Ethics

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As we are all aware, one criterion for iGEM teams is to address issues of public, environmental and researcher safety. This is a critical first step towards greater social responsibility and it should be applauded. However, we feel that it is critical to examine ethical and societal issues specifically related to synthetic biology. Here we determine what makes societal and ethical issues in synthetic biology unique; we examine why they are vital to address with enthusiasm and in a timely manner; and we postulate new regulatory frameworks which deal with the unique set of ethical and societal issues in synthetic biology.

What makes ethical issues in synthetic biology unique?

It is undoubtedly very important to address safety concerns in synthetic biology. However, it is insufficient to assume that all safety concerns or ethical considerations are the same across the numerous and often very different fields of science. Synthetic biology, like other areas of science, has unique potential problems in society which can only be understood as a function of its origins and content.

Synthetic biology takes methodologies, scientific rigor and conceptual frameworks from basic scientific research, and combines these with engineering principles of part modularization, ground-up design and circuit construction. But pure science and engineering are quite different: pure science is an open-ended exploration which should not have one end product in sight, whereas the purpose of engineering is to define an ambitious goal and singularly focus on reaching it. Significant is the fact that synthetic biology takes more after the engineering side of its lineage, focusing on synthesizing genetic circuits which run the gamut from being intellectually fascinating to economically feasible. This is drastically different from something like basic genetics research or animal behaviour studies.

We wish to bring the unique characteristics of synthetic biology to the attention of the reader early in this paper, as they will permeate the major argument we wish to make: safety concerns in synthetic biology are especially important to address pre-emptively and with enthusiasm; and that the proposed self-regulatory safety structure will foster more societal unease than uniformly applied top-down regulations by a team-independent body.

Why are open discussions of ethics so important in synthetic biology?

Why are they sometimes dismissed?

Scientists working in synthetic biology have an obligation to discuss and address ethical issues resulting from their work, perhaps even more so than in other fields because they work

with a biologically active product which may increase risk and influence public perception. By ethics, we refer to discussions of how a practical application of research will be used in society; anything from how many people potential products may harm, to how it improves the quality of life for citizens, which is distinct from the economic gains one may derive from it.

Discussions of ethics are often either dismissed in science, or are conducted with a distinct lack of alacrity compared with the flurry of excitement surrounding discovery. We want to look at why this is so, and then examine whether the ethics paradigm which has been created for basic research can be superimposed on top of the new field of synthetic biology. The resistance to discussions of morality in basic research may arise because it is inherently difficult to predict the ethical implications which may emerge from a basic research experiment. The goal of experimentation is to discover processes and characteristics of the natural world, so before these conditional truths and paradigmatic frameworks have been elucidated, it is hard to predict practical applications and associated ethical issues which arise from the basic research. This characteristic may lie at the heart of explaining why fundamental theoretical researchers generally avoid preemptive ethical discussions of their work. This reasoning is sound: it is unproductive, imprecise and possibly misleading to discuss the morality of undiscovered natural processes. But applying this value structure to synthetic biology generates problems due to the field's engineering roots. In synthetic biology, researchers start with a finished construct in mind, as well as possible uses of this construct; this is diametrically opposed to the processes in basic research in which no consensus theory or application exists before a battery of experiments are performed. Therefore, in synthetic biology, before scientific investigations even begin, the end construct is known as well as implied potential applications. Because of this it becomes irresponsible to dismiss ethical concerns, as is sometimes done in basic research where the focus is on revealing an unknown natural structure to the world.

Rather than a burden, we should look on this as a unique opportunity to discuss ethical issues, a discussion which usually presents difficulties in fundamental scientific research. These discussions may help introduce an awareness of ethical and societal responsibilities to synthetic biology, from a practical standpoint, scientists can influence public perception of their field in a positive fashion.

History is rife with examples of how science failed to address ethical issues at the same time as rapid technological development, leading to public outcry and misunderstanding. Nanotechnology and genetic modification of foods are the most recent fields to come under the intense and sometimes malicious scrutiny of the general public. Although regulation for both these fields was eventually proposed, the public perception issue had its roots in the fact that the regulatory measures came after technological and industrial achievements. It is possible that the growing public concern about both fields would have been lessened if regulation and ethics were concurrent with the scientific advances. And why shouldn't they have done this? Both of these fields are based on engineering, defining an ambitious end goal and concentrating resources and manpower on achieving this; therefore

they could have conducted open, transparent public discussions on safety concerns and morality, and they could have proposed regulatory bodies while the products were being developed.

Perhaps what stopped them doing this was their adherence to an artificial and outdated idea of ethics which was borne from basic research. Perhaps the most important backdrop to discussing ethical concerns comes from the thalidomide case. Thalidomide was introduced in 1950's as a miracle drug capable of suppressing pain, including morning sickness in pregnant mothers. Unfortunately little risk assessment or controlled testing was performed prior to its release. Over 10 000 children were born with significant defects due to thalidomide's action as a strong teratogen when taken by pregnant mothers. This caused legitimate public outcry and resulted in much stronger drug safety laws worldwide. The social shock waves from this drug can still be felt today, influencing ordinary citizens' demands for rigorous risk assessment and testing of products coming to market.

Can synthetic biology break free of this mold to influence public perception of the field, and be open and accountable about risks pre- emptively before products come to market? Can it accomplish this while at the same time remaining scientifically rigorous? We believe it can ?

What kind of regulatory body is appropriate for iGEM?

A series of safety criteria have been proposed on the iGEM website, which ostensibly force the recognition of safety and ethical concerns by each team. We want to discuss two main suggestions about how we can improve these regulations. The first suggestion is that, alongside iGEM teams analyzing their own safety and ethics, a collective iGEM regulatory body should also analyze the work for any ethical flaws. This regulatory body could be comprised of experts and a random mix of other team members. The second suggestion is that a clear distinction should be made between forseeable and unforseeable consequences of a project, as analyzing the former involves knowledge and background research, while analyzing the latter involves documenting a series of experiments to test safety on an ongoing basis, using clinical trials.

Traditionally science is able to regulate the quality of its data by the peer-review system, since scientists have a vested interest in being accurate, honest and complete to see elucidation of the natural truth on which they work. The safety criteria listed on the iGEM website do not include a similar peer-review system, and instead rely on the teams themselves to do research into possible ethical and safety concerns, with the judges giving the team's work a quick check (we will refer to this as a self-regulatory structure from now on). We strongly suggest that at the very least, this structure is amended to include peer-review by other teams, or by scientific experts, toimprove accountability and transparency.

A self-regulation structure has historically failed when applied to societal and ethical concerns. One only has to look at how numerous drug companies selectively omitted studies on their products, and attempted to misinform the public, to appreciate the limited success of self-regulation. This may be because self-interest plays a part in regulatory decision making wherever it can, and this self-interest exists to a far greater extent when one's usefulness to society is at stake, versus when the rigor and validity of a scientific experiment is being examined. The former is personal, whereas the latter is intellectual. Therefore we do not see success using a structure where each iGEM team investigates potential societal ramifications of their project, as self-interest may play a large role and cause omissions of possible societal ramifications or of

previously published data in the literature which indicates an ethical problem with the project may exist.

Ideally, the regulatory system would not involve peer review and would instead rely upon a standard set of regulations made by disinterested observers. This is because society has learned from adverse incidents in both pharmaceutical and environmental areas that top-down governmental regulations are necessary to protect society; and that industry cannot work by a kind of internal peer-review process due to financial conflict. The benefit of this is that there exist regulatory frameworks for drugs and environmental standards for products. Rather than working from first principles or one can utilize these existing frameworks to inform regulation that investigates the potential risk of unfinished research. This is a crucial set of criteria since any product will have to fulfill precisely the same criteria.

We propose a team-independent iGEM regulatory body which would look at the possible hazards involved if each project were finished and being marketed, based on current scientific knowledge. The body could consist of either experts in the field, or students from iGEM groups.

It could examine each project proposal before the jamboree, and research possible hazards. At the jamboree, the body could discuss their concerns with each group, judge whether the answers are satisfactory, and then assign a safety rating out of 10. Specific safety ratings could be designated as requirements for medal standings. Arguably this would not be unduly complex, or place too much pressure on teams; while at the same time it would raise public awareness about how scientists are addressing public safety issues in synthetic biology. Furthermore, it would train undergraduate researchers to rigorously and consistently analyze the ethical dimension of their work, which is a novel idea fit for an innovative field.

The real questions revolve around the content and makeup of “safety ratings”. I’d like to propose a series of general guidelines which the iGEM regulatory body could follow. This makes the distinction between forseeable and unforseeable consequences. It is important to realize the difference between a regulatory body which evaluates the potential ethics and social context of unfinished research; and a body which evaluates actual risks of a product about to go to market. Any iGEM regulatory body would be the former rather than the latter, looking at probable causes of uncertainty of unfinished research. Therefore, we must relate the pre-product iGEM regulatory body here (which evaluates the type of research) with any iGEM regulatory body evaluating the product just before it goes to market. This is the purpose of the distinction between forseeable and unforseeable consequences.

Forseeable consequences:

What current scientific understanding is available for the issue being dealt with? What hazards can be predicted? How severe are the hazards and who would they affect?

Unforseeable consequences

What testing has been proposed to address unforseeable consequences? Do scientific methods exist to accomplish this? How will the consequences be continuously monitored?

How does this relate to our project?

Our project involves the design of a probiotic bacterium which produces cellulose to exert numerous health benefits on humans. Clearly, then, numerous ethical concerns and potential risks have to be addressed. Optimally an outside body would do this, but we will attempt to do our best. We hope this will add credibility to our project and show the effect that a regulatory body, as proposed above, would have on the overall atmosphere and accountability of þiGEM.

We feel that the unknown risks of our project deserve the most attention. While probiotic yogurts are already sold by various companies, our bacteria is different because it produces cellulose and thus might pose a health risk. We propose a comprehensive set of tests to evaluate our bacteria: Biofilm testing. A vital question is whether our probiotic bacteria will outcompete other gut flora, which would be undesirable since a precise balance of bacterial species exists in humans' guts. Biofilms are a multicellular bacterial population attached to a surface, and the scientific expertise exists to use biofilms to test bacterial competition in the gut. Therefore we plan biofilm tests in coordination with Dr. Thien-Fah Mah at the University of Ottawa, who is a biofilms expert. We will mimic the normal composition of gut flora in a lab biofilm, and add our genetically modified strain in varying amounts. We will then test how well our genetically engineered strain competes with the other bacteria by surface area coverage or GFP expression, over the span of 1-2 weeks. We predict that our genetically engineered strain of Lactobacillus plantarum will be outcompeted since it carries out the extraneous function of cellulose production, which will likely reduce reproductive rates and therefore overall fitness. Mouse trials. We intend to feed a group of mice modified L. plantarum, and compare overall health with a control group of mice. We expect weight be lower in the L. plantarum group after a period of time, but we will also monitor the mice for signs of unexpected adverse effects. We plan to measure blood pressure and heart rate, as well as to measure long-term disease resistance, birth defects, cancer resistance, and overall size. This will ensure a relatively comprehensive safety assessment of the modified bacterium before it reaches the market.

Human trials. We plan a long-term clinical trial on humans to act as an additional buffer against unknown side effects.

We can predict some of the known risks of this product. The most pressing concern is an ethical one: we must guard against the bacterium being marketed to the public as an easy weight-loss alternative. We would like to emphasize that although reducing obesity levels is one of the potential advantages of this bacterium, we find it ethically dubious to concentrate marketing on this, as it contributes to the current climate of socially induced anorexia in healthy women. We feel that the bacterium has many other potential health benefits, such as increasing dietary fibre naturally, helping diabetes, and reducing mutagens. Because of this, we would impose marketing restrictions on companies which want to sell the bacterium as a probiotic. We would prefer the bacterium be marketed as a probiotic culture which improves all-around health through genetic engineering. However, it is important to recognize that the bacterium may provide a painless and natural solution for individuals who are obese due to an underlying genetic condition, and it may

have the potential to improve their quality of health significantly. In this case we would allow it to be distributed by medical professionals in a controlled manner. We find this ethically acceptable.