Controlling Food Environment and Obesity Via Synthetic Biology

Keerthi Shetty[1] and Arvind Chavali[2]
[1]Yale University, Department of Immunobiology, 300 Cedar Street, New Haven, CT 06520
[2]Yale University, Department of Biomedical Engineering, 10 Hillhouse Avenue, New Haven, CT 06520
Corresponding author: arvind.chavali@yale.edu

A recent study on the global prevalence of obesity published in *The Lancet* estimated that nearly 2.1 billion people around the world are overweight (with a body mass index ≥ 25 kg/m^2), and of these, 671 million are classified as obese (with a body mass index ≥ 30 kg/m^2) [1]. Since 1980, global overweight and obesity rates have increased by 27.5% in adults and 47.1% in children [1]. Previous research on the complex causes of obesity suggests that drastic changes in food environment, including a decrease in the relative price of calorie-dense foods and an increase in caloric consumption may be partly to blame for the obesity epidemic [2]. Given that obesity increases downstream risk for cardiovascular disease, diabetes, musculoskeletal disorders, and cancer [3], there exists a real need for creative and innovative approaches to 'control' the food environment and reduce overall food intake in obese patients. Recent scientific inquiries in the area of synthetic biology have aimed to (a) design genetic sensors to directly monitor food quality and help promote satiety or (b) engineer probiotics in foods to monitor the gut microbiome.

Synthetic biology is the application of engineering principles in the design of life. Armed with modern biological tools such as DNA sequencing and DNA synthesis, synthetic biologists strive to re-design existing biological entities or even invent novel systems to accomplish specific tasks [4]. For example, the design and construction of novel biological systems have been used for various applications, ranging from commercial uses such as biofuel production [5], to therapeutic ones that combat diseases such as obesity [6-8]. Synthetic biology exceeds the scope and scale of genetic engineering in that it can rewire the genetic circuitry of living organisms [9] or even assemble a genome from scratch [10] as opposed to simply transferring genetic material from one organism to another. The availability of complete genome sequences, low-cost sequencing and chemical synthesis of DNA, and increased investment in bioinformatics have allowed for rapid advancement of this field. In this article, we highlight recent developments in synthetic biology in the fight against obesity. Furthermore, we advocate for an open and informative dialogue among scientists, policy makers, and consumers regarding the potential for synthetic biology to deliver novel treatment options by effectively controlling food environment. Given the many ethical and legal implications of synthetic biology research, we also encourage active participation by social scientists to serve as facilitators of this dialogue by assessing societal impact of novel treatment regimens [11]. Finally, given the interdisciplinary nature of synthetic biology, non-traditional actors such as artists and designers can provide interesting perspectives on the role of design in this evolving field [12].

For the treatment of obesity, scientists have developed clever ways to monitor, process, and report food quality and high fat levels in blood by designing therapeutic gene circuits that act as sensing devices. In a recent study, the fat-sensing capabilities of a designer circuit were coupled with the expression of a clinically licensed peptide hormone, pramlintide, which serves to promote satiety [6]. Obesity can be very challenging to treat using a simple 'one-drug-one-disease' paradigm as it can exhibit inter-dependent and very complex pathophysiology with other metabolic disorders such as hypertension, hyperglycemia, and dyslipidemia. Therefore, another recent study used synthetic biology techniques to engineer a therapeutic gene circuit controlled by the anti-hypertensive drug, guanabenz, to affect expression levels of anti-hyperglycemic and satiety hormones [7]. When mice suffering from obesity were implanted with these synthetic constructs, both of the above experimental studies reported significant reductions in food intake and body weight. These studies also provide a proof-of-concept for the use of synthetic biology approaches to simultaneously affect a range of inter-dependent disorders by constantly monitoring fat-levels in the blood and effectively controlling food intake.

Obesity has also been linked to diet-influenced structural alterations in the gut microbiota and their interactions with human cells [13, 14]. Lately, probiotics – edible bacteria that help improve the balance of beneficial microbes in the gut microbiota – have received a lot of attention for their potential in treating diet-related diseases. Besides keeping harmful bacteria in check, probiotics can aid in improving digestion and nutrient absorption, while also playing a vital role in modulating immune function [15, 16]. Studies have shown that certain strains of these bacteria led to decreased fat tissue and body weight in mice or improved body mass index in patients [17-19]. Moreover, rather than passively replenishing the gut flora, scientists are currently seeking to re-engineer the probiotics in foods by creating a network of genetic circuits that can sense and actually respond to disease [20, 21]. For example, a probiotic can be programmed to detect obesity-induced damage in the intestinal lining and deliver appropriate signals to neighboring cells in the gut to help fix it.

The idea of consuming "altered" food products or re-engineering of natural systems has historically sparked debate among the public and regulatory groups. A national poll surveying 804 adults found that only 6% percent of respondents had heard "a lot" about synthetic biology with the remaining having heard "some" (17%), "just a little" (30%), or "nothing at all" (45%) [22]; and, in another more qualitative survey, participants feared the societal and environmental impacts of synthetic biology research [23, 24]. Furthermore, the public may not always be trusting of a food product processed by a new technology because often the science or regulatory oversight involved to bring the food to market can be difficult to comprehend. For example, the first major synthetic-biology food additive, vanillin (vanilla flavoring created by a culture of synthetic yeast), which will become commercially available later this year, generated mostly negative and fearful reports [25]. Unfortunately, this does not set a good precedent for the marketing of synthetic food products with a healthy rather than "cosmetic" purpose.

Although therapeutic gene circuit implants or edible biologically engineered organisms are still in the research phase and are yet to be introduced widely, an open dialogue among synthetic biologists and other key stakeholders should start as soon as possible. A diverse committee comprised of synthetic biologists, physicians, non-scientist ethicists, social scientists, patients/consumers, as well as non-traditional actors such as artists/designers all working on synthetically bioengineered food products for obesity-related disease treatment should collaborate with advocacy groups concerned about food safety. Furthermore, the committee should periodically report to the Food and Drug Administration (FDA) on new scientific developments as well as on assessments of societal impact. In fact, progress has already been made on this front with the 2010 report on the ethics of synthetic biology protocols by the Presidential Commission for the Study of Bioethical Issues [26]. The committee advised the President with a list of 18 recommendations involving research, coordination, risk assessment, oversight, ethical evaluation, and respectful engagement between scientific, religious, and civil society groups. We suggest additional discussions regarding synthetic biology in the specific context of food policy.

More studies need to be conducted in order for scientists to provide enough evidence that these engineered systems do not pose major health, environmental, or societal risks before public opinion is prematurely aligned against them. A report by the Organization for Economic Cooperation and Development (OECD) titled "Emerging policy issues in synthetic biology" also notes the importance of public opinion and argues for increased engagement of the scientific community in debating the societal implications of their research [27, 28]. The report additionally states that current perceptions for synthetic biology research are closely linked to those surrounding genetically modified organisms (GMOs), and thus, synthetic biologists may be confronted with existing and potentially very demanding regulatory frameworks [27]. In order to better guide public perception and correct misinformation, frequent communication with radio, online, television, or print media outlets such as NPR, CNN, New York Times, and Mashable as well as open discussions at local "science cafes" can allow for scientific knowledge to be broadly accessible to the public.

Additionally, engaging with advocacy groups and holding public lectures and workshops would be highly beneficial. In closing, we argue that it is vital for synthetic biologists to collaborate with other key stakeholders, understand how their research might affect consumers, play an active role in tailoring appropriate regulations, and hold an open and informative dialogue to communicate the enormous potential for their research. These strategies need to be implemented *now* in order to encourage better knowledge transfer and develop innovative policies towards controlling the food environment for the treatment of obesity.

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Arvind Chavali

Arvind is currently a post-doctoral associate at Yale University working on aspects of HIV latency. Prior to Yale, he received a PhD in bioengineering from the University of Virginia where he focused his dissertation on metabolism of infectious parasites that cause neglected tropical diseases. He also holds a Master's degree in Public Policy from Princeton University where he specialized in health policy and international development. Arvind has broad interests in infectious disease and global health, and he is passionate about the use of simple and innovative technological solutions to address grand challenges in health and medicine.

Keerthi Shetty

Keerthi is a Ph.D. candidate in Immunobiology at Yale University in New Haven, CT. She graduated from Princeton University with an A.B. in Molecular Biology. Her thesis research focuses on the process of how antibodies are formed. Keerthi is interested in making science interesting and accessible to the general public. For the past two years she was the co-President of the Yale Science Diplomats, a campus group devoted to educating the public about science issues that affect them and encouraging scientists to become engaged in the political process. She hopes to pursue a career in science policy after graduation.