

Bioengineering and Metabolism Voices

To explore the world where technology fuses with the life sciences, we asked a diverse group of scientists to tell us about bioengineering innovations that impact metabolism and physiology. From miniaturized models of physiological systems to smart drugs with feedback control, we take a journey with them through the frontiers of biomedicine.

Delivery of Biologics for Treatment of Type 2 Diabetes



Ashutosh Chilkoti
Department of Biomedical Engineering, Duke University

Peptide and protein drugs are promising for the treatment of type 2 diabetes (T2D), but a major limitation is their short duration of action. Beginning with the development of long-acting insulin, and more recently with the clinical adoption of long-acting versions of glucagon-like peptide 1 (GLP-1) and its analogs, there is a strong push to create long-acting versions of biologics for treatment of T2D. Different molecular engineering approaches have been employed to achieve this goal, such as the recombinant fusion of these drugs with long circulating proteins such as albumin and the Fc regions of antibodies. To develop even longer acting versions, approaches spanning molecular engineering and innovative devices hold promise. We, for example, have developed a recombinant fusion of GLP-1 with a thermally responsive elastin-like polypeptide (ELP) that can be injected as an aqueous solution, forming a depot under the skin under the action of body heat, from which the ELP fusion is released for an extended period of time. An optimized ELP depot controlled blood glucose levels for 10 days in diabetic mice and showed sustained levels of the drug for up to 17 days in monkeys. Another promising approach: a matchstick-size device that can be surgically implanted under the skin to release a controlled dose of peptide or protein drug for months to a year.

While the evolution of molecular to macroscopic innovations will continue to bear fruit, the next grand challenge is to devise delivery approaches that can mimic the transient temporal duration of the native peptides and proteins that control glucose homeostasis in humans, yet only require infrequent dosing. Solving this challenge represents the next frontier for the design of delivery systems for T2D treatment.

Curing Disease, Not Symptoms



Martin Fussenegger
ETH Zurich, Basel, Switzerland

For centuries, strategies for the treatment of metabolic disorders have been misdirected. Instead of preventing and curing disease, strategies for the treatment of metabolic disorders have focused on symptomatic treatment using small-molecule drugs. Patients have symptoms and are already sick when they seek medical advice, and drug dosing is often just based on body weight. Such treatment is late, poorly dose-controlled, and lacks a dynamic interface with metabolism. We need a paradigm shift from symptomatic treatment to preventing and curing metabolic disorders. Future treatment strategies must dynamically link detection and diagnosis with dosing and delivery. Synthetic biology principles enable robust, precise, and predictable programming of novel cell functions for engineering human designer cells that can monitor systemic biomarkers and tune production of protein therapeutics in a closed-loop manner. Equipped with sensor-effector gene circuits and implanted subcutaneously inside immune-protective microcontainers, these cells vascularize, watch critical metabolites in the bloodstream, and provide automatic feedback control of production and secretion of protein pharmaceuticals. Closed-loop connection of detection and intervention merges diagnosis with treatment and enables prevention and cure of metabolic disorders. Proof-of-concept studies for preventing and curing experimental diabetes, auto-immune disorders, and obesity offer a pathway to clinical implementation, which will allow us to take control of our metabolism.

Monitoring Molecules



Tony Cass
Department of Chemistry, Imperial College London

It is becoming apparent that many molecular markers of health show a natural pulsatility with a frequency much larger than the familiar circadian rhythms. These are often associated with endocrine or neurological secretions associated with fundamental biological processes including sleeping, reproduction, and food intake and metabolism. There is also emerging evidence that disturbance of such rhythms is associated with pathologies that are easily missed when relying on a single point "reference" measurement. The challenge in studying these phenomena is that traditional methods such as venous blood sampling are highly invasive, expensive, and carried out in very artificial conditions.

Ideally, investigations of these pulsatile changes should be performed continuously with a wearable device that allows normal daily activities to be undertaken, and while we are familiar with wearables that can monitor changes in pulse rate, oxygenation, or even cardiac activity, the corresponding reliable measurement of molecular markers introduces many additional challenges.

One answer to the challenge of continuous monitoring of molecular changes in the body is to employ microneedle sensors that painlessly pass through the outer layer of dead skin cells and sit in the underlying tissue, which is bathed in interstitial fluid. The microneedles are electrically active and suitably modified so that their reaction with the target molecules results in a change in current or voltage. Microneedle sensors have already been shown to be capable of measuring important molecules such as glucose and lactate or antibiotics such as penicillin. Developments in molecular engineering, device fabrication, and signal processing will extend these to many more molecules, opening new insights into human biology in health and disease.

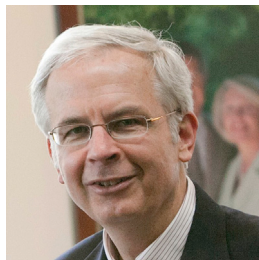
So a Cell Biologist, Immunologist, Clinician, and Engineer Walk into a Lab...



Cherie Stabler
Biomedical Engineering and UF Diabetes Institute, University of Florida

No, the title is not the setup of a bad joke—it seeks to highlight the “odd” partnerships that are increasingly becoming the new normal for studying diabetes. As a multi-faceted disease, transdisciplinary research teams are considered optimal for tackling knowledge voids in innovative ways. An exciting example of this is the development of a “pancreas-on-a-chip” device. Engineering a benchtop microphysiological system (MPS) incorporating human-sourced β cell in 3D niches under controlled dynamic flow can provide insights into diabetes that are not achievable in rodent models. Currently, our MPS platform supports the durable culture of human islets, permitting the efficient screening of agents that may support β cell survival, proliferation, and/or function. These devices can also be leveraged to provide an *ex vivo* window into pathological events, such as the incitation or propagation of type 1 diabetes (T1D). Such a feat requires the close collaboration of biomedical engineers with those knowledgeable in immunology, β cell biology, stem cell differentiation, and pathology. Integrating this team and current technological advancements, a device that incorporates stem cell-derived β cells and an autologous immune cell repertoire within precisely controlled 3D niches that support dynamic flow and bioanalytics is now feasible. We hope that resulting “diabetes-on-a-chip” devices can be broadly utilized to identify novel β cell-immune cell interactions, examine features that promote or inhibit disease progression, and/or screen therapeutics that delay, prevent, or treat T1D.

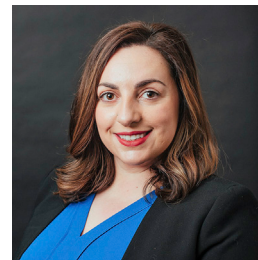
Engineered Muscle Metabolism



George A. Truskey
Biomedical Engineering, Duke University

Engineered microphysiological systems made with human cells represent an exciting opportunity to model human tissue and organ function *in vitro* and overcome the limitations of animal models to replicate human disease states. These systems can replicate the structure and key functions of tissues. Differentiating induced pluripotent stem cells (iPSCs) to skeletal myoblasts, it is possible to model disease states, particularly genetic diseases. As an example, engineered human muscle has been developed that replicates the native fiber structure and organization, although fiber length is shorter than *in vivo*. The engineered muscle can be made over a range of scales from 0.01 to 1 cm. Contractile force and metabolism (oxygen and glucose uptake, metabolomics) can be examined. Exercise conditions can be modeled using repeated electrical stimulation and neuromuscular junction models have been developed using optogenetic stimulation. Duchenne’s muscular dystrophy using iPSC-derived muscle has been examined. The systems are not without limitations, however. Foremost among these is the need to differentiate the cells to a mature state found *in vivo* and to adequately replicate chronic diseases, such as metabolic syndrome and diabetes. Culture conditions need to be modified to better replicate the *in vivo* environment where oxidative metabolism is the major metabolic pathway. Further advancement of microphysiological systems will require close collaboration among biomedical scientists, bioengineers, and bioinformaticians to improve upon these systems to better simulate the *in vivo* environment and model disease states.

Why We Need to Grow More Fat



Evangelia Bellas
Department of Bioengineering, Temple University

“Why do you need to grow fat in the lab? I have plenty; take some of mine!” This is the response when I say we engineer fat in the lab. Obesity, in simple terms, is excess fat and has reached epidemic levels, affecting nearly 40% of U.S. adults (<https://www.cdc.gov/>). Yet obesity is not a simple disease; it is associated with major comorbidities, like type 2 diabetes, stroke, and cardiovascular disease, and recently has been linked to some cancers. Obese adipose tissue has distinct differences from lean tissue aside from larger adipocytes; these differences include cellular composition, extracellular matrix, and vascular components. As we start to unravel the complexities of obesity and its potential to influence other organs, we must develop appropriately complex obesity models. Our approach is to no longer study adipocytes in simple, 2D models, but to provide them with a microenvironment and cellular crosstalk. We found that merely putting them in a 3D environment allows them to respond to disease cues and remodel their environment like in the body, a response that was undetectable in 2D systems. We have engineered adipose tissue with increased complexity, including cellular and matrix composition and mechanical forces, thereby no longer excluding these key pieces in the obesity puzzle. Organs-on-a-chip allow us to observe the impact of vascularization on adipose tissue function and eventually to connect to other organ systems involved with obesity. This multidisciplinary approach opens new doors in which to study this disease, in a manner that begins to mimic the complex changes seen between lean and obese tissue.

Vascularizing Organoids

Reiner Wimmer and Josef Penninger
Austrian Academy of Sciences

The global epidemic of diabetes, affecting ~422 million people worldwide, is currently one of the major challenges for our healthcare system. According to the WHO, diabetes is a major cause of blindness, kidney failure, heart attacks, stroke, and lower limb amputations that can be primarily attributed to diabetes-mediated blood vessel damage. While mice are a useful tool to model some aspects of the disease, studying diabetic vascular complications in mice remains challenging. Stem cell-derived organoids that recapitulate the architecture, functionality, and expression profile of human tissue hold great promise to study metabolic diseases. Organoids can be genome edited and used for disease modeling, drug testing, or transcriptome/proteome comparisons. In our lab we developed self-organizing blood vessel organoids from human pluripotent stem cells, which, upon transplantation into the mouse, specify into a mature and fully human vascular tree. These blood vessel organoids recapitulate various hallmarks of diabetic vascular complications, such as vessel regression, leakage, or basement membrane thickening. Drug screening approaches and *in vivo* transplantations of organoids showed that endothelial-pericyte interaction via Notch3/Dll4 is crucial to initiate basement membrane thickening, which ultimately leads to vessel dysfunction.

Of course, organoids in general have limitations. For instance, they lack the interaction of the tissue with the native microenvironment. This will be the next challenge in the organoid field: to generate more complex organoids that take into account tissue-stroma interactions. In the case of our blood vessel organoids, that would mean the creation of a tissue-specific vasculature or the interaction with immune cells.

Human Metabolism-on-a-Chip

Dan Dongeun Huh
University of Pennsylvania

Remarkable progress in life science and technology in the past century has advanced our understanding of human metabolism beyond our imagination. The ever-increasing knowledge in this active area of research, however, has done surprisingly little to change the way we emulate and probe the inner workings of the human metabolic system *in vitro*. Even today, we rely on the century-old practice of traditional cell culture to model this tremendously complex and dynamic physiological system. While laboratory animals provide an alternative approach, undeniable interspecies differences in key metabolic processes remain an inconvenient truth that raises significant concerns.

To tackle this long-standing, fundamental problem, microengineers are forming alliances with biomedical scientists to generate innovative *in vitro* technologies. This emerging effort exploits the power of microfabrication techniques derived from the microelectronics industry to develop more realistic and predictive models of the human metabolic system. As part of the NIH-sponsored Human Islet Research Network, our team has developed a microphysiological model of the human pancreas that enables the production and long-term maintenance of vascularized and perfusable pancreatic islets with physiological secretory function. The same approach has been leveraged for modeling other organs, such as the liver, intestine, adipose tissue, and muscle, during health and disease. This technology is still in its infancy, and reverse engineering the complexity of metabolic organs in manmade systems remains a distant goal. But pursuit of this ambitious vision will create tremendous opportunities for innovation and interdisciplinary cross-fertilization, which may lead to major breakthroughs in the study of human metabolism.

Mining Elite Microbiomes for Next-Generation Probiotics

Jonathan Scheiman
FitBiomics

I'm interested in utilizing genomic tools to understand super fit and healthy phenotypes to identify what is unique, what is enriched, and essentially what works in optimal physiology. Taken a step further, can we transfer these beneficial properties to the general population to promote health?

Our research is focused on elite athletes, as a model for understanding optimal physiology, and analyzing their biological data to develop nutritional interventions. In particular, we're focused on the microbiome of elite athletes—looking to identify and isolate novel probiotics to disrupt consumer health and wellness. Our microbiome dramatically influences energy and protein metabolism, neurology, and immunology. Therefore, we're working with athletes that excel in endurance, strength, mental toughness, and recovery to determine which microbes are associated with, and potentially support, these physiological demands. We've discovered differences in the microbial composition between athletes and non-athletes, athletes from different sports, as well as how athletes' microbiomes change between performance and recovery phases. In turn, we've mined these metagenomic data to identify, purify, and functionally validate next-generation probiotic candidates.

There's great potential for translation of the microbiome. It's dynamic, mutable through dietary and environmental interventions, engineerable through synthetic biology tools, and amenable to extraction, purification, and transfer from one person to another. I believe athlete microbiomes provide exciting new opportunities to both understand and transfer beneficial health properties, with applications beyond a sports nutrition niche. The health and wellness industry is a \$4.2 trillion market. Can we do better than the status quo? Think about obesity, diabetes, under- and malnutrition, inflammation, etc. What if we had next-generation probiotics derived from super fit communities that could help alleviate these health crises?

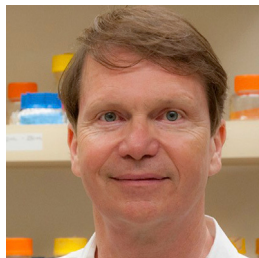
Designer Microbes Serving Society



Jens Nielsen
Chalmers University of Technology, Sweden

Microbial fermentation has been used since ancient times for production of fermented food and beverages. In more recent times, microbes have been recruited as cell factories for production of food ingredients, transportation fuels, antibiotics, hormones, and vaccines, and today microbial fermentation represents a +USD50 billion industry. In the last 15–20 years microbes have been engineered to produce heterologous products as well as to produce endogenous products more efficiently. In more recent years, the use of microbial fermentation has further advanced for a number of reasons: (1) our ability to efficiently perform directed genetic modifications, e.g., using CRISPR/Cas9 technologies and other genome editing tools; (2) our increased understanding of metabolism and its regulation, obtained through detailed systems biology analysis of widely used cell factories such as *E. coli* and *S. cerevisiae*; (3) large and concentrated efforts toward engineering cell factories for production of certain chemicals have provided much knowledge about the plasticity and rigidity of different parts of cellular metabolism; and (4) automation has enabled a significant decrease in costs and increase in number of designs that can be tested. Despite these advancements it is, however, still costly (particularly in terms of time) to engineer a cell factory to meet the requirements for industrial scale production. We therefore need to further improve our ability to rapidly design new cell factories, and here I foresee that design based on mathematical modeling will be essential, as this will enable a 10× decrease in cost, which will be transformative for industrial biotechnology.

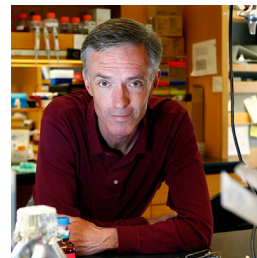
Mining the *E. coli* Metabolic Pan-genome



Bernhard Palsson
Bioengineering and Pediatrics, UCSD

The first seminal description of metabolic engineering was given in 1991. Even before we had full genome sequences, ambitious engineering efforts to build *E. coli* strains that over-produced metabolites were undertaken. Since then metabolic engineering has become a vibrant field with many success stories. As sequencing technology broke through critical cost barriers, many sequences of *E. coli* strains appeared. The first analysis of the metabolic capabilities of multiple *E. coli* strains revealed diverse strain-specific catabolic capabilities that were the source of defining metabolic traits relating to colonization sites and autotrophies. Last year, the detailed analysis of over 1,200 *E. coli* strains revealed the pan-metabolic genome of *E. coli* as a species. The principles of phylogenetic barriers to protein expression are beginning to be elucidated, suggesting that phylogenetic relatedness is a possible solution to one of the main challenges of metabolic engineering: namely, the successful expression of heterologous genes in the host strain. Finally, I mention that the pan-genome of pathogenic strains is likely to be a source of particular metabolic traits we want to engineer. For instance, the genotoxin found in the pathogenic NC101 strain is synthesized by a polyketide synthase. Subsequently, many biosynthetic gene clusters have been described in *E. coli* strains, suggesting that engineering of secondary metabolism in *E. coli* hosts may be on the horizon. Exploring and mining the metabolic pan-genome of relatives of desirable host strains may thus play a significant role in the future of engineering metabolism.

Altered Metabolic States



James J. Collins
MIT

There is growing, compelling evidence that antibiotic efficacy and pathogen metabolism are intricately intertwined. Recent work on this topic has led to four key tenets. First, the metabolic state of bacteria influences their susceptibility to antibiotics. Second, antibiotics alter the metabolic state of bacteria, and these alterations contribute to the resulting lethality, stasis, or tolerance. Third, bacteria can enhance their tolerance to antibiotics by altering their metabolic state. And fourth, we can enhance the efficacy of antibiotics by altering the metabolic state of bacteria. This last point is critical given the rise in antibiotic resistance and the near collapse of our antibiotic pipeline. Our lab and others have shown that one can boost the ability of existing antibiotics to treat persistent infections by adding certain metabolites, thereby priming the metabolic state of the target pathogen. While promising, these approaches are compromised, in many cases, by the challenges of ensuring suitable bioavailability of the metabolite or metabolites at the site of infection. To address these challenges, we need to launch biodiversity mining and synthetic biology efforts to identify and/or design metabolites that selectively impact bacterial pathogens. Moreover, we need to recruit and motivate bioengineers to develop targeted means to deliver antibiotics and metabolites in suitably high doses at infection sites. Bacterial metabolism is emerging as a critical, underappreciated point of vulnerability that we should be able to exploit in our ongoing battles against resistant and tolerant infections.

Metabolic Engineering in Human Health and Disease



Martin L. Yarmush
Biomedical Engineering, Rutgers University

Metabolic engineering has long been applied to the improvement of yields of important biochemicals produced in fermentation biotechnology. In parallel with that goal is the development of tools that progressively integrate genomic, proteomic, and metabolomic information, as well as their interactions, to enable quantitative predictions of metabolic pathway fluxes, intracellular metabolite pools, and the impact of purposeful genetic modifications and environmental factors (such as the composition of the culture medium). An increasing number of studies are adapting these tools to mammalian and human tissue and organ systems to better understand and treat human diseases. In recent years, we have been particularly excited in using these tools to model and understand liver metabolism, the main metabolic center in the human body. For example, we might develop treatment methods to improve recovery of livers grafts that fail to meet donor criteria for transplantation, decrease fat content in livers to address nonalcoholic fatty liver disease, or alter the fate of amino acids in liver to alleviate muscle wasting disease in systemic inflammatory conditions ensuing from severe trauma and burns. Such models may be developed for other organs and tissues, as well as important biological processes, such as wound healing. Ultimately, we may be able to develop whole-body models that would better predict the impact of diet and a host of environmental factors on health.

Toward a Predictive Virtual Metabolic Human



Ines Thiele
National University of Ireland, Galway

Personalized, or precision, medicine is an emerging research area that focuses on improving disease prevention, diagnosis, treatment, and care through better understanding of genetics, biological mechanisms, and interactions with the environment. Personalized medicine represents a paradigm shift, moving away from the one-drug-fits-all approach, by accounting for inter-individual variations. Compared to the genetic mark-up, other factors influencing drug response, such as co-medication, diet, and the gut microbes, can be modulated. Due to the complexity of possible interactions, sophisticated, predictive computer models (“virtual humans”) are required. These computer models must encapsulate biochemical, anatomical, and physiological knowledge and describe underlying cellular and physiological properties in a mechanistically accurate manner. Genome-scale reconstructions of an organism’s metabolism are fulfilling these criteria and have been generated based on extensive literature mining. The Virtual Metabolic Human database (<https://www.vmh.life/>) hosts the metabolic reconstructions of human and human-associated gut microbes, and interlinks them with hundreds of metabolic diseases and to dietary components found in thousands of foods. Recently, we have generated the first physiologically accurate, organ-resolved mechanistic models of whole-body metabolism and connected them to microbiome-level metabolic models. Using physiological, biochemical, and (meta)genomic data of an individual, this new generation of computational models represents a first, pivotal step toward personalized, predictive modeling and will be instrumental in enabling personalized medicine and nutrition.

Charting Human Metabolism



Roland Nilsson
Karolinska Institutet

The charting of human metabolites and biochemical pathways has been pivotal for the development of modern medicines. Yet in 2019, our knowledge of human biochemistry is far from complete: with modern analytical chemistry methods (“metabolomics”), we now routinely detect thousands of compounds in human bio-samples, and it is clear that many of these compounds are not listed on our biochemical maps. Here is a large, uncharted territory that holds great promise for new discoveries.

For this to come to fruition, I think two major issues must be addressed. First, merely detecting compounds is not enough. An unknown signal in, say, human plasma from a cardiovascular disease patient could be a breakthrough—or it could be a mere artifact from sample handling. Stable isotope tracing methods are key to solving this problem; an example is the deep labeling technique developed in our lab, which uses a highly ^{13}C -enriched culture medium to systematically identify metabolites produced by human cells. The underlying biochemical pathways can then be unraveled by targeted isotope tracing experiments.

Second, metabolomics data are notoriously unstructured and difficult to analyze, and data sharing and re-analysis are poorly developed. Tackling this problem will require concerted efforts from analytical chemists, computer scientists, and metabolism experts to systematize and standardize data processing.

Metabolic Imaging to Trace *In Vivo* Flux



Kayvan R. Keshari
Memorial Sloan Kettering Cancer Center

With a dramatic rise of interest in metabolism across biomedical disciplines, we have become increasingly aware of the limited tools we have at hand to quantify metabolic processes. There exists a fundamental need in the field to ask what new tools engineering can provide to efficiently trace metabolism *in vitro* and *in vivo*. What methods can we develop and use to visualize metabolic flux from a nutrient to a product of interest without destroying the sample? This would change the way we approach problems—for example, in the setting of cancer metabolism and therapy—across a wide range of diseases, affecting multiple organs in the body.

Recent work from our group and others has pushed the development of approaches in the field of hyperpolarized magnetic resonance, a generalized strategy to combine conventional NMR/MRI with pre-polarized nutrients and apply this to model systems as well as humans. Regardless of the methodology for preparing the nutrient, once introduced into a living system it provides an opportunity to follow that molecule as it's converted through expected, and in some cases unexpected, metabolic pathways. Though we have had a fundamental understanding of biochemistry for decades, these new engineering tools allow us to truly observe and interrogate metabolism *in vivo* and in a range of pathologies.

Metabolic imaging is a true example of the power of combining developments in physical chemistry and bioengineering to answer poignant metabolic questions. As our questions about real-time metabolic flux become more intricate, the engineering-metabolism field may be able to provide the tools necessary to answer them.

Label-free Metabolic Imaging



Kyle Quinn
University of Arkansas

Since Britton Chance and colleagues first began characterizing the natural fluorescence of NADH and FAD over half a century ago, optical assessments of cell redox state have revealed key insights into cellular respiration and mitochondrial dynamics. In recent years, the continued adoption of new technologies has resulted in a renewed interest in NADH and FAD autofluorescence imaging. Two-photon excited fluorescence microscopy has opened the door for intravital imaging of cell metabolism without exogenous dyes. Fluorescence lifetime imaging has allowed for the assessment of NADH protein binding status, and new image processing techniques are enabling the characterization of mitochondrial organization from these autofluorescence images. Historically, the biomedical optics community has focused on cancer applications for these imaging technologies, in which the metabolic phenotype of tumor cells can be exploited for early detection or predicting the response to therapy. Our research group has been exploring other applications for NADH and FAD autofluorescence imaging, such as non-invasively characterizing chronic skin wounds. A number of researchers are also exploring new applications for label-free imaging in tissue engineering, developmental biology, and cardiovascular research. With the new possibilities created through advances in label-free microscopy, it is an exciting time in the field of metabolic imaging.

3D Metabolic Imaging



Irene Georgakoudi
Biomedical Engineering, Tufts University

An explosion in metabolic studies has been fueled by advances in sequencing, radiolabeling, and mass spectrometry. However, metabolic changes are heterogeneous at the (sub)cellular level and highly dynamic over timescales that span milliseconds to years. Exploiting the natural fluorescence from NADH and FAD in combination with high-resolution, multiphoton optical imaging is well suited to help us unravel the role of these aspects of metabolism in 3D *in vitro* and *in vivo* specimens. The intensity and lifetime of these signals are sensitive to subtle changes in the relative rates at which different pathways contribute to energy production or biosynthesis. Further, the intensity fluctuations of NADH multiphoton images can report on dynamic changes in mitochondrial organization, which occur upon the onset of stimuli or diseases. All of these metrics can be assessed simultaneously and have the potential to serve as sensitive markers of metabolic changes with exquisite resolution. Their combination with computational models and machine learning will provide more specific insights regarding the metabolic origin of changes. Instrumentation that will enable imaging via miniaturized probes promises to bring label-free functional metabolic readouts to the clinic, so as to implement personalized medicine decisions regarding diagnosis and therapy for numerous conditions that are associated with metabolic dysfunction.

Overcoming Cancer Metabolism**Kevin Yarema**

Biomedical Engineering, Johns Hopkins University

Abnormal metabolism in cancer is an age-old hallmark of the disease dating back a century to when Otto Heinrich Warburg observed that cancer cells fermented copious amounts of glucose as an energy source while largely forgoing the more efficient route of oxidative phosphorylation. Efforts to starve cancer of sugar as a therapy to overcome this “Warburg effect” began in earnest as early as the 1950s but remain largely unsuccessful even today. One problem is that approaches often used involve blocking glucose transport into cells or its transit into glycolysis—because of severe off-target effects (many healthy cells critically require sugar!).

In recent years, “metabolic glycoengineering” — a technology pioneered and popularized by Bertozzi and Reutter groups about 25 years ago—is showing increasing promise as a precise tool to target abnormal sugar metabolism in cancer cells with negligible harm to healthy cells. For example, our group has shown that non-natural, azido-tagged monosaccharides can be selectively partitioned into tumor-associated carbohydrate antigens found on certain oncoproteins, opening the door to novel biomarker discovery. In some cases, these probes also dampen oncogenic signaling, positioning them as attractive “theranostics.” The next challenge in this field will be to transition metabolic glycoengineering from the laboratory to the bedside, a promising endeavor that is currently in its infancy.

Feedback Responsive Therapy**Michael Strano**

Department of Chemical Engineering, MIT

An exciting new frontier in drug design and mechanism is the use of therapeutic endpoints to dynamically, and in real time, adjust the dosing, potency, or modality of a given drug. The closed-loop artificial pancreas could be considered an early example. However, it is increasingly possible to encapsulate the entire feedback control loop within a therapeutic molecule itself. The analogy in this case would be the glucose-responsive insulin (GRI). It relies on a reaction or interaction between glucose and the drug to produce a modulated potency or dosing of a resulting insulin derivative to provide a constantly varying feedback response. We can generalize this to the category of Feedback Responsive Therapeutics, which seeks to actively control some prescribed therapeutic endpoint by modulating the dose, potency, or mode of action. They encode a mathematical feedback loop as would a state machine. We can therefore use computational models of human biochemistry and physiology for their design. My laboratory at MIT has been interested in the computational design and synthesis of so-called Feedback Responsive Therapeutics and how state machines can be programmed for complex biomedical tasks. We’ve come to the realization that new types of molecular recognition will be central to this effort and therefore have advanced a program to expand the number and bounds of biomolecular recognition. Feedback Responsive Therapies promise a new generation of drug technologies with vastly improved efficacy, control of side effects, and encoding of personal characteristics.