QNS: What is your latest research and how does it relate to gene editing?
One of my latest project is to use zinc finger nucleases to introduce a therapeutic gene into primary mammalian cell to treat a disease called haemophilia.

QNS: In your opinion, how promising is gene editing as a diagnostic or therapeutic tool?
For diagnostic purposes, it is less well-developed. But, there is a lot of interest and excitement about the potential for genome editing for therapy. But I think it is still very early and there are both scientific, technical and ethical issues to resolve.

QNS: What are some examples or some problems that you can see?
On the scientific technical side, I think there are many considerable obstacles currently that we need to overcome. One question would be of safety because the genome editing tools are not as specific as we like them to be. And the question of – how does one evaluate safety, is an unresolved question. In other words, what are the standards of safety we are willing to accept before we take this into the clinic. Currently, there is no consensus on that. There are also questions about what cells should be edited. And also depending on the disease you're trying to treat, the question is – can you produce enough to treat the disease? How do you prevent over-synthesis or excessively expression of the gene. For some disease like diabetes, it's essential to be able to control the gene that you introduce. You cannot be secreting insulin all the time that is a bad thing. There are many obstacles. Another obstacle that I am currently very much aware of is, primary cells is very difficult to transfect or transduce, unlike cell lines. So the question is, do we have efficient drug delivery mechanisms or methods that do not kill the cells or harm the cells in some way that make them unsuitable for treatment. That is another unresolved hurdle.

QNS: Based on all these hurdles, what are some of the risks?
I think the risks are different, if you are talking about gene editing of somatic cells, I think the risk mainly are whether the editing process has been accurate and precise. Whether it has only made the changes the investigator intended to make or whether there were other changes that were unintended. And whether these unintended changes have bad consequences for the cell and therefore for the patient or the animal in which it will be implanted.
if you're editing somatic cells, you are many concerned with the precision and accuracy you have made, whether those changes will have negative effect on the behaviour of the cells and what these cells might do when transplanted into an animal or eventually a patient. It would depend on, whether the changes you have made, quite apart from whether they are accurate or precise, another aspect of the changes is, whether the changes you've made is biologically appropriate for the disease you're trying to treat. I think when one talks about germline cells, that's quite a different proposition – here we are talking about altering something that would be inherited by subsequent generations and that's a big ethical minefield that generally the consensus globally is that we are not ready to do that yet. Because altering the genome of germ cells will have consequences that are very difficult to reverse because they are inherited.

QNS: With regards to germline cells, do you think the risk for RNA editing will be more mitigated? Because it's not a permanent change.
RNA is not in the germline, it's not inherited, that could be much more accepted in the sense that, even if someone did something unintended it would not be a permanent problem.

QNS: In your opinion, what is the outlook for gene therapy in our current field?
it's been interesting because gene therapy went through a very dark period when people had lost interest, the field had got a rather suspicious reputation. But, recently we have all been encouraged as gene therapy has emerged from that dark period. There have been a number of successes – most notably in haemophilia B, which is a bleeding disorder. So, viral gene therapy has been used on a small number of men with the very serious form of this disease, it's worked very well and it's worked for a long time – for 5 years or more. That's not the only example, there have been other examples that have really positive results, as far as we can tell, they have been safe. So, I think that [has] been a positive recent development, people I think are more interested in gene therapy, companies are rushing in to really take this further into the clinic.

QNS: What do you think are some of the gaps between lab researching to actually translating the research to clinical?
That's a big transition to make and frankly, that would almost necessitate a partnership with a commercial entity that has the financial resources and the motivation to do all the pre-clinical toxicology, testing before it goes into a clinic so there would not only be the pre-clinical test and also clinical-trials to show that it's efficacious and safe. Then, it would go into standard clinical treatment. Currently, I think the cost would be a consideration because the gene therapy products that have been approved are extremely costly.

QNS: As we are talking about DNA editing, one of the most prominent techniques we talk about is the CRISPR technology. So, what do you know about the CRISPR technology?
The CRISPR-Cas9 technology has really exploded in the research field, mainly because in a way it's democratized genome editing. Genome editing used to be rather specialized, difficult to do, rather expensive sometimes. But with CRISPR-Cas, everybody, in your kitchen almost, you can do a CRISPR-Cas experiment. It's really really made it possibly for many many more laboratories to get acquainted to use the technique for whatever purposes they have in mind.

QNS: Given that CRISPR-Cas9 technology has exploded, do you think there are any negative perspectives with regards to this explosion?
I think that all the genome editing tools, even and especially CRISPR-Cas, one must be especially sensitive and aware of the fact that the accuracy is often not good. So, it's not as advertised – you just make a particular modification and that's all you do, that's not true. I think depending on the conditions of the experiment, the type of cells you are using, there are many variance now for CRISPR-Cas, they can all have different levels of accuracy. I think the other consideration with a technology like CRISPR cas, because it becomes so easy to do, people

are literally doing it in their kitchens. I think the question of biosecurity needs to be considered. Whether people could be using this for applications that the world would not approve of like bioterrorism, because now you can do a lot of things outside of a conventional laboratory.

QNS: In terms of Singapore, what are some of the biosafety related topics that are more prominent?
in terms of working with embryonic cells and embryos that's prohibited or subjected to very close scrutiny. I don't think we yet have legislation on genome editing but that probably will come about soon really because CRISPR-Cas has become such a widespread technology.

QNS: As you know that a lot of the research has been done on CRISPR-Cas 9, which is DNA editing. Our group is doing CRISPR-Cas13 which is RNA editing. What is your take on RNA editing as a potential upcoming field?
I myself have not worked on RNA editing, it seems to be downstream of the genome. If it can be done efficiently and safely, again one needs to be concerned about the accuracy of the editing, that one is only making the intended changes. One consideration would be whether the effects are sufficiently durable. It really depends on what you want to do with RNA editing. For certain applications, you may not be looking at a durable effect. For different types of application, you may want to look at what is the half life of the RNA in question, and whether the editing changes the half life and for the application you have in mind, whether that RNA change persists long enough to achieve your purpose. As we said, I think that RNA editing because of the nature of RNA, I think should be safer because any adverse effects don't last forever anyway.

QNS: In terms of RNA editing, for the ethical issues wise it would be less complicated compared to DNA?
I would think so.

QNS: Because RNA editing is not permanent, there is a need for long term therapy – so what is your take on this?
I suppose RNA editing could be used for applications, I am a physician so I look at this whole field through the eyes of a physician, and eventually I'm looking at patients. So RNA editing could be used for disorders where the disorder does not last for a long time. For example, in very severe infections that are not treatable with antibiotics, that might be a field where RNA editing could be useful because infections don't last forever, they are not like genome diseases that last a lifetime for an individual. Inflammatory conditions, infectious conditions, which of their very nature last only for days to week might be a good area in which RNA editing could be helpful because the effects if over when the infection is over. You need not worry about leaving a footprint in the person or the cells you have modified. So that might be an area for RNA editing.

QNS: RNA editing is rather transient, what do you think are some possible techniques that can be used to overcome it? Or is there a need to overcome the transient property of the editing?

The challenge here since you're using the CRISPR-Cas13 is the RNA itself, because the principle of CRISPR-Cas will be the same, whether you're editing DNA or RNA, you will still need that guide, you will need to consider how to design the system for accuracy. There are many variants that I see now. That's all out in the field and being developed every week and every month. There'll people who come up with new variants, new nucleases that are better, more effective. But I think for RNA editing, as distinct from DNA editing, RNA itself is a rather delicate molecule – it's easily degraded, it doesn't last for [a] long time. So, I think one needs to probably pick a RNA that doesn't have such a short half life that you cannot edit it in a biologically meaningful way. I would see that as a major challenge if you want to produce RNA by in-vitro transcription and then edit it and then put it back into the cell. You need to have a RNA that is durable enough that you get to see a phenotype. If it's a RNA that is too short-lived, you may have achieved the editing but you'll never get a chance to see whether the phenotype of the cell can be changed. I see that as a technical challenge.

QNS: Before our meeting, we conducted an online survey about genetic engineering. We asked the question "what is enhancement" or specifically "what is genetic enhancement"? We'll like to ask you the same question as well.

Enhancement, taken without all the emotional baggage that goes with that word, would mean to increase a favourable characteristic or possibly to confer a positive or desirable characteristic that wasn't there to begin with. That would be my definition of enhancement.

QNS: There are some myth and misconceptions that we identified from our survey and I'll like to ask you to debunk these for the public. The first one is "gene therapy is an experimental technique that introduces genetic material into cells to enhance the physical characteristic of the individual.
That is completely untrue, gene therapy today is used only to treat medical disorders. None of the gene therapy that has been approved or are being researched have as their purpose enhancement of any kind of biological characteristic. So, it's completely wrong to say that it's for enhancement.

QNS: Myth 2: gene functions are modular and changes are predictable.
The idea of modularity is that the gene functions kind of in a vacuum as single entities but that is completely false. In the cell, genes never function in isolation. They are always part of a network of many other genes. It's the proteins really, genes don't function as genes, they function as proteins, as regulatory RNA. So, you're quite right, a single gene can never be absolutely predictable. A gene can have a different behaviour in different cells. So, the context matters a great deal.

QNS: Current genome editing techniques are able to make changes to all genetic information in the cell.
That's not true. Even for genome sequencing, we haven't sequenced every part of the genome. There are parts of the genome that are very difficult to sequence. To be perfectly honest, we

don’t know how many real genes there are. We have an approximate number of protein coding genes. But we know that there are transcription units that make RNA that actually function as RNA. They don’t make protein, nature didn’t intend these RNA to function as proteins. We have no idea, the RNA world is still opening up. If we include the RNA genes, that will be a whole lot of genes. I don’t think it’ll be ever possible for us to change every single gene.

QNS: DNA bases in the gene cannot be changed or altered in our body.
Well, yes they can be. With somatic genome editing, at least some cells will have had their genome changed and theoretically if germline editing were ever performed, that would change the base composition or base sequence.

Before we finish this section, I want to go back to the question of enhancement. Because it’s a very common misconception that with genetic technologies, in the popular media, you hear this concept of “designer babies”. Parents can decide how tall the child will be, what color hair, whether the child will be a talented musician or a world winning athlete. I think it’s such a great misconception that we can enhance human characteristics. I will give you an example of intelligence. Many parents will wish to have super intelligent children. In fact, the contribution of the genome to intelligence involved a huge number of genes, hundreds of genes. The aggregate contribution of these hundreds of genes to intelligence is in fact very small. So, I don’t think it will ever be possible really. Even if we wanted to enhance. Each of these characteristics that make each human being unique is the result of the interaction of literally hundreds of genes and we don’t even know which genes they are. So, I think the public needs to understand that genetic enhancement will ever be possible, even if it were desirable.

QNS: Now that we are talking to the public, how will you explain DNA editing to the public?
People usually use the example of a pair of scissors. If you’ve seen diagrams of genome editing, that’s something the public can understand. You have one pair of two pairs of scissors cutting a thread and then putting something in between the gap. I think that’s a simple way of explaining genome editing without going into the technicalities because each of the genome editing tools works in a slightly different fashion and to go into the technicalities is not useful for a lay person. Just to use the example that it’s a kind of genetic surgery, if you like, some people use that term, genetic molecular scissors is a metaphor you can use. Of course, genome editing is not only about inserting something. Sometimes it’s about deleting something that deleterious, sometimes it’s just about making a simple base change. There’re many aspects to editing, it’s not just cutting, sometimes it’s just changing a typo. Something has been spelt the wrong way and genome editing is a way of correcting the single word and getting the spelling right. These are ways to try to explain the concept to the public.

QNS: Now we want to pose a challenge abit, and explain RNA editing to the public.
RNA could be like the letter that somebody writes and the letter has mistakes. The RNA editing will be using a method of correcting those mistakes I guess. The idea will be to try and get a lay

person to understand that RNA is downstream to DNA and that it's a temporary molecule unlike DNA that is a permanent molecule.

QNS: Last question for more technical stuff, if you were to explain the relevance of your research to the public, to genetic editing, how will you share your research expertise?
in one of the diseases I'm working on, I think it's very easy to get a non-specialise to understand. Haemophilia A is a disease that affects about 1 in 5000 male babies it's a bleeding disorder, a genetic disorder that causes a lot of disability. Because these boys bleed very easily and the bleeding disorder can either lead to death at a fairly young age. Or they receive some kind of treatment it leads to a lot of disability as these boys and man actually bleed into their joints and muscle. They become very disabled because their joints become stiff, they often become wheelchair bound. The tragedy about haemophilia, which is the disease I'm working on, although we understand the biochemistry, the genetics, the molecular biology of this disease extremely extremely well, the treatment of haemophilia A is extremely expensive. Currently, it's being treated by the administration of a recombinant protein which is very expensive. Which means that, if you look at the entire world population of people with haemophilia. Most of them, especially those that are not in the wealthy countries, either have no treatment or very little treatment. So, what we are trying to do, and others are trying to do with gene therapy and cell therapy is to devise a different way of treating haemophilia that will be accessible to all patients with haemophilia. In the case of this disease, in the case of a good social justification because so many people with haemophilia, especially in the low resource countries, get very little treatment, some of them even get no treatment at all. I think for diseases like that, where there is treatment but the treatment is beyond the affordability of most families. I think this is where new forms of treatment that is based on the genome or the gene are well justified.

QNS: Talking about affordability, what do you think about accessibility of gene therapy?
That's a very interesting question because currently as we've said before, although gene therapy and cell therapy that's based on research done in academic institutions and laboratories, in order to transition that into the clinics, always requires the financial investment of commercial entities. Commercial entities are not charities. Therefore, the initial products are always priced extremely high. My personal view is that, we should not regard this as a discouragement to continue along this line. As with all new technologies, the price of the products tends to decrease with time, as we get more efficient, as other people get into the game and produce products as well. I envision that gene therapy and cell therapy will in the future will be less expensive and more affordable. The high prices today, even though they shock us, should not dissuade us from continuing this line of treatment.

QNS: Is there a possibility that genome editing will be abused?
Definitely, I think in jurisdictions in countries where there are no good regulations and regulatory oversight, especially with methods like the CRISPR-Cas method, there's literally nothing to stop people from doing experiments which the rest of us will disapprove of. They could be done, so I I think it's necessary for the global community, for each country to have it's own good regulatory framework.

QNS: To understand more about regulatory framework, what are some of the current laws or legislation that cover genome editing in Singapore?
As I said, anything that has to do with work on embryos beyond 14 days is prohibited. We don't want people to be tampering with genome of embryos and taking them beyond 14 days to a place where the effects are bad and undesirable. With respect to genome editing per say, we will not be allowed to work with germline cells in Singapore. With respect to somatic gene editing, somatic gene editing does not present new ethical problems that are different from other new therapies. It is simply another new therapy and it needs to be examined for safety, for efficacy like any other new drugs.

QNS: So what do you think are some of the ethical issues that the public might surface with this type of new technology?
Well, I think again it's the question of the safety aspects, the consideration of fairness. If for example, a particular gene or genome editing method is shown to be efficacious and safe for a particular condition. The question then could become, does everybody who need it have access to it? The fairness of access would be something that we need to consider as a society. We will certainly not want to have good treatments that only the wealthy can access. Of course, the public is always concerned about genetic enhancement, which is completely a mistake. But, that will not be something that is of a real concern.

QNS: With regards to ethical frameworks, in Asia Pacific, do the surrounding countries have similar frameworks?
Different countries are in different stages of developing their own regulatory frameworks. I think Singapore is perhaps a little bit ahead of the region. But even a country like China is beginning to tighten up what its researchers are allowed to do. Countries like Indonesia need to be looking more closely, I think Malaysia is probably not very different from Singapore.

QNS: As we have more research with DNA and RNA, what do you think are some of the ethical issues you may foresee in the near future?
In the near future, I think the ethical considerations in the near future will be whether commercial entities will be offering treatments that have not been properly tested. That's a real danger. Now that people can go on the internet, advertise what they claim hey can do. One needs to aware of private efforts to market therapies or tests which have not be well studied or vigorously validated.

QNS: How do you think bioethics acts as a checking mechanism for genetic advancements?
I think the Bioethics Advisory Committee (BAC), the Ministry of Health (MOH) can only have oversight over public and private institutions that want to be doing the right thing. It really cannot know what is being done privately. There is no compulsion that you need to tell MOH what you are doing because of the democratisation of some of these genome editing tools. In theory, people could be doing it privately without notifying the public authorities. Obviously, we will not

want that to happen. In theory, that could be happening and we will not know. The public institutions and the major private institutions will not want their reputations to be undermined and to be seen to be doing something that is ethically wrong or unapproved.

QNS: Talking about the BAC, what are some of the most prominent bioethics questions that have to be address or a popular talking topic in Singapore?
Currently, we are finalizing our guidelines on mitochondria genome replacement. So, that's another area that's been abit contentious because mitochondria diseases are basically untreatable. Some of them are extremely severe and these children don't survive for very long. So, it's now possible to treat these diseases or to prevent them really by replacing the mitochondrial genome of a woman carrying mutations so that her future children will be at much lower risk of having the mitochondrial disorder. This is an area that the BAC is in the process of finalizing the guidelines. It's been around the contentious area not only in Singapore but throughout the world. We also have guidelines on neuroscience research because that's an area that does raise fears of control of people through manipulating brain functions.

QNS: You were mentioning that you actually engage in global discussion, compared to countries with similar scientific progress how mature do you think our bioethical frameworks are?
I think we are pretty much on par with the Western countries, mainly Europe and North America. Singapore has a smaller population. We will justifiably want to wait and see how these new technologies will play out in countries that have made the decision to move forward. For example, for mitochondrial genome replacement, we are going to wait and see how the UK experience is, before Singapore decides whether it's a technology we want to develop for our own families in Singapore. And I think that's just a question of being cautious in a good way because some of these new technologies have long-term effects that currently no one can claim to know. I think it would be better to allow a country that has more resources, a larger population of these families to test it out. And for us to be monitoring them really closely.

QNS: The way the bioethics frameworks are shaped, is there a large correlation with the population make up or background of people in the country? Let's say in Western countries, will people be more open-minded compared to Singapore?
I think yes, in public consultations, I think the lay public in Singapore tends to be less well-informed about Science. I think they get their information largely from the media, from online sources that are not always accurate, they don't always present a balanced view but that seems to be the main source of information if at all, or not it will be word-of-mouth by families or friends. The level of scientific literacy among the lay public in Singapore is not as high as elsewhere.

QNS: Given the standards that Singaporeans have for scientific literacy, do you think it's important for public engagement to navigate the ethics for genome editing techniques?
It's always necessary to find out what the community knows, community concerns and what they want to happen in the society. What the community values are. I think it's always right to

consult the public. It's also an opportunity for the public to learn more. It's a two-way process, where the BAC learns about what the community's perspectives are and also the community to learn from so-called experts and specialist on what technologies do or don't do. I think that in every country we need to be sensitive about what the society at large is willing to do. I don't think specialists should force on the community something that they're not ready to do, regardless of scientific aspect. I think public consultations are extremely important and they should always happen.

QNS: In our survey, we asked if public engagement is necessary. Some people think that it's unnecessary for BAC to engage the public because the general public may not be able to understand such issues and it might be better to leave it to the professionals in case the public might be chaotic. So, what are your views on this?

I think that's a very condescending attitude, a very elitist attitude that I completely disagree with. I think while the lay public might not be very well-informed in Singapore, they are not stupid. They are able to understand concepts if they are presented in simple, not over-simplified, and clear ways. Once they understand the intentions of scientists, the lay public is able to then think about the implications of [these technologies] on a society-wide basis. I will completely disagree that decisions should be entirely left to the specialist. That would never be a good thing.

QNS: In Singapore, what type of outreach events have actually been done for ethical issues?

Speaking for the BAC, we do various things to try and help the public know a bit more about Science. So depending upon the topic we are working at the moment, we might have movies, exhibitions in the Science Centre. We will often bring in world experts from overseas to not only offer their expert opinion but invite the public to meet the expert. It's like a science café, where members of the public can meet the world leading expert on the technology and ask the expert all the questions they have on their minds. The BAC has made a regular practice, before we finalize our guidelines on any topic, we always invite the public to first of all submit by email or by written submission, their views on it. We invite them for a face-to-face discussion and we take note [of their concerns and views]. We take minutes of these discussions and the submissions made to us in other ways, so the public views are in record. We don't just listen to them and forget about them. We record what the public has said to us so we know at this point, these were their concerns, there were their aspirations, there were their questions. And I think we take that all together, with a specialist perspective and come up with the guidelines.

QNS: How receptive is the general public to this type of discussion?

It varies, for example in the mitochondrial genome consultation, we had about maybe 30 to 40 people [who] come. Some of them were adults and many of them were young adults who seem to be themselves either Science graduates or working in [the] Science [fields] themselves, probably in a research lab. One of them recently graduated from one of our universities. They understood all the genome technology. It varies with the subject. I also should mention that for every one of these topics the bioethics committee considers, we will also invite others. We invite representatives of the religions in Singapore. Not only the main religions, we invite religions with

a smaller number of adherences. So recently in the mitochondrial genome replacement, we invited representatives of the Muslim community, the Christian community, the Buddhist community , the Hindu community, the Sikhs, the Jews, the Parsis to tell us because each religion look at the technology in slightly different ways. We need to know what all of their perspectives are. Are there certain areas that they say “No, definitely we will never do this”? Or maybe there are some areas where well perhaps we can do this provided there are some precautions. We also make a point to consult the religions because it’s not the lay public view but also the views of people who have some kind of religious affiliation.