News Letter

NO.2

2015. 5. 31 Today's Topic

Show our projects and ethical discussions

Welcome to our newsletter.

· Amoy · Paris_Bettencourt · Pasteur_Paris ·

T O D A Y ' S T O P I C

SHOW OUR PROJECTS AND ETHICAL DISCUSSIONS

Dear all,
Here comes the second issue for 2015 Newsletter.
The publication contains two parts:
project introduction & ethical discussions.

We really appreciate it that more iGEM teams are joining us!
We would like to express gratitude to all the writers as well as the readers, especially teams which contribute to this issue.

(in alphabetical order)
Project Part (8): Freiburg, HUST-China, NJU-China; Oxford, SCAU, Uniandes_Colombia, WHU-China and Zamorano,

Ethics Part (16): CAU_China, ETH-Zürich, HUST-China, NCTU_Formosa, NJU-China, OUC-China, Oxford, Paris_Bettencourt, Pasteur_Paris, SCAU, SJTU-BioX-Shanghai, Stockholm, SYSU-Software, Valencia_UPV, Zamorano and ZJU-China.

Thank you all for being so supportive!

If there are any questions, please reach us at igemxmu@gmail.com

All the best!

iGEM Amoy
2015-5-31

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PROJECT

By: Eight iGEM Teams
Show you our projects

PROJECT SUMMARY

Synthetic biology is an interdisciplinary research area that aims for the design of new biological systems through genetic modification (Church et al., 2014). One of the fundamental challenges of synthetic biology is the efficient assembly of biological systems, a difficult thing to accomplish because of the variability present in these systems (Kwok, 2010). Standarization of genetic parts is a key for the integration between biological systems (Shetty et al., 2008). The objective of our project is the integration between biological systems and electronics, this integration would have applications in different areas spanning from computational biology to the design of environmental and medical biosensors.

Among the different bacteria with electric properties, the most studied genera are Shewanella and Geobacter (Shi et al, 2007). Previous groups have developed electrical signals using these bacteria ("Bactricity", 2008; Webster et al., 2014). However, these previous systems are not capable of lowering the electric signal once the biological signal disappears. Our aim for our iGEM 2015 project is to build a functional prototype of a bacterial system based on Shewanella and Geobacter, capable of changing their electric resistance in response to biological signals. We will accomplish this though the use of modeling tools, available from computational sciences, engineering and physics; and molecular biology procedures.

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iGEM Freiburg

DIA CHIP
Freiburg 2015
Enlightening diagnostics

Freiburg iGEM Team 2015 – The DiaCHIP

Even though the previous iGEM Freiburg teams worked very successfully on genetic editing methods, we decided to strike a new path: after weeks of brainstorming, finding and discarding possibilities we came up with a new idea. We decided on using a technology for protein interaction detection and combineit with the flexibility of cell-free protein expression to screen for various diseases. The DiaCHIP was born!

The idea

The core of our project is a glass-slide endowed with various antigens. Running a blood sample over this slide allows the detection of antibodies binding to the antigens using a label-free optical detection system. This detection system is called iRIf (imaging Reflectometric Interference), which allows the observation of minute increases of the layer thickness on the slide. We are therefore able to detect the binding of antibodies to the antigendue to the increase of thickness at the respective antigen spot. To produce the antigen slide we start with a DNA- coated with

DNA fragments coding for the antigen sequences which is easier to handle and more resistant than a protein-microarray. The DNA portions also contain the sequence for a binding tag. The glass slide and the DNA-microarray are placed next to each other in a microfluidic system so that they are separated by approximately 50 µm of distance. The space between them is flooded with a cell-free expression mix. The DNA from one side gets expressed and the antigen diffuses to the other side. Due to the fused tag, it binds specifically to the second glass slide and thus protein-microarray is produced.

After the proteins are expressed and bound to the glass slide, we exchange the cell-free express ion mix with a patient's serum. If there are antibodies present against any of the antigens on the glass slide, the antibodies will bind and the thickness at the specific antigen spot will increase. A camera included in the iRIf setup allows the real-time measurement of the binding process.

The principle of iRIf is based on light beams being reflected by several layers inside the chip's surface coating. Those light beams are interfering, resulting in specific pattern. A change in the thickness of the reflective material (the glass slide coated with antigens) results in a phase shift of the light's wave length. This phase shift leads to a change in light ray interference and a resulting alteration in the intensity of the reflected light.

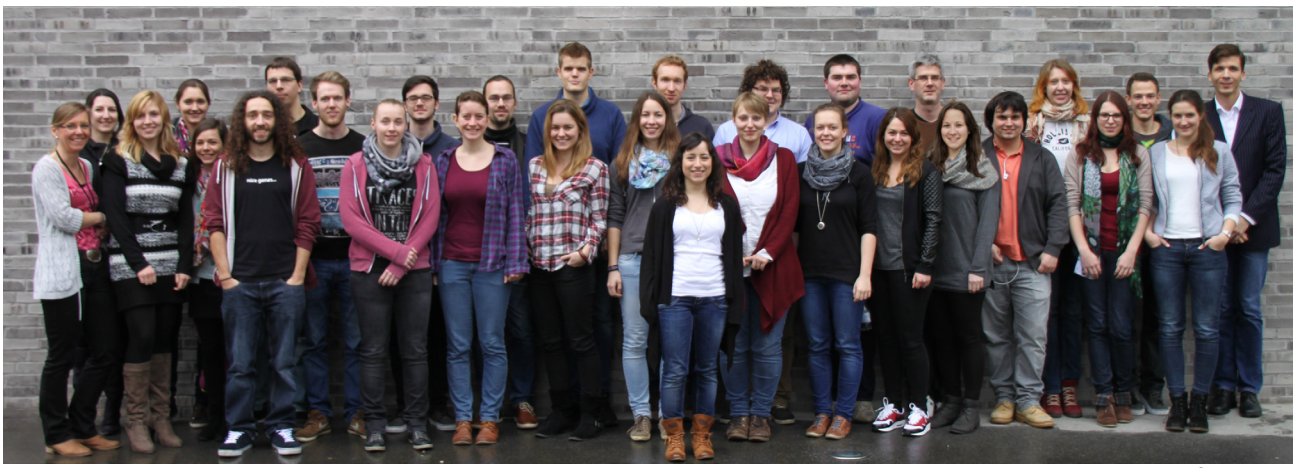
Our DiaCHIP can be used for various applications. The aim is to provide medical professionals with a universal diagnostic chip with every known antigen coupled to the surface. This would allow the fast, easy and low cost differentiation of diseases. A patient could therefore be provided with the best treatment available much earlier.

Another application we propose is a chip with ispecific antigens for a pre-pregnancy care screening. For women planning a pregnancy it is recommended to get tested for several nfections and confirm their immunity against different diseases including German measles, Chickenpox and HepatitisB. Nowadays these tests are performed separately, making it a quite elaborate procedure. With our DiaCHIP all these tests would be performed at once, avoiding unnecessary inconveniences for the mother to be and saving lot of time and money.

The DiaCHIP is not only useful to screen for diseases but could also be used to check on current vaccination statuses. However, for the realization of this application, we have to find a way to adequately quantify the amount of antibodies in the patient's blood. Unnecessary immunizations could be avoided and pharmacists could also perform this simplified procedure.

The team

This year there was a great interest among students in being part of the iGEM team Freiburg. It is composed of twenty highly motivated students with different scientific



Team members

backgrounds like chemistry, physics, biology, biochemistry, informatics and medicine from four faculties of the Albert-Ludwigs-University of Freiburg. We are sure that such adiverse team is a key feature when dealing with a project on the boundary between molecular biology, medicine and engineering and we are curious to get involved in real interdisciplinary work and investigate the social impact of our project.

If you want to know more about our project or if you consider a cooperation with our team don't hesitate to contact us!

iGEM 2015 team

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OUR PROJECTS

1. Reclaiming Land from the Sea with yeast sounds fascinating for countries' thirst for ground, isn't it?

We hope to reach our goal with the help of existing sediment in water. Biological methods will be used to easily consolidate them. Also, an environmental controlled switch would be applied, aiming at an automatic gene expression after our cells are settled at a proper depth. The biggest challenge of our project is the use of a new chassis, a special kind of yeast, which is not so widely studied like E.coli. Will any of you share some points about pathway regulation in it with us?

2. Biocode

Morse Code is a widely applied approach of massage transferring, but a simple Morse Code has no function for encryption. But when synthetic biology was mixed in, it would be a different kettle of fish. As you may have guessed, we use several kinds of fluorescent protein to represent the symbols of Morse Code. But it's not the only highlight of the project. To complex the coding system, recombinase is applied to operate the expression of fluorescent proteins, which is done via the overturn of our sequences. The application prospect of this project is promising. What's more it is kind of meaningful for synthetic biology and that is why we decide to pull it off .

OUR TEAM: Huazhong University of Science and Technology

Our team has a short history in participating in the competition and has been known for several success in surface display. This year, our vigorous undergraduates double our efforts--we challenge to combine two projects and pull the off at the same time.

iGEM 2015 team

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Our team

We are NJU_CHINA iGEM team. When it comes to iGEM(International Genetically Engineered Machine Competition),our team is pretty acquaint with it thanks to the experience in this competition over the last few years. Not only can this wonderful competition expand our horizons and enrich our experience but also it provides a golden chance for us to show creativity, enthusiasm and our great passion for science , so that's why we participated in the competition again this year. We expect to witness all the teams' exceptional performance and develop long-term friendship with you.

Our project

As is known to us all, the synthetic biology has undergone dramatic growth throughout the past decade, and it's playing increasingly important role in our everyday lives. We've been devoting ourselves to explore the way how to utilize the synthetic biology to treat drug relapse and disease. I'll show a few key points about our project here.

Point 1 How did we come up with this idea?

Even if you only know a little bit about drugs, you'll be shocked by the damage they have caused. The addicts spend the last penny to get treatment, yet ending up with relapse and new disease caused by the side effect of the treatment. Therefore, a more effective solution to this burning question emerges at this proper time.

There is a complex relationships among drug addition, reward effect and dopamine system. In a word, the drugs break the balance of dopamine system through stimulating the reward effect abnormally. Our team try to seek a way to destroy the receptors of the drugs in order to block the signal path and then radically resolve this problem.

Point 2 How do we destroy the receptors of drugs?

RNA interference (RNAi) refers to guide sequence-dependent gene silencing mediated by either the degradation or translation arrest of target RNAs. Our team will utilize the siRNA of the receptors to down-regulate the mRNA levels and then there is no doubt that the amounts of the receptors will decrease significantly.

Point 3 How do we transport our siRNA to the place where it work? How can it get through the Blood-Brain-Barrier? How can we guarantee its specificity to its target?

Microvesicles (MVs) is our choice. You may have heard that MVs could be utilized as a delivery vehicle to transport therapeutic siRNA or anti-sense microRNA for tumour therapy. This time we choose 293T cell from which MVs are secreted abundantly. Besides, MVs can also be engineered to express specific ligands on the membrane surface, these artificially modified MVs can then enter into specific tissues. In our study, we engineer the exosomes from dendritic cells to express the neuron-specific rabies viral glycoprotein (RVG) peptide, which binds to the acetylcholine receptor expressed on neuronal cells, to allow these exosomes to efficiently pass through the blood-brain barrier (BBB) .Thus, the RVG-modified exosomes allow for the delivery siRNA into the brain.

Point 4 How many parts will our team submit? What kind of roles will these parts play during our experiment?

MOR siRNA sequence
GFP siRNA sequence
RVG-Lamp 2b
Molecular motor related genes

Our Team

Point 5 What have we accomplished? What's our further step?

The experimental frame has been built for a long time, besides, we have successfully accomplished some key links of the experiment and gained the critical experimental data. However, there still exists some unsolved problem such as sensitization assay, the removal of other protein on the membrane of MVs, and exploration of the ways to increase the secretion of MVs. So for our teams, it's in the process of further refining our project. Time permitting, we'll pay more attention to our details and involve more experimental contents in our project so as to get the best results.

Project Overview

We are interested in developing an autonomous antibacterial system using an E. coli chassis through synthetic biology. Our antibacterial strategy involves a two-step mechanism:
i) Destroy the bacterial biofilm which confers the bacteria encased within significantly increased resilience against antibiotics.
ii) Destroy the liberated bacteria by directly lysing their cell walls.
We will be experimenting with antibacterial action against E. coli and P. aeruginosa.

iGEM 2015 team

Oxford

Antibiofilm action

The cartoon above shows two of the major structural components of bacterial biofilms - extracellular polymeric substance (a.k.a. EPS, in blue) and extracellular DNA (in pink). The Doctorbacto system will release the following enzymes targeting these structural components:

Dispersin B	Destroys E. coli biofilms by hydrolysing beta-1,6-N-acetyl-D-glucosamine, which is the major EPS in E. coli biofilms
Thermonuclease	Also commonly known as staphylococcal nuclease, this enzyme should be able to destroy P. aeruginosa biofilms by hydrolysing its extracellular DNA (novel usage, untested as of yet)

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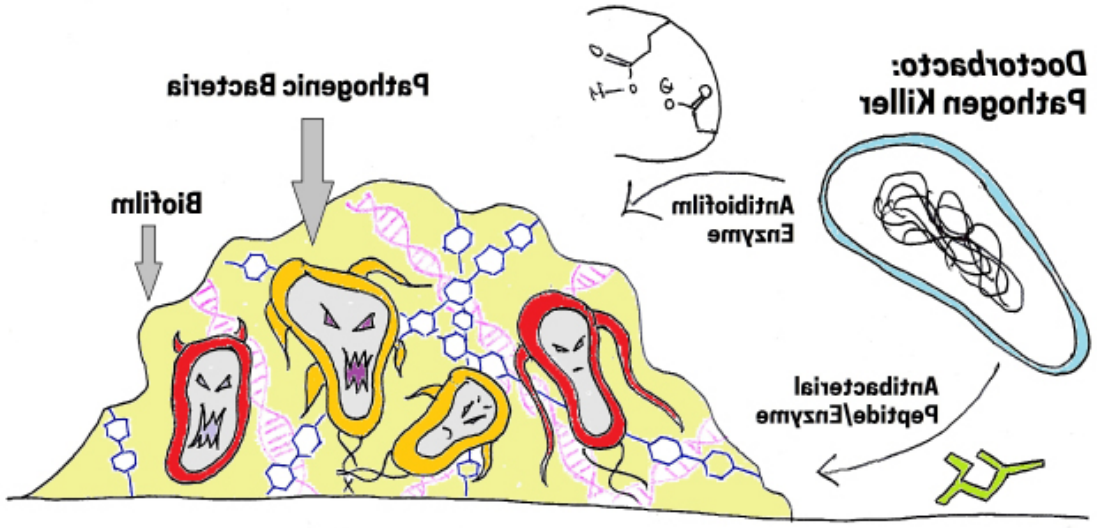

Antibacterial action

Doctorbacto will release "artilysins", which is a class of combination biomolecules made by fusing endolysins (phage-derived enzymes that hydrolyse bacterial cell walls) with SMAP-29 (a transporter peptide that brings the complex through the bacterial outer membrane such that it can get in contact with the cell wall). Endolysins are species-selective in terms of the type of cell wall which they hydrolyse, and as such Doctorbacto will be making two different artilysins:

Art-175	An artilysin specific for P. aeruginosa comprising endolysin KZ-144 and SMAP-29, invented in 2013
Art-E	An E. coli-specific artilysin, comprising T4 endolysin and SMAP-29, conceptualized and designed by our team (novel design, untested as of yet)

Overall design

We intend to construct two variations of Doctorbacto - one that synthesizes and accumulates the antibacterials and antibiofilms within itself before releasing them all by self-lysing upon detection of the presence of group pathogenic bacteria behaviour (via quorum sensing), and another one that constantly secretes moderate levels of both antibacterials and antibiofilms. With the secretor design, we are also interested in studying the secretion efficiency of our biomolecules of interest through different secretion mechanisms.

Potential applications

The original inspiration that led us down the path of looking at biofilms contributing to the overarching problem of antibiotic resistance was George (one of our team members)'s experience from working at a urinary tract infection (UTI) clinic, hence we are definitely interested in exploring how we can incorporate this biotechnology as a form of prophylactic application for preventing recurrent, nasty biofilm-mediated infections from forming on indwelling urinary catheters. Other than that, Doctorbacto can also potentially be used in antibiofilm plasters or even industrial contexts such as self-cleaning, antifouling pipelines.

iGEM 2015 team

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We are the third IGEM Team of South China Agricultural University. Since last two months we have been preparing for the IGEM competition, which will be held in the year 2016. Recently we get progress constantly and fortunately, projects also go well in our team.
So far , our team consists of 23 teammates in total. Innovatively, compared to the past two IGEM teams , this year we recruits teammates in the field of humanity sociology as well as one student from College of Agriculture , which enriches the variety of our teammate constitution. Students are from different grades ranging from freshmen to juniors. Though from various grades and college, teammates have already made acquaintance with each other and also built up good relationships after two months.
Plenty time is allowed for us to prepare our project about nearly two years, consequently we set up higher standards. With idea-center model, we divided our team into different groups. Each group conducts their projects respectively by the way searching for foreign papers and studying the latest technology. And we hold the symposiums periodically to share the updated progress that every group has achieved, through which every single team member can have a better understanding of the development in other groups.

Our Team

iGEM 2015 team

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We call our project "counting sheep",while it's nothing to do with lulling onself to sleep.

Actually,we are trying to build a counter at the DNA level which use binary system to record the critical state of "all or none".

Our project can be roughly divided into sensing system and counting system. Sensing system is about recording the critical state. Because of the different length between the activated promoter and the non-activated promoter, only in the critical state can the sensing system generate signals for the sensing system,thus transform the complex signals into simple "all or none" pattern.

As for the counting system, it is composed of several flippases, each flippase plays the role of a binary digit. We created special genetic circuits to count based on binary system.

Besides, we designed another project to test the original project. Tooth decay is a common clinical disease, as we know, many bacteria can result in it.We designed another system,that is when bacter metabolites exceed standard, antibacterial peptides can be produced, thus kill harmful bacteria.

Our Team

iGEM 2015 team

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We had a rocky start with our Project. Our team participated on iGEM for the first time ever last year on the track of Policies and Practices. The team competed on this track since we did not have any biobricks to add to the iGEM repository. We were planning on competing on the same track this year. However, when two members of our team went to an iGEM meeting at Monterrey earlier this year, we were practically told we had to restructure our entire project.

Our Team

Coming back from our end of trimester vacations, we were told the news and started working right away. Also, with the Policies and Practices track future uncertain, we did not know if we were going to be able to compete at the Jamboree this year at all! After a lot of brainstorming and frustrated ideas, we finally have a new project. The iGEM Zamorano Team 2015 will be making an insecticide. Our project consists of three main parts. We will be working with two parts from previous iGEM projects and will be introducing our own gene to the bacteria. As a result, we will also be competing in a different part of the competition.

Since we are a little out of our league with this new project, we are getting capacitated and advised by different people. We began with a capacitation by a microbiologist from the university. On June, we are expecting a specialist from Mexico that will guide us in the making of the bacteria. We are also expecting an expert from Argentina who will teach us how to make a proper risk assessment.

We are really thrilled because we are making something new and getting full support from alma mater. Even though we have a lot of work to do in a really short time we are very excited for the competition. We are expecting September very anxiously!

Our Team

By: Sixteen iGEM Teams
Ethical discussion

The researchers, headed by gene-function researcher Huang Junjiu at Guangzhou's Sun Yat-sen University, modified in human embryos a gene responsible for beta thalassaemia, a blood disorder that can be fatal.

SYSU - Software

[OUR TEAM]

We are SYSU-Software Team from Sun Yat-Sen University, China. This is our fourth consecutive year in iGEM competition, and we are now fully prepared.

We are a passionate team with diversity which is composed of undergraduate students majoring in Biological Science, Software, Information Science and Technology, Mathematics and Computational Science or Communication and Design. With a shared interest in synthetic biology and software design, we gather together and want to make a difference in this field. This year, we will keep tracing our road and spending efforts on the design of software to facilitate the research in synthetic biology.

[COMMENT]

We acknowledge that work done by Prof. Huang's team is certainly a great achievement in editing human genome. Their work revealed the possibility of the medical usage of CRISPR/Cas9, though the 'non-viable' embryo is such a critical model. If we just focus on the technology and the procedures of their whole studies, we can say that they did quite a rigorous work. Besides their targeted editing, they examined the 'off-target' rate carefully to show both the possibilities of, and the obstacles to, gene therapy.

We noticed that Huang made a clear statement that, if someone want to apply this technology on normal embryos, he or she need to ensure a close-to 100% efficiency. Meanwhile, they urged the world to reflect on the challenges of the clinical applications of CRISPR/Cas9, for there are a number of 'off-target' phenomena happening during these kind of studies. At this point, their job exerts a meaningful impact on this area.

However, scientific research is always interconnected with the society and the humanity. In our view, there are debatable ethic problems in Huang's studies. To some extent, the way western countries view the ethic problem of the study is different from that of China. They focus more on the rights of creature and they highly respect the principle of nature. We speculate that this is the reason why Huang's work lead to a world-wide debate. We are aware of the application of CRISPR/Cas9 on non-viable embryos being a new model of human, and the establishment of a new model can be a milestone in the research. However, unlike other animal models, the problem will become complicated in the case of a new model related to human. To strike the balance between the ethic and science, an instruction on this kind of issue should be discussed and published. Above all, we need a better and more ordered way to conduct the scientific research on human-related subject.

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CAU_China

[Chinese scientists genetically modify human embryos]

When the first life born on the earth, nature had been trying to make a balance between lives and environment. Thanks to the long anagenesis, nowadays we can live in a colorful world.

From an evolutionary perspective, human being is a species full of curiosity and confidence which wants to know about everything about nature and themselves which is also beyond nature's imagination.

To completely cure disease that is led by genes is a dream of all human beings living in the world. However, we know that this gene defect is a kind of method used by nature to choice people who can live longer but who cannot. Just to make a balance among people, other species and the environment. From an evolutionary perspective, human being is a species full of curiosity and confidence which wants to know about everything about nature and themselves which is also beyond nature's imagination.

To completely cure disease that is led by genes is a dream of all human beings living in the world. However, we know that this gene defect is a kind of method used by nature to choice people who can live longer but who cannot. Just to make a balance among people, other species and the environment.

As students studying in biology, we know that in our body, there are many complex pathways working together to keep us healthy whose principles are like many big enigmas. What we can make sure is really rare. So in my opinion, to do human genetic modification is still a high risk work.

By Xiaotong Shang
From CAU, China

ETH-Zürich

[Genomic Editing of Human Embryos]

The Holy Grail of medicine or a path to the Dark Side?

The idea of "superhumans" is as old as mankind itself. We are all familiar with the Ancient Greek folklore about the mighty Hercules and other demigods. In more recent times the list of fictional characters with supernatural powers was greatly expanded as the likes of Superman and Spiderman were conceived by visionary dreamers who greatly influenced our popular culture.

While "superhumans" have been the stuff for legends and science fiction for millennia, the concept is nowadays gradually approaching the realm of reality. This may be a bold statement. However, revolutionary advances in molecular biology and biotechnology could at least in principle be used to improve our mental and physical abilities to a degree unmatched by nature.

The modern genome-editing technique known as CRISPR/Cas9, developed by Emanuelle Charpentier and Jennifer Doudna, who were awarded the 2014 Breakthrough Price for their discovery (1), allows researchers for the first time to precisely edit the genetic code of any organism, including our own species.

The method has since been successfully used to replace segments of DNA with modified variants in living cells. The ability to overwrite a "misspelled" gene with a functional variant offers great hope as a potential way to cure many inherited genetic disorders as well as genetic predispositions for certain types of cancer.

A proof of principle has been achieved in adult cells and more recently in mouse embryonic cells (2). Given the success in rodents it was only the logical next step to do similar experiments on human embryos. A team of Chinese scientists around lead author Puping Yang drew worldwide attention last month being the first team to use the technique to modify the genome of human embryos. Their work is published in the May issue of the online journal Protein & Cell (3). The embryos used for the study had been created for in vitro fertilization. However, they carried a third set of chromosomes due to double fertilization, which prevents them from developing into a viable fetus. As a target to modify the researchers selected the HBB gene, which encodes human β-globin, an important component of red blood cells. A mutation in the HBB gene causes severe anemia in early childhood, while the disease is as yet not curable and usually fatal.

The proof of principle to overwrite genes in human embryos turned out to be successful, which is the key finding of the study. However, the authors pointed out that their editing of the HBB gene was in no way efficient enough. Of the 86 embryos treated only 4 were successfully edited. There are also a number of technical problems that have to be solved before the CRISPR/Cas9 system can be routinely used on human embryos. As co-author Huang puts it: "If you want to do it in normal embryos, you need to be close to 100%. That's why we stopped. We still think it's too immature."

While the study of Yang and colleagues constitutes an important milestone on the way towards curing genetic diseases, it sparked a heated debate about the ethical implications of such work (4). Fore one, genome editing poses a potential risk due to unanticipated side effects, such as random insertions in other parts of the genome. And since human germ lines are affected, these side effects would also be transmitted to future generations. Some critics take the idea even further and complain that the technology, if out of control, will someday in the near or distant future be used not only to cure diseases but also to edit embryos for convenience. Once the development of the technology is sufficiently advanced, so goes the argument, it will be almost impossible to control. A simple ban of embryonic genome editing in the developed world (which is already the case in many countries) is not going to prevent shady practitioners from offering their services to a rich and powerful clientele. "Would you like a boy or a girl? Rather tall? Please select eye, hair and skin color on this chart. How about an athlete child? A mathematician maybe? A talented musician? All at once (for additional charge)?" If such a scenario should become reality social

injustice will be inevitable. One might even imagine a dystopian future in which society is divided into a lower class of "naturally conceived" people and a ruling class of genetically engineered "superhumans".

This sounds a lot like science-fiction once again. The slippery slope argumentation that has been put forward by many opponents is certainly very useful to raise consciousness and to encourage people to actively engage in public discussions and sustainable policy making. However, the present-day technology is nowhere near ready for such applications. What we define as "intelligence" or "talent" or "beauty" is not simply determined by a handful of genes. In fact, reality is infinitely more complex. Likewise, most diseases are caused by a combination of genetic factors and environmental influences. While the CRISPR/Cas9 technology applied to human embryos is still in its infancy, it is doubtful that it will be the immediate solution to every imaginable genetic disorder. However, given the overall potential of the method it is certainly going to be highly beneficial for modern medicine.

We are not going to shake hands with Hercules and Superman anytime soon. But it is by no means too early to discuss the ethical aspects of research involving human embryos and to develop an international consensus about the extent to which emerging technologies should be applied.

(1) http://www.hhmi.org/news/jennifer-doudna-shares-breakthrough-prize-life-sciences
(2) http://www.sciencedirect.com/science/article/pii/S1934590913004621
(3) http://link.springer.com/article/10.1007%2Fs13238-015-0153-5
(4)http://www.nature.com/news/scientists-sound-alarm-over-dna-editing-of-human-embryos-1.17110

HUST-China

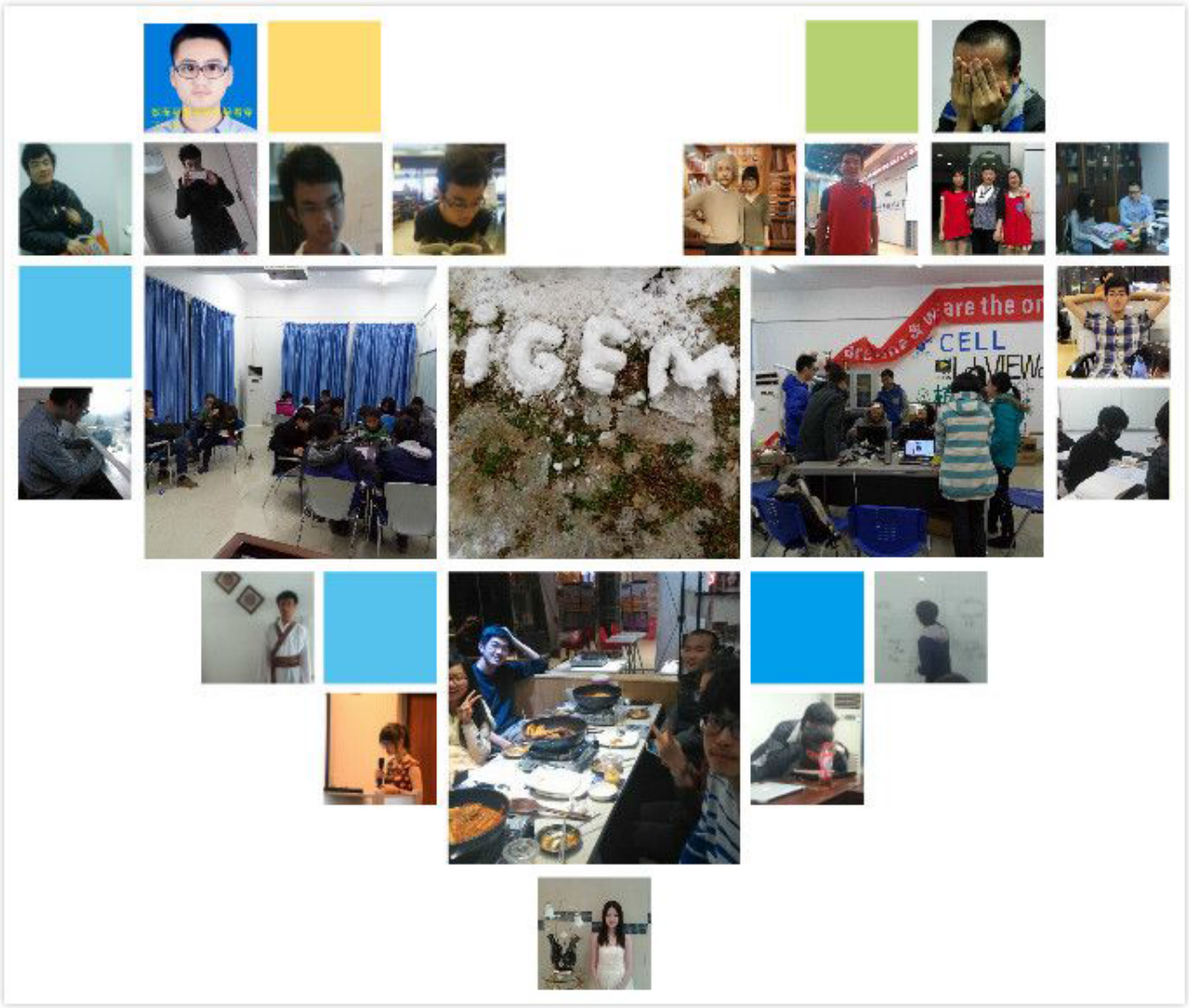
ETH ICS

[discussion&team's info]

Huang's paper, recognized as a cautionary tale about ethical line by some journals, is the first report of CRISPR/Cas9 applied to human pre-implantation embryos. We need more discussion about how to keep balance between science technology development and ethical issues .This article is to evaluate this event covering two aspects: the technical level of CRISPR and the challenges in terms of traditional morality.

Although this paper is a landmark in the medical field, the basic theory which supports it to be used in clinical seems to remain the same as before, even after experimenting on human embryos. For instance, this study is not able to explain the low efficiency which happen in these embryos. What makes this question complicated was that Mr Huang banned the embryos from a live birth in some way before they start the gene-function experiment .And his results were rejected by Nature partly because of ethical objections .Actually ,we sometimes cannot see the person hood of an embryo within the scope of the law .Meanwhile modifying human embryos would not be accepted by the medical communities as well as the majority dispite abnormal embryos . We believe that the first problem to be solved is the great number of off-target mutations. It is clear that the technology is too immature to be ready for testing to eradicate disease genes ,because the genetic changes of embryos, known as germ-line modification, are heritable and they may have an unpredictable effect on future generations .We need more date from animal models, before we start the study about modifying the genomes of human.

What's more, our cognition of technology should keep pace with the development of that .Otherwise we will be caught in no-win situation.



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NCTU_Formosa

[Reporter Discussion]

After realizing this new issue, we have a good perspective on this technology. Applied to clinical experiments, congenital diseases patients can really benefit from it. However, this kind of issue is controversial because it is about modifying human gene. Hence, it still has a lot of space for discussion. Moreover, although this gene modification technology could be fully developed, those who will use this technology is very scarce. But the one thing we make sure is that the technology of CRISPR/Cas9 will have a bright future.

NJU-China

ETHICS

Human embryos have been at the center of a debate over the ethics of gene editing since the results of Huang's team were published in the online journal Protein & Cell. There is no doubt that a majority of people believe such experiments cross an ethical line. Nevertheless, I'd like to voice my opinions about this kind of work in some other aspects.

First of all, I wish to emphasize that the embryos that Huang's team used in their experiment can't result in a live birth owing to an extra set of chromosomes. They had been created for use in in vitro fertilization, yet ending up with fertilization by two sperm. Therefore, I can tolerate that they use such 'non-viable' embryos to conduct an experiment like this. What's more, I can relate to those who take ethical considerations, but only ethical issues is not good enough to convince me to ignore the great potential such experiments have in medical. However, there still exist some more severe, unsolved problems when we get down to such work.

The technology is not well developed. I believe anyone who read this paper would come to a conclusion that it's far from mature. Just have a look at the data, the inefficiency surprises us. The number of unintended effects is precisely why this technique is not appropriate for use in clinical applications. We can't even predict what consequences those "off target" mutations would cause eventually. How can we make sure that the patients would be healed if we can't guarantee the precision and specificity of gene editing?

Another reason why we're supposed to take pause before moving forward is that it's not a proper time now. It may sound ambiguous and puzzling. Living in a technologically advanced world, we have the ability to explore the unknown areas of science. How come it's not a proper time? When is the right time? You may not realize that we are still living in a world with violence, war and terrorist attack. Since science can be a double-edged sword, there is always the need to guard against any improper use of new technologies. It may be a powerful tool to eradicate devastating genetic diseases, yet it may also be a deadly weapon for those terrorists with abnormal mentality. I cannot imagine what our world will be if bad guys take the advantage of scientists' experimental data and skills to make designer humans. There is a comment written by an enthusiastic netizen that I can't agree more: "This science has ethical implications because all we see around us is greed, war and hate. Until we get those things in order, advancing scientifically to this degree is a no-win situation. We're putting the cart before the horse..."

As a junior student majoring in biology, I feel both worried and inspired when reading such paper. Although it's clear from the results they describe that there are lots of problems with the application of the technology. Who knows? As the science advances, as the technology matures, we can make it eventually, of course, in a more peaceful and harmonious environment. I believe it with all my heart.

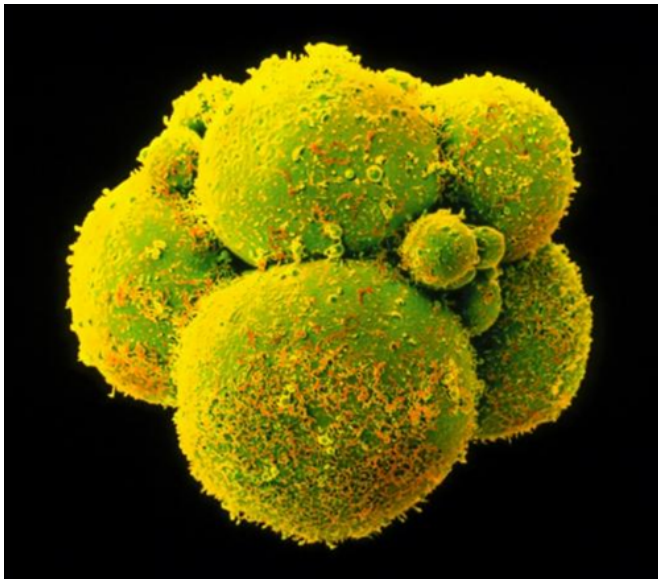
OUC-China

Sufficient argument is necessary for making code of conduct of Biology, especially the big news related to human embryos. Everyone should think about it carefully, since we have bad examples of disasters caused by advancing technology, such as atomic bomb and white pollution. We'd better make sure its safety is okay at first.After all, we don't want to live in a BRAVE NEW WORLD.

By: Qikai Qin
Team: OUC-China

Oxford

[The First GM Human Embryo: Has a Line Been Crossed?]



In April 2015, Junjiu Huang and his research team in Guangzhou, China, released a report confirming that they had genetically modified the DNA within 86 human embryos. This has prompted furious ethical debate amongst scientists across the globe, and raises serious questions about the course of gene editing research in the years to come.

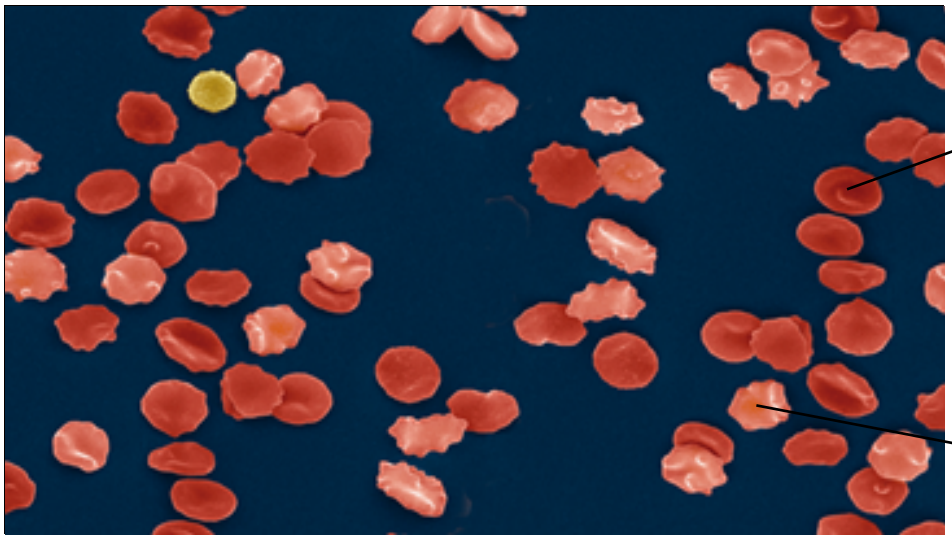
· **Human embryos? Really?!**

Yes, human embryos, but not the type we would normally think of. It turns out that 2-5% of embryos formed by IVF consist of an egg fertilised by two sperm, instead of the usual single sperm cell. This event makes the embryos non-viable, such that they cannot result in a live birth. Huang's research team collected 86 of these non-viable human embryos from a fertility clinic, and these were the cells which were used in the experiment.

· **Treating the disease: β-thalassaemia**

Huang and his colleagues were looking for ways to cure a hereditary disease called β-thalassaemia, which is a blood disorder that can prove fatal for some individuals. The disease is caused by the mutation in the HBB gene, which contains coding information for building the oxygen carrier hemoglobin, found in the blood. A mutation in this gene, a mistake in the genetic instruction manual for building haemoglobin, means that an individual with β thalassemia had a reduced

capacity to carry oxygen in their blood. As a result, sufferers of the disease described above experience tiredness, shortness of breath and other symptoms associated with a lack of oxygen supply to the organs.



capacity to carry oxygen in their blood. As a result, sufferers of the disease described above experience tiredness, shortness of breath and other symptoms associated with a lack of oxygen supply to the organs.

· **Repairing the instruction manual: CRISPR/Cas9**

Huang's research group used an effective, low-cost gene-editing technique called CRIPSR/Cas9, which was first put to use in 2013. In this experiment, the CRISPR/Cas9 complex, and other molecules designed to replace the faulty DNA of the HBB gene, were injected into the cell of interest, and subsequently travelled to the nucleus. Once inside the nucleus, CRISPR/Cas9 was intended to cut and replace the faulty region of the HBB gene.

· **Procedure and Results**

The team injected 86 embryos with CRISPR/Cas9, along with the other molecules required to replace the faulty DNA. The researchers then waited for 48 hours, by which time the embryos would have grown to roughly 8 cells each. Of the 71 embryos that survived, 53 were genetically tested. This revealed that only 4 of those 53 embryos had seen their HBB gene corrected.

"If you want to do it in normal embryos, you need to be close to 100%" says Huang, commenting on his results, "That's why we stopped. We still think it's too immature". In addition to their low success rate, his team found that CRISPR/Cas9 had caused a surprising number of off-target mutations in these cells, something that would have had potentially fatal consequences for a viable embryo. Huang suggests that the abnormal environment of the doubly-fertilised egg cells could have been responsible for the large number of off-target effects caused by CRISPR/Cas9, a case not observed in experiments using human adult cells or animal embryos.

· **A Community Divided: The Backlash**

Some feel that the report, published in scientific journal Protein & Cell, has crossed an ethical line. "No researcher has the moral warrant to flout the globally widespread policy agreement against altering the human germline," Marcy Darnovsky, executive director of the non-profit Centre for Genetics and Society in Berkeley, California, wrote in a statement. Edward Lanphier, president of Sangamo BioSciences in Richmond, California believes that the low success of this investigation should be enough to prompt a ban on such research using human embryos; "I think the paper itself actually provides all of the data that we kind of pointed to," he says.

However, many people have arguments to support Huang's research. George Church, a geneticist

at Harvard Medical School, claims that the technology is not immature at all, and that the CRISPR/Cas9 'kit' used by Huang was not the most up to date version available. John Harris, a bioethicist at Manchester University believes "It's no worse than what happens in IVF all the time, which is that non-viable embryos are discarded". Harris sees no justification for a ban on research in this area, and argues that the technique could eventually be used in clinics, just so long as the potential harm of the treatment is outweighed by the downsides of having the genetic disease untreated; "It's not as if the alternative is safe," he says. "People with genetic diseases are going to go on reproducing."

· **In My Opinion…**

This report marks a positive step in gene-editing research. If more of this can be done (that is, using only non-viable embryos), the improvement on our understanding of early human development could increase dramatically, and could potentially lead to effective treatment of thalassaemia and many other genetic diseases such as Huntington's and cystic fibrosis, which currently have no cures. As of May 2015, four other teams in China are believed to be conducting experiments using non-viable embryos, and Huang's team aims to develop a technique to decrease the number of off-target mutations introduced by CRISPR/Cas9, this time going back to the use of adult human cells and/or animal models.

There is, however, a danger that Huang's paper could be the start of a slippery slope. His research comes as close to the ethical 'line' as one can get; let us hope that no one stumbles over it.

Pasteur_Paris

[There was a controversial research in April]

The researchers, led by gene-function researcher Huang Junjiu at Guangzhou's Sun Yat-sen University modified a gene responsible for beta thalassaemia, a blood disorder that can be fatal, in human embryos.

The human biology lessons followed by the members of the iGEM-Pasteur team often highlights the ethic ambiguity about the research on embryonic stem cells. On one side, France is proud to have an ethic and thoughtful approach, based on the respect of the products of the human body with an important legislative and politic system on those questions. On the other side, the researchers (CNRS, Institut Curie,...) tend to favor the work on embryonic cells. The Huang Junjiu research on the Sun Yat-sen University had a considerable impact in France. Indeed, the

researchers expressed their wish to set France on the "Stem Cells" competition.

In agreement with the predominant public opinion in France, we think that the research of Huang Junjiu must confront the question of which path the science should follow.

On one side, the priority of medical research is « to avoid or to relieve the suffering », no matter the cost. From this perspective, we rather agree with the work of this Chinese researcher, since he follows this understanding of research.

On the other side, the problem is in the perspective we have of « human life ». Indeed, the priority we value is to « sanctuarize » the human body : are men able to undertake the role of "creator of life" ?

The French authorities, supported by institutions such as the Agence de la Biomédecine, agree with that : a certain amount of limits discussed by specialists (philosophers, biologists, ethicists,...) must be set up to fight against the excesses of research, without, however, obstructing it.

SCAU-China

[Position about the issue "Chinese scientists genetically modify human embryos "]

The issue concerning the human's survivals and development shouldn't be ignored and avoided. Indeed, modifying the genes of the human embryo is hardness to be acceptable among people and this kind of acts are hilarious and incredible because it's definitely impractical and dangerous and scarcely earns any practical benefits apart from a blockbuster in the press so far.

Yes, it flash back my memory of a propaganda film from Peking University .A professor in Peking University urges one of his non-professional students to pursue his dream and never care about other people's teasing about you. After all, we are here after numerous giant intellectuals having been suspicious of.

Similarly, when the vaccines were initiatively discovered, a tremendous debate about whether the infusion of the inactivated vaccines into human bodies appropriate and ethical furiously aroused. However, hundreds of years later, it works out. Till now, every infant in an early age are enforced to take injections to get the body immunity tougher and in turn maintain the physical health.

As long as the theory continually be completed sophistically plus the clinical trials should be conducted again and again to the extent that it can be 100% accurate. I hold the faith that the safety of the technical appliance can get promoted.

And we should lay the emphasis that so far the experiment conducted by SYSU just dwells on the theory rather than the clinical appliance, so I don't think it should be overly criticized.

SJTU-BioX-Shanghai

[Views of the debate from the first human genome editing by researchers from Sun Yat-sen University]

The controversial research which was just experimented in Sun Yat-sen University recently caused a fierce debate among scientists all over the world. The team attempted to modify the gene responsible for β-thalassaemia, a potentially fatal blood disorder, using a gene-editing technique known as CRISPR/Cas9. Here we will express our views on both science and ethics.

In the scientific research, no one will say something if you use genentech to change the genome when your experimental subject is animals or other creature except for human. But it seems like forbidden to do the same things on mankind. Why us humans own the right that we above all species? Can we assert that human beings are Ante Omnia by ourselves? Perhaps only people without much education will affirm these claims with impunity. Leaving the philosophical issue aside, the inviolability of human rights is obvious in human society.But the researchers aren't too 'devoid of humanity' to use a living person or viable embryos. They choose the 'non-viable' embryos, which cannot result in a live birth to avoid the ethical issue. So the criticism on the experiment itself is not very convincing.

The opposing views mainly focus on the outcome of this technique. The genetic changes to embryos, known as germline modification, are heritable, they could have an unpredictable effect on future generations. Some scientists have also expressed concerns that any gene-editing research on human embryos could be a slippery slope towards unsafe or unethical uses of the technique. Why are those elites so sensitive about this event? The most likely reason could be the fear of the unknown result from the technique which we can't control yet. This situation is encountered in the study of artificial intelligence(AI) and the Large Hadron Collider(LHC), and will occur in other researches like these. This may be an obstruction for the development of science, but still necessary if we want society to maintain stable. It's essential to be sane and cautious in the research like this in conclusion.

Now in the China, there is no corresponding laws prohibiting related research works which is considered risky. Science must move forward even if sometimes it will conflict with ethics. The

correct approach is to reconcile the irreconcilable between these rather than stop or pause the study. The research shouldn't be forbidden anyway, meanwhile, the government also need to convene experts in this field to legislate to make sure the study won't be out of control. The real issue which is required debate should be on how to properly research and apply a variety of human genetic manipulation techniques. At the same time, we should pay more attention to the basic research of life science, strengthening our understanding of life, understanding life from a more fundamental level so that control the phenomenon of life to benefit all mankind without hurting us.

Stockholm

[Germline Modification – a threat or an opportunity?]

It seemed that the scientific world stopped for a brief moment last April, when the group of Junjiu Huang from Sun Yat-sen University in Guangzhou published a paper in Protein & Cell1 describing the first gene-editing of human embryos. The reaction upon this article was a broad ethical debate in the scientific community. But what has actually happened?

The Chinese group used the CRISPR/Cas9 system, a novel genetic tool originating from bacteria, which has been described to cut site-specific DNA sequences. For this purpose, the researchers use a RNA-guided DNA endonuclease, called Cas9, which is directed to as specific genomic sequence via a single guide RNA (sgRNA). After hybridization of sgRNA to its complementary sequence, Cas9 can introduce a DNA double strand cleavage at the side. By adding an external gene fragment, the researchers are able to integrate any gene fragments at the nicked site. With great foresight regarding the ethical concerns that their experiment would cause, Huang and his colleagues used non-viable human embryos to modify the gene mutation causative for β-thalassaemia, a fatal blood disorder. This monogenetic disease would be easily prevented by replacing the mutated version by its wild-type. Molecular techniques such as CRISPR/Cas9 could be the future for preventing heritable monogenic diseases. Researchers have addressed quite recently their concerns in the high-prestigious journals Science2 and Nature3 in which they criticize the procedure known as germline modification.

There are serious obstacles coming along with using powerful tools for gene-editing. The ethical discussion can be divided into two main sections, a biological section and a social section.

- **Gene-editing – the biological view**

Biologically spoken, editing genes in embryos give humanity the tools to take over the steering wheel of evolution. Mankind can then decide on which genes, which mutations are acceptable and which once are undesirable or need to be replaced. This way of engineering the human genome raises ethical concerns in which extend future generations may be affected by unpredictable effects.

Mutations, if beneficial or devastating to individual human beings, are an innate part of life. The so far pre-dominant concept of life is now at stake. Considering a world in which we design humans regarding our best knowledge of health and beauty, we will end up with a decreased genetic pool. This may put the entire human race at risk as genetic diversity is preventing the spread of diseases and increases the chances of species survival.

On the other hand, research on human embryos may give new insights in gene functions and provide us with more meaningful disease models which are by far closer to the real disease state. George Daley, a stem-cell biologist at Harvard Medical School and supporter of Huangs' research, believes that "gene editing could also be used to engineer specific disease-related mutations in an embryo, which could then be used to produce embryonic stem cells that could act as models for testing drugs and other interventions for disease". This longing is not the only reason for supporters such as Daley to promote gene-editing research in human embryos.

Germline modification may help us someday to prevent familial genetic diseases and improve quality of life of potential patients. We could finally overcome serious diseases such as Huntington disease and cystic fibrosis (also known as mucoviscidosis). Bringing molecular techniques such as CRISPR/Cas9 into clinics may be an influential new tool for preventive medicine. By using this technique, we would also be able to decrease health care costs immensely as we start the eradication of many pre-dominantly genetic diseases.

· **Gene-editing – the social view**

In 1997, the movie masterpiece "GATACA" from director Andrew Niccol showed a futuristic world in which children are designed at the computer. In his movie, Niccol addresses the concern of a two-tier society. Every parent, if only wealthy enough, can chose from the best genetic material and create their child without blemish. Poor parents will conceive their children on natural ways. These children will be floaters in a society dictated by the "perfect" humankind.

Imagining now that we bring molecular techniques for germline modification into clinics, then we cannot circumvent an in-depth ethical discussion on the exact usage of these powerful techniques. Researcher and experts in the field of gene modification are obliged to pave the way for the correct handling of CRISPR/Cas9 in future. Without prior enlightment of the board society of the world, we cannot expect that methods for gene editing will be restricted to only disease prevention. Examples from the past have proven that a premature introduction of new technology may have tremendous negative effects on mankind and societies.

Researchers have addressed their concerns about experiments made on human embryos in the March edition of Science and Nature. They argued for a moratorium on such research. "No researcher has the moral warrant to flout the globally widespread policy agreement against altering the human germline," wrote Marcy Darnovsky, executive director of the non-profit Centre for Genetics and Society in Berkeley, California, in a statement.

· **What will happen next?**

Huangs' team and their article were just the first toppling stone in the row of many more. Rumours in the field tell that several groups are currently working on gene editing in human embryos. As tempting and interesting this research is, we will not be able to evade a long and profound ethical discussion on the usage of these techniques.

A moratorium might not yet be needed as Huang could show that his gene replacement worked but he also saw an increased number of off-target effects. It seems that the technique is still very much immature. Others disagree such as George Church, a geneticist at Harvard Medical School. In his opinion side effects of the technique may have been avoided or at least lessened by using the most up-to-date CRISPR/Cas9 techniques. However, these contradictive positions are raising safety questions demanding

for answers. How harmful might eventual off-target effects of gene editing be? Would that harm or eventually be worse than the genetic disease itself?

Without an in-depth ethical debate, we will not find answers to these questions. Researchers and politicians as well as the society need to agree on a way how to handle CRISPR/Cas9 in appropriate fashion. We need clear rules for the usage and a gradual introduction of this technique into modern medicine. CRISPR/Cas9 systems have been one of the most ground-breaking innovations in the biomedical field in last decades. Now, we need to carefully dissect their powerful advantages, but also their tremendous downsides.

However, research on this topic should not stop as the potential benefits of the technique are too great to abandon. At least four more Chinese groups are currently pursuing gene editing in human embryos. Their results may give new insights in the maturity of the technique and keep the ethical discussion on CRISPR/Cas9 alive.

· **Acknowledgements**

I would like to acknowledge Roger Chang (RNA Club Stockholm) and Sarah Wideman (RNA Club Stockholm & iGEM Stockholm) for cross-reading and giving their suggestions on the article.

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By Felix Clemens Richter
(iGEM Stockholm)

Valencia_UPV

[Researching & human inviable embryos]

There have always been a lot of controversial aspects about the modification of human embryos. On the one hand, the way of publishing those results is critical, because every person would react differently to that information. In the other hand, the modification itself leads to tones of bioethical questions.

We would like to begin with the results of the study:

Junjiu Huang's team from Sun Yat-sen University in Guangzhou successfully modified inviable embryos using the CRISPR/cas9 method and avoided the expression of a gene related disease.

This sounds promising; the eradication of gene-related diseases, but the debate comes while thinking about the possibilities of this new technique. Will this be just used for research? Or will be

applied also as a pre-born therapy? In that case; why stop there? Why not make humans stronger or more intelligent…? (We can't stop thinking about the film Gattaca).

Seriously, we believe that inviable embryo modification is a very promising way for finding new techniques for fighting diseases that now are impossible to treat because, by taking the words from John Harris, a bioethicist at the University of Manchester, UK. "People with genetic diseases are going to go on reproducing." So there is a transmission possibility that will be there. Even with the possible side effects that this new treatment can cause, there a chance that newborns don't present the illness. With a lot more researching, of course, this could be the correct mean to affront next steps for stopping genetic diseases.

Of course, a lot of regulation should be done for those cases, but we prefer not to comment this part because the opinions in our team differ too much for meeting in a common point.

Although that, we coincide in the point that inviable embryos are good for researching, but just for that. The mechanism is not totally perfect and unintended mutations could be harmful for the future baby or could be transmitted to the offspring.
So, for closing this issue, we would like to highlight that we are impressed about Junjiu Huang's team results, and we expect near future progresses in battling gene-related diseases.

Zamorano

ETHICS

[Bioethics on human experimentation]

Experimentation on humans is always a sensible topic. Nowadays, any kind of human experimentation is restricted on most parts of the world. This brings both, positive and negative consequences. The negative part is that it restricts the growth of research and progress on human topics. For instance, genetic and degenerative diseases which is what Junjiu Huang from the Sun Yat-sen University was doing. If studies like this do not get funded, or are not allowed to take place, we might never know many diseases to their core or find a cure for it. On the other hand, if scientists got a free pass on human experimentation, we cannot even fathom what the consequences would be!

We believe it should be allowed to make experiments on humans, because there is no way science can progress without experimenting, but there should be a thorough regulation on the experiments done. There should be a risk assessment done before every experiment performed and it should be approved by either a national or international committee on bioethics. It is time that the double standard is over. There have been experiments performed on animals for the longest time and truly the best way to understand what happens with our organism is experimenting with our own kind, beginning with human embryos.

ZJU-China

[Is that a Pandora's box?]

Scientists from SYSU published the results of gene editing of human embryo cell this year. Unsurprisingly, this behavior made all the scientific community surprised.

To tell the truth, it is not a hard job for SYSU to overcome the technical difficulties to edit gene in human embryo cell, because of the smashing development of Crisper/Cas9 and bioinformatics. Actually, in the past few yeas, all the biologists are waiting for someone to try first. They just keep in silence to see if there is anyone can pass over the line. Everyone knows that one day it will be adapted to human cell, but here we come to the point.

Is that a Pandora's box? Will it be filled with hope or disasters or both? No one can tell the answer now. However, when those so-called ethical workers speak out the words they have prepared for years, supportive or not, it's not a condition which can be described in one sentence. Human beings, as one living thing in the world, have taken too much from nature. There is no denying that we are now being pushed by the technique we created. People always anticipate to see new things but not to take response to them, so does the gene editing. We are scared of the potential demons made by our curiosity. The only thing can be predicted is that this will not be the last try of breaking ethic laws, and one human will be used to the new things converse to tradition.

No one can stop the step of technique developing and human's self –destruction, if everything in our cosmos follows the second law of thermodynamics. People will experience a long-time debate whether to open the box or not.

Paris_Bettencourt

Earlier this year, a chinese team used CRISPR/Cas9 on human nonviable embryos to edit a mutated version of the betaglobin gene, which is responsible for a potentially fatal genetic disorder. Without thinking about offtargeting, one can reasonably ask whether this way of genetically modifying embryos to prevent disorders should be applied to humans or not. At first glance, this new tool CRISPR/Cas9 looks like a great chance for medicine, as it could prevent some genetic diseases from appearing in human beings. But who can decide on whether or not to use

CRISPR/Cas9 on an embryo? It is easy to see how the use of this technique could lead to bad eugenics policies; or how it could create injustices if only the more wealthy have access to the technology.

Eugenics as it appeared broadly in the early 1900's encouraged different methods that were meant to improve the qualities of the human species. This ideal can easily lead to abuses when governments decide which traits are desirable and which are not and adopt eugenics policies. And our history is full of those abuses, from constraint on marriages and restrictions on immigration to forced sterilization. In Nazi Germany it even led to mass murder.

After WWII, eugenics policies were gradually abandoned in most countries, and the word took a very negative connotation.

Then another way appeared, sometimes called "individual eugenics", to contrast with the "population eugenics" of the 1900's. This way is to let parents decide by themselves for their own children. According to this principle, no third party can tell parents what trait is desirable or not, and whether they should keep their baby or abort, for example. This principle could also be applied to the use a tool like CRISPR/Cas9, to modify the mutation responsible for a disorder in their embryo's DNA. Then the use of genetic techniques would only serve to prevent diseases in one specific child they wouldn't be the tool of a grand plan to improve the whole human species.

With these limitations, if science can prevent some terrible genetical disorder to appear in some people, then parents should be given the chance and the choice to help their children.

But this way can also be discussed. Are the parents the most informed people to make decisions about their children? When it comes to vaccinations, many states have made several of them mandatory, and parents aren't given a choice. They have to accept that the state will proceed to a medical measure to ensure the health of their children, even if they don't agree with it. And personally, I think that the state is right to make vaccinations mandatory, because we know that this method works fine, and prevents very dangerous diseases.

In that regard, if genome editing in embryos were to become 100% safe, shouldn't the state make it mandatory in order to help the children? It's a debatable question.

There is also the problem of how to determine which genes we can alter in an embryo. Where is the limit between modifying the DNA to prevent a disorder, and modifying it just to gain more desirable characteristics that are not strictly necessary? Should the latter be authorized, too, or would it lead to some excess? I think it will be the role of the state to determine which genes we can alter and which we can't.

Even though there is still room for many debates, and several regulations will have to be put in place, I believe that we can, and should, continue the research started by this chinese team. DNA editing on embryos could significantly improve the life of many people, and that should be reason enough to try to make it work.

Sophie Gontier
for the iGEM
ParisBettencourt team


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Feedback

1.Is this issue useful for your team?
A. Yes. It may help.
B. No. I cannot see any important reference value to my own team, because each situation differs.
C. Maybe a little.

2. How many passages are suitable for each issue?
A. Not more than 5.
B. 6-8
C. 9-12
D.13-15
E.15-20

3. How often should we publish Newsletter?
A. Weekly.
B. Biweekly. (The same as last year)
C. Triweekly.
D. Monthly.

4. Is is necessary to add new content besides project & update?
A. Yes. (Run to 5)
B. No (Run to 6)

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B. Experts' interviews.
C. Summary information for Biobricks.
D. Wiki technology.
E. Art & Design.
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