Leveraging the advances in sensing and computation, the challenge that remains is to engineer the systems that will interface to the brain and will allow us to intervene to make the brain tick normally. A healthy brain is precious for our well-being. Over the past decade we have seen remarkable advances in our ability to record and manipulate the brain which promises to revolutionize our understanding of brain function and the causative natures of its malfunction. Simultaneously, artificial intelligence is being named the 4th industrial revolution presenting tremendous opportunities to advance our understanding of the brain. Leveraging these advances, we propose as a grand challenge to engineer the systems that will interface with and make the brain tick normally.

B. Challenges

1) Measurement of Normal and Pathological Brain Function: We are mapping the human brain across nearly 10 orders of magnitude in spatial scales, spanning nanoscale with electron microscopy, to microscale including both the structural connectivity and electrophysiological characterizations as well the molecular and cellular transcriptomic identities, and the mesoscale with diffusion, anatomical, and functional magnetic resonance imaging. Invasive measurements inside the brain are both deleterious and are unable to broadly establish the alterations in molecular physiology associated with the onset of neurodegeneration. Newly emerging synaptic and cellular scale measurements rebuilding the true metric of the brain cell by cell such as spatial transcriptomics is highly invasive. There remains the major challenge of creating new methods that can be used in human for multiscale, albeit non-invasive measurements of normal and pathological brain function. In some cases such measurements can be invasive coupled with a functional feedback. This points to the need and our ability to engineer such innovative brain measurement devices.

2) Neuroaugmentation of Human Function: (Neuroprosthetics): Our memory is the single most defining property of our personal human identity. Even after all infectious diseases are cured, humanity will still suffer from neurodegenerative

diseases. Neuro-cognitive augmentation will impact everyone, the aging, and their descendants. Multi-scale structural and dynamical models of brain systems are emerging that encode information storage and representation. Biological tasks such as memory are no longer an abstraction; progress in cognitive science and Alzheimer's disease is resulting in detailed understanding of the circuits associated to memory behavior and loss. Such representations present the opportunity for almost complete in-silico simulations of the behavior of neural circuits and for the building of predictive models of neural activity and neurodegenerative disease trajectories. The opportunities for integrating molecular function with 3D-printed scaffolds derived from individualized stem cells enabling biomedical engineers to synthesize and implant functional artificial neural circuits for augmentation of cognitive process presents the next venue for disruptive technologies. Given the advances in multiscale, multi-modal brain measurements, coupled to AI data-based modeling of anatomy, physiology, and behavior, and new capabilities of synthesizing organoids and other 3D technologies to manipulate neural activity, we believe our generation next Grand Challenges is to build physiologically realistic brain organoids to explore normal and pathological function. This can be complemented by memory chips for augmenting the cognitive function of human memory. The grand challenge then is to understand the design principles of the brain and its circuitry and engineer biologically realistic organoids that will mimic one or more aspects of brain function and enable deciphering and treating pathologies.

3) Brain Organoids as Microphysiological Systems: Engineered models of the human brain are a great challenge and final frontier in brain research. We have the ability to create human pluripotent stem cell derived models of neurons, but to engineer them into complex brain organoids is an enormous challenge and warrants new technologies and models. Such brain organoids need to capture the complexity in terms of cells such as neurons, astrocytes, endothelial cells and microglia in the brain, but also the circuitry that mimics that in the brain. Further these organoids need to be vascularized and have the equivalent of the blood-brain barrier to probe the brain in a realistic manner. Such brain organoids that can serve as avatars of normal and diseased brains have the immense potential through multi-omics measurements to reveal the alterations in myriad functional pathways in disease and offer therapeutic interventions. Towards this, bringing an interdisciplinary approach involving engineering, human physiology and medicine is not merely a challenge, but an imminent necessity if we have to create engineering models of the brain and its pathological alterations.

4) Engineering the Exocortex: A healthy brain is essential for our well-being. In the last few decades, our ability to record and manipulate the brain has begun to revolutionize our understanding of brain function and dysfunction. Interfacing between the external device world and internal brain world through brain and computer interfaces is progressing rapidly. Examples now abound of researchers using noninvasive neural and brain computer interfaces to actuated neuroprosthetic limbs and interface the human brain to robotic limbs and externally controlled systems. The potential application of such a device

for paraplegic human patient activity is potentially transformational, but also represents a vista into the grand possibilities of interfacing the external internet/device world with the internals organic brain world. We propose the grand challenge of combining AI, brain sciences and engineering to design AI systems that will interface with the brain, a grand challenge that we call "engineering the human exocortex". This grand challenge presents the opportunity to improve human health, happiness, and productivity. The interfaces to the brain can be non-invasive and/or invasive devices communicating with AI systems such as artificial neural networks that will act as an extension of the human brain. The grand challenge of engineering the human exocortex which will enable ex vivo measurement of sensory inputs into the human brain and serve as an "personalized avatar" of the human brain.

5) Neuroscience in the Everyday World: The sum is larger than the parts. There is a great need to enable scientists to link brain activity to human movement, perception and cognition, and social communication and interaction continuously, in real time, and in the Everyday World. Such tools will provide profound new insights into not only how the healthy brain works, but also when and why breakdowns occur in movement, perception and cognition, and communication. The current state of the art, led by fMRI, has driven profound advances in our understanding of brain function under well-controlled and constrained conditions. While we are gaining greater understanding of how the brain functions in single-snapshot experiments under restricted lab settings, we do not know how it works in dynamic, complex and multisensory real-world environments. To push this important work forward, we need to be able to continuously track human brain function and behavior in real time to understand how a healthy brain works and how and when failures in simple human actions occur. We call this effort "Neuroscience of the Everyday World," and biomedical engineers will play an important role in developing, adopting, and applying the new technology needed to make this vision possible. As a start, we envision the use of functional near infrared spectroscopy (fNIRS) and EEG as two safe and non-invasive neuroimaging techniques that enable brain imaging under naturalistic settings. fNIRS is an alternative to fMRI that maps hemodynamic responses to brain activity and allows researchers to collect data in ecologically valid settings, it is less susceptible to motion artifacts than fMRI, and thus it has great potential for studying natural behaviors and neurological populations. EEG measures fast electrical responses associated with neuronal activity and has been widely used for studying brain activity in naturalistic environments. EEG and fNIRS complement each other through combining EEG's ability to capture neural activity with millisecond time scale and fNIRS's ability to measure slow and integrated hemodynamic changes with better spatial localization. In addition, it will be necessary to combine fNIRS and EEG with eye-tracking/pupillometry to time-lock the brain responses to behavioral data and to obtain a more complete picture of brain activation patterns in the Everyday World through vascular and neural responses and their interactions. The grand challenge is the design of wearable sensors that are not cumbersome to track human behavior in the context of society.

F. Enabling Technologies

Several existing and future technologies will provide the basis for Engineering the Brain.

Brain computer interfaces and dynamic monitoring systems: Clinical neurology, neuroimaging and neurosensing technologies have significantly advanced over the last two decades, dramatically accelerating our understanding of the functioning human brain. Non-invasive and invasive technologies are becoming more and more powerful and portable and will enable continuous functional neurosensing of electrical, hemodynamic, and molecular signatures of brain function, paving the way for engineering the systems for making the brain tick. Brain cytoarchitecture mapping involves multimodal, meso-scale imaging, electrophysiology, and omics sequencing methods.

Neuromodulation technologies: Neuromodulation technologies spanning from invasive deep brain stimulation by electrical stimulation to non-invasive methods utilizing magnetic pulses, electrical currents, ultrasound, and light are used in modern brain investigations. The combination with neurosensing, control system, neural modeling, and data science technologies is essential for making the brain tick. Neural modeling and simulation of axon tracts in peripheral nerves is highly developed and is beginning to be used in the spinal cord to simulate the likely consequences of new electrode technology and new stimulation paradigms. Comparable techniques are being used to simulate tracts in the brain to improve electrode targeting, electrode design, and stimulation patterns.

Neural sensing, modulation, and control systems: Control systems technologies have advanced for developing effective interventions for neurological disorders will often require responsive systems that measure outcome variables and adjust the intervention via stimulation in real-time.

Electrode technologies: Interfacing with neurons in the brain for both recording and stimulation for deep brain stimulation electrodes, ECoG arrays, penetrating cortical arrays, have been applied in the brain in people to both clinical and scientific problems. Similarly, stimulation and recording electrodes have long been used in the periphery and spinal cord (e.g., spinal cord stimulation for pain). Emerging technologies are improving channel counts in the brain, allowing interfacing with small unmyelinated axons (e.g., in the autonomic nervous system), and the use of conduction block as well as activation.

Neuro-rehabilitative technologies: Enabled by the engineering of neural interfaces, technologies are emerging to work in concert with traditional rehabilitative medicine to dramatically improve outcomes for people recovering from stroke and brain trauma, and to improve wellness for people with neurodegenerative diseases. New technologies for neuro-scaffold for cell growth and therapeutics are emerging.

Microphysiological systems: The human brain model systems include neurons from pluripotent stem cell differentiation and vascularized brain organoids. Investigation of brain in vivo involves minimally invasive diagnostic markers and electrocortical techniques. Therapeutic interventions require drugs to cross the blood-brain barrier. Exo-brain also requires the development of low power, high bandwidth telemetry devices, and higher density power sources.

Data science and artificial intelligence (AI): AI and Machine Learning are allowing for understanding the huge amounts of relevant data that can be recorded from the nervous system. So, enhancing our understanding of the underlying neural systems and the impact of treatment mechanisms will depend on recently emerging data sciences techniques.

G. Multi-Disciplinary Teams and Core Competencies

Traditional neuroscience and neurophysiology have undergone dramatic changes in the past two decades. For instance, a neurologist today is required to have a multiscale perspective of brain function from the firing of single neurons to deciphering cognition towards recognizing normal and abnormal function. Electrical circuitry of the brain has become a part of modern curriculum in neuroscience. Both implantable and exobrain electrodes are now routinely used to assess neurodegenerative disorders. The grand challenge of the exobrain will require strong collaborative teams involving neuroscientists, neurologists, biomedical and electrical engineers, computational scientists and experts in imaging optics.

The core competencies of researchers addressing the associated challenges include: understanding of brain and central (CNS), peripheral (PNS) and enteric (ENS) nervous systems, possessing intensive knowledge of AI and computational skills, neural interface technologies, including electrical, optical and chemical stimulation, recording technologies, and working knowledge of signal processing techniques that are capable of extracting information from neural signals needed to develop neural biomarkers, allow responsive inventions, estimate parameters for models, and improve our understanding of neural system performance.

V. GRAND CHALLENGE 4: IMMUNOENGINEERING – HARNESSING THE IMMUNE SYSTEM FOR HEALTH AND WELLNESS

A. Societal Need

The burgeoning field of “immunengineering” is ripe for developing and applying quantitative tools to understand the underlying principles driving immune responses and their connections to other human systems. With this knowledge we will develop the capacity to modulate the immune system using materials, engineered therapies (both artificial and biological), and devices resulting in the ability to address unmet health needs and improve quality of life. Each challenge is motivated by a major societal/medical need. We also summarize the most important supporting technologies that need to be developed or advanced, which presents an additional set of challenges.

Our ability to harness the immune system for human health is hindered by our limited understanding of the basic science underlying its function. Over the past decades, our knowledge has advanced substantially from implicating a single immune cell to the complex immune cell repertoire and population dynamics we understand today. However, many functions are not understood yet, and new cellular actors continue to be identified. Despite limited understanding, we are now able to engineer the

immune system to deliver improved responses as exemplified by immunotherapy for cancer treatment.

B. Challenges

1) Creation of an Immunoengineering Toolbox: The burgeoning field of “immunoengineering” critically needs new quantitative tools to understand the underlying principles driving immune responses and their connections to other human systems. With this knowledge, we will develop the capacity to modulate the immune system using materials, engineered therapies (both artificial and biological), and devices, resulting in the ability to address unmet health needs and improve quality of life. The entry of engineering into immunology is recent and brings a new suite of approaches and tools that complement those used by immunologists. The toolset includes the interplay between enabling technologies to precisely quantify immune cell phenotype and function including single cell technologies such as spatial transcriptomics, enabling technologies to modulate immune cell function such as with biomimetic materials, and enabling technologies in biomedical data science for analysis. This toolset accelerates treatment development.

The nonlinear spatial and temporal responses of the immune system are poorly understood. Understanding immune function will benefit from engineered in vitro and in silico models and high-content in vivo imaging and single cell analysis that span a wide range of spatial and temporal scales. Insights and enabling technologies from data science and machine learning are positioned to unlock new understanding of immune cells, their networks, and their microenvironments. This type of complex system is exactly what engineers are trained to understand, model and design.

2) Engineering Immunotherapies: The immune system is a critical interface between an individual and the environment. We live in a time when the environment challenging our immune system is changing rapidly including climate, diet, activity, and exposure to pathogens and other disease-causing agents. The immune system is recognized as an individual’s physiological memory of trauma, exposure, and overall health, protecting us from external assault. Its dysregulation is implicated in a multitude of diseases. As an example, an underactive immune system drives tumor progression, while immune system overactivation underlies autoimmune disease. As highlighted by the 2018 Nobel Prize in Medicine, new treatment modalities in cancer now offer patients transformative opportunities for survival; however, these therapies only work in a small subset of patients, and in ways that we do not fully understand. Immune therapy brings a host of challenges including rapid disease resistance and promotion of autoimmune disease. In addition, mounting evidence suggests a link between cells and molecules driving immunity and other human systems in the context of aging, neurological disease (Alzheimer’s), or trauma (concussion). Our gut microbiome interacts with our immune system in similarly mysterious ways. The composition of bacterial gut flora drive response to immunotherapies, both positively and negatively, and antibiotics further affect these outcomes. Further, the immune system is key to wound healing, transplantation, and regenerative medicine.

As these examples demonstrate, harnessing the immune system will be transformative for human health and disease.

Once the functions of and key actors in the healthy immune system are unraveled, changes that occur upon disease states need to be understood and effective therapeutic interventions developed. Immunological effects are known to underlie conditions as disparate as cancer and traumatic brain injury. Using the same engineering tools, immune adaptations can be identified for all diseases, particularly those that are most prevalent. Immunomodulatory therapies can then be developed to replicate or regulate immune function and treat disease. These treatments will take diverse forms including conventional drugs, protein therapies, cellular therapy, gene delivery, biomaterials and novel treatments that are still under development.

3) Next Generation of Vaccines for the World: While immunotherapies focus on treatments to modulate an ongoing immune-related response, there is also tremendous challenge and opportunity in being able to program the immune response ahead of time through the development of innovative vaccines. Over 17 million people die from infectious diseases worldwide each year, and many of them are children. Reducing these deaths is a global challenge. Biomedical engineering innovation is needed to develop new vaccines quickly to meet the challenges of rapidly evolving viruses, including the current pandemic. Similarly, engineering innovation is needed to increase the effectiveness and accessibility of existing vaccines in the developing world. Vaccines are needed that are safe and effective, low cost, and able to be administered without specialized equipment or expertise. There is a great need for single administration followed by self-boosting over time so that a patient does not need to return to a healthcare worker. There are opportunities for new vaccines based on nucleic acid based technologies (RNA vaccines), and nucleic acid encoding antigen, rather than protein, that could lead to greater potency and faster development. Equally important are challenges with widespread, quickly developed, easy to manufacture, and low cost diagnostics that can provide critical information to epidemiologists and policy makers in times of crisis. Computational approaches also are needed from more precisely modeling viral infection on a subcellular level to the spread of infections through populations to predicting antigen and genetic mutations to improve vaccine design.

There are critical challenges for engineering advanced vaccines for purposes beyond infectious diseases. For example, cancer vaccines can inoculate a patient against a specific cancer that they may be predisposed to or already have and ensure that their body mounts a robust adaptive immune response so that such a cancer is not able to grow, spread, or recur. Development of the biomaterials, nanobiotechnology, formulation science, and related engineering technologies for advanced vaccines also open new frontiers such as opioid vaccines and other anti-drug vaccines that can prevent the action of a target substance. Through biomedical innovation, tolerogenic, or “reverse”, vaccines can also be developed that can establish immunological tolerance in autoimmune diseases such as multiple sclerosis and type 1 diabetes. Thus, the needs are great and a central challenge of next generation vaccines for the world is also to improve accessibility so that all these potential gains can benefit those most in need.

C. Enabling Technologies

Several existing and future technologies will provide the basis for Engineering the Immune System.

Cell sequencing and genome editing: In the past decade, we have dramatically improved our ability to sequence single cells in healthy and disease states, edit the genome precisely, and create genes, proteins, and cells to modulate biological function.

Cell manufacturing and material science technologies: The development of new progenitor cell provides the opportunity for essential therapies on a scale of days to weeks, rather than months. A new generation of materials to constructively interact with the immune systems are available to deliver therapeutic modalities. Despite these advances, we still lack the ability to rapidly produce immune cells from stem cell progenitors, which prolongs the time between disease diagnosis and treatment.

CAR-T Therapies: Cancer models for translating successful approaches to tumor treatments, significantly restricting the impact of current CAR-T therapies are needed.

Platform technologies: Technologies are needed to interrogate the large spectrum presented to the immune system, examine the development of memory and recall in the immune system, and build predictive immune learning models that will further advance treatments. As the interface between the immune system and environmental agents becomes more clearly defined, models designed for immune-based treatment of individuals will transition to models of immune health in populations. Additionally, the immune system is often dysregulated in numerous pathologies such as autoimmune disease and cancer, and sensors for immune activity may detect disease prior to significant progression and can monitor the response to immunotherapy.

Mathematical modeling and biomedical data science: A framework to predict and manage the complications that can emerge when manipulating the immune system and manage the complicated differences in the immune system across species, and across patients is needed. The challenge remains that we do not yet know the governing equations for the immune system.

D. Multi-Disciplinary Teams and Core Competencies

The development of engineered immune systems for modulating health is being recognized by all clinical disciplines. Inflammation is being recognized as a causal agent in neurodegenerative disease, cardiovascular health, and bone and joint disease. Because the immune system is the interface between people and their natural and built environment, we expect that forward looking ventures in the immune health will include clinical and environmental scientists to predict how changes in the food supply, patient microbiome, and natural environment will act as pressures on the immune system to evolve and introduce new health risks in the population. Specifically, trained bioengineers and material scientists/engineers, and systems engineers with biomanufacturing expertise,

Stem cell and systems biologists and technologists, together with developmental and systems/synthetic/computational biologists will play a very important role in understanding the immune system. Specific coursework needs to be developed at

the interface of immunology, systems physiology and engineering. In the design of immune-based therapies and vaccines, biochemical engineers and biotechnology companies are playing an important role and will continue to influence future immune-based disease interventions. Systems and network engineering principles applied to the immune system will be important in developing new therapies.

VI. GRAND CHALLENGE 5: ENGINEERING LIFE – ENGINEERING GENOMES AND CELLS

A. Societal Need

Genomes encode the rules of life. Aberrations in the genome and/or its execution underlie many human diseases. If we could undo corresponding errors in the intact living organism we could reverse many ailments, both inherited as well as somatic. In this regard, over the past two decades researchers have engineered exquisitely specific and efficient tools to engineer genomes, such as the CRISPR-Cas systems. These provide a degree of molecular precision not fundamentally feasible by small molecule medicines. For instance, one can both repress as well as activate genetic targets, and perturb many targets simultaneously in a single cell, aspects that most modern drugs cannot achieve. But there are two fundamental challenges to their deployment: 1) limited understanding of the plasticity of the human genome and epigenetic regulation, such that genotype-phenotype relationships for most genome aberrations remain poorly understood and well defined targets that could modulate phenotypes for many chronic diseases remain to be discovered; and 2) a lack of efficacious in vivo delivery tools, and the severe constraints on delivery and associated manufacturability have made most gene therapies limited in their capability and also prohibitively expensive.

Human cells perform a myriad of diverse functions that are required to guide normal human development, buffer homeostasis, and to safeguard against human disease. Despite the overarching relevance of these functions to human development, health, and disease, we have an incomplete understanding of how they are coordinated, and even less clarity on how they can be engineered and repurposed to improve the human condition. Truly remarkable advances in engineering human T cells to encode chimeric antigen receptors (CARs) have paved the way for innovative and life-saving cell-based therapeutics, however engineering other important prophylactic behaviors into human cells has not progressed as rapidly nor as successfully. Efforts to spur progress in repurposing human cells as living drugs will revolutionize our ability to diagnose and treat a wide array of human diseases. In breast cancer, current genetic testing is often unable to resolve the underlying driver of the patient's malignancy. Understanding how genetic sequences dictate cellular phenotypes is needed to discern between normal and diseased tissues improving clinical standards of care and spare patients from unnecessary surgical procedures. Alternatively for late-stage prostate cancer, CT, PET/SPECT, and MRI are often performed to design the regimen of radio, chemo and surgical therapies. At the same time, better imaging of tumor cells is needed to more precisely identify the location of cancerous cell masses. More sophisticated engineered approaches are also needed to

redesign human cells *ex vivo* for subsequent transfusion and precision targeting of metastatic cancer cells that are difficult to remove surgically. Further, there is great opportunity for *in situ* genomic engineering of human cells *in vivo* within the body. These approaches can be enabled by nanomedicine technology and are critical as they can dramatically reduce costs and broaden accessibility of these biotechnologies for health and wellness and facilitate equitable access around the world.

These examples highlight the challenges of harnessing the fundamental mechanisms that our cells use to precisely orchestrate our development and maintain our health and illustrate the tremendous promise of redesigned human cells as therapeutics and medically useful technologies. Realizing this immense promise presents several grand challenges that span the central dogma of molecular biology including improving our ability to engineer genomic sequence information (DNA), expanding our ability to control the levels of transcription (RNA), and advancing our capacity to reformat pathways and complexes (proteins) within living human cells.

Overcoming these challenges can be accomplished by combining engineering principles with innovations in genome, epigenome, and protein engineering, nanomedicine technology, functional genomics, and synthetic transcriptional control.

B. Challenges

1) *Repurposing the Blueprint for Life. Genomic DNA:*

DNA encodes the design rules that animate all life on earth (apart from certain RNA-based viruses). Thanks to the monumental efforts of the human genome project (HGP) completed in 2003, nearly all the ~ 3 billion bases of genomic DNA that orchestrate human existence have been mapped. The Encyclopedia of DNA Elements (ENCODE) consortium has made remarkable progress in identifying segments of the mapped genomes that display regulatory activity, how it changes across human cell types and with the 4D Nucleome project how our DNA is functionally organized within the nuclei of our cells. Engineering the sequences of the human genome at the resolution needed to revert complex disease pathologies and build cells that contain new therapeutic molecules remains a challenge. Four key obstacles are limiting our ability to engineer genomic DNA at this scale. First the efficiency of homology directed repair (HDR) is low in many human cell types, which results in a costly need to select and/or screen for correctly modified clones. Second, although we can map nearly any portion of the human genome at base-level resolution, we do not yet fully understand how the local context of nearby genetic *cis* sequences and their activity dictate function. Third, incorporating large segments of new or corrected DNA into the human genome is inefficient and, in the case of megabase-scale or highly complex sequences, impossible. Fourth, our ability to control the activity of *de novo* integrated DNA, and specifically prevent silencing over time, is inadequate. The grand challenge then is to understand the design principles of the human genome and its activity to engineer new functionality into human cells and enable new ways to understand the genetic bases of human diseases and build new cell-based therapeutics.

2) *Building Epigenetic Tools for Precision Control of Cellular Transcription and Cell Fate:* If DNA sequences are

considered the “hardware” of the genome, epigenetic regulation is a key of the “operating system” of the genome. While transcriptional regulation of genes in segments of open chromatin can modulate cell function, the change of cell phenotype or cell fate, which is critical for stem cell differentiation and cell reprogramming, requires the conversion between the open and closed chromatin structures to turn on or turn off certain genes. To be able to engineer cells and control cell fate, we need to integrate biophysical, biochemical and biological approaches to: (1) understand molecular spatial interactions and epigenetic regulation by genome-wide molecular analysis such as Hi-C and ATACseq and super-resolution imaging, (2) engineer biomaterials and extracellular signals to facilitate the epigenetic changes, and (3) develop genetic engineering tools to change the open/closed state of the chromatin structure. Transcription from the human genome is coordinated at multiple levels including general transcription factors (TFs) that recruit RNA polymerases (RNAPs) to specific locations to initiate RNA synthesis, to modifications to DNA and chromatin, to local chromatin compaction largely governed by nucleosomal occupancy, to global dynamics in chromosomal architecture within the nuclei of human cells. Our understanding of these different levels of control over human gene expression have been driven by advances in microscopy, computational modeling, and genome and epigenome editing techniques most recently catalyzed by new CRISPR/Cas9-based technologies. Shifting from measuring and perturbing these nodes to engineering their function *in situ* is needed to redesign human cells as therapeutics. This shift represents an important opportunity for biomedical engineers to apply expertise in instrumentation, genome and epigenome engineering, and computational modeling. For example, human cells encode hundreds of TFs to precisely tailor the expression of human genes. Furthermore, the ability to engineer other mechanisms that control human gene expression, such as post-translational modifications, nucleosomal occupancy, and global chromosomal structure remain limited. The grand challenge is the engineering of transcription from the human genome at the level observed in healthy and diseased cells to enable new treatment modalities and disease models that faithfully recapitulate patient pathologies. In addition, the engineering of epigenome may allow us to reverse the epigenetic clock of cells and rejuvenate cells *in vitro* and *in vivo*.

3) *Building Solutions for the Delivery Challenge of In Vivo Genome Engineering:* At scale genome interpretation via rapid progress in genome engineering technologies over the past two decades is enabling us to systematically unravel drivers of disease. In the coming years, medicine will move increasingly from treating the symptoms of a disease with broad acting small molecules, to treating the direct causes of diseases, and in some cases curing diseases, on the fundamental genetic level with gene therapies. For human cells as therapeutics, great strides can be made by next-generation nanomedicine-enabled delivery technologies, improving both *ex vivo* and *in vivo* genome engineering capabilities. However, effective and targeted delivery of genome and transcriptome engineering tools in intact living organisms remains daunting. A key challenge to enable robust gene therapy is a delivery system that is simultaneously: 1) safe, 2) efficient and tissue-targetable, 3) tunable, 4) redosable,

and 5) manufacturable for broad accessibility. Specifically, key challenges include minimizing toxicity, orders of magnitude improvements to efficiency of delivery across the extracellular and intracellular compartment, and tunability of a generalizable and flexible delivery vehicle capable of delivering a range of genetic payloads including DNA, RNA, and protein. Gene therapy must be re-dosable so that the effective dose and its durability can be tailored and monitored by a clinician and tailored to differential gene therapy for multiple tissue types. Finally, manufacturability for broad accessibility including low cost and easily scaled manufacturing operations to produce off-the-shelf gene therapy products are required. While delivery has historically been a formidable challenge, breakthroughs in each of the key attributes needed for achieving robust and low cost gene therapies are now on the horizon. The grand challenge is thus for the design and engineering of a new transport technology, not unlike in some ways a space shuttle, but built on the nanoscale and designed for precise transport through the microscopic world within the body. A gene delivery vector or nanotechnology that is simultaneously safe, efficient, tunable, re-dosable, and manufacturable will open a new powerful paradigm to all of medicine, including enabling in situ engineered human cells as therapeutics.

4) *Developing Cellular Sense and Response Modules:*

Human cells sense inputs, such as mechanical forces, small molecules and metabolites, and different ligands, responding to stimuli via changes in gene expression and/or protein function(s). Synthetic biology harnesses the multitude of combinations of natural sense and respond behaviors displayed by human cells representing a vast repertoire of biomedically important and engineerable opportunities. Engineering human T cells encoding CARs for robust cancer immunotherapy is a major success of synthetic biology. Platforms for synthetic biology including SynNotch and the Modular Extracellular Sensor Architectures (MESA) platforms are enabling new ways to leverage the native ability of human cells to sense and respond for clinically important applications. Expanding the design rules of these technologies will create a slew of new diagnostic and therapeutic methodologies. In the short term these efforts could produce engineered human cells that sense metastatic cells or the boundaries of solid tumors and respond with tumor cell killing, the release of inflammatory payloads, and/or bioluminescence to help guide surgical excision. Longer-term sense and respond designs could include cell-based vaccines that recognize and quarantine novel pathogens and simultaneously alert the immune system, or engineered cells that improve local wound healing, release analgesics, and/or seamlessly integrate with implanted or wearable scaffolds. The grand challenge is to build sense and respond modules that function predictably and reliably when deployed in any primary human cell and that are amenable to prolonged use and clinical-scale manufacturing and banking.

C. *Enabling Technologies*

Several existing and future technologies will provide the basis for Genetic Systems Engineering.

Genome engineering: Advances in biotechnology provide a vast repertoire of enablers for next generation efforts in genome

engineering. In vivo genetic alterations including insertion and deletion of genes using CRISPR-Cas technique is revolutionizing modern cellular engineering.

Genomics and epigenomic sequencing: In addition, genomic, epigenomic sequencing and other omics technologies are exponentially evolving and offer exceptional scope for precision genome engineering.

Biomedical data science: The ability to analyze the vast amounts of data to develop genome-scale models of cellular function provide further impetus for genome engineering-driven biomanufacturing.

D. *Multi-Disciplinary Teams and Core Competencies*

The development of human cells for therapeutics requires interdisciplinary strategies that combine every domain of biological and engineering sciences. Modern training in genomic biomedicine involves core competencies in Omics technologies, microfluidics, nanoengineering, bioinformatics, computational and systems biology and data sciences.

Genomic intervention warrants precise molecular engineering approaches such as that evidenced by the CRISPR-Cas method. In addition, scaling of such method warrants design of miniaturized scalable chemical reactors, and design of cell and tissue manipulation devices. This will require interdisciplinary collaborations between biologists, chemical engineers and systems engineers. We envision that the future genome manufacturing industry will involve professionals trained across these disciplines.

VII. CONCLUSION

The five challenges outlined by the Workshop have several common underlying themes. As demonstrated in each of the grand challenges, interdisciplinary collaborations between life science-based and engineering disciplines harbinger the future. Next generation training of physicians and clinicians is needed in more technologically and quantitatively driven sciences. We anticipate that the future will involve a holistic approach to human health and disease, in which myriad measurements, mostly non-invasive, will provide a detailed map of “human wellness quotient” and provide lifestyle recommendations. Two major factors will determine the future: the ability to build inter and transdisciplinary collaborations and expertise, and the training of an entirely novel generation of professionals who can adapt technology (devices and sensors), measurements, data analytics and systems-level integration. In addition, funding agencies and organizations will have to explore multidisciplinary research involving multiple domains of expertise and team science collaborations.

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