Writing our Genome

Speakers:

Jef Boeke, Director, Institute for Systems Genetics and Biochemistry and Molecular Pharmacology Professor at NYU Langone Medical Center

Nancy J Kelley, President and CEO, Nancy J Kelley + Associates and Founding Executive Director, New York Genome Center

Dr. Robert Klitzman, Director, Masters of Bioethics Program, Mailman School of Public Health, Columbia University

Moderator:

David Ewing Duncan, Cofounder, Curator, and CEO, Arc Fusion

(Transcription by RA Fisher Ink)

Nancy Kelley: Good morning, everybody. So this morning I want to tell you about a meeting we had last week, when 220 participants from ten countries came to the New York Genome Center to explore a grand challenge in engineering biology and the name of the project is GP-write. Just as the Human Genome Project aimed to read DNA in order to understand the genome, GP-write aims to write DNA in order to understand the biological basis of life. So the project will focus on using synthesis in genome editing technologies, basically to understand, engineer, and test living systems of model organisms in cell lines, plants, and yes, even the human genome.

So the goal of GP-write is not only to deepen our understanding of life, but also to develop pragmatic technologies of general use in biology to improve the cost and delivery of DNA synthesis, the delivery of assembly in cells, and the testing of many different DNA variations in tissue characteristics. So the participants in this meeting were not only academic scientists but also ethicists, lawyers, educators, citizen scientists, artists, policymakers, technology geeks, companies, and laypersons, all of whom were intensely engaged and interested in this project. And so for two days, we explored the concept of this project and what direction it could take to solve some of the most important problems that we face in the world today, how to understand biological systems in order to improve life, how we move from a carbon-based economy into a biologically based economy that is sustainable, how to advance the cures for human disease, and just as importantly, how do we communicate responsibly these advances to the world.

So when my work establishing the New York Genome Center was over, the Sloan Foundation invited me to explore the field of engineering biology and I didn't know anything about this science at that time. But over the last four years, I've come to understand the power of these technologies being created in this field and what they offer, the promise they hold for the world in so many fields. And the way that I like to describe it in shorthand is how do we feed, fuel, and heal the world? That's the promise of these technologies. For example, GP-write could allow

scientists to create new cell lines that are resistant to infection, radiation, and even cancer. The results might lead to new drugs, advanced stem cell therapies, novel gene therapies, new biofuels, and even clean, fresh water.

There are also social, legal, and ethical implications of these new technologies that we as a society are going to need to wrestle with and this project will help to stimulate that conversation, and hopefully generate a consensus around some of the more important issues. Jef?

Jef Boeke: Well, thank you Nancy for leaving me exactly 38 seconds to tell you all about GP-write.

[LAUGHTER]

So this is a project that really supports technology development in the writing of DNA, and that can be broken down into genome design, synthesis, and then evaluating the biological impact. The reason I got involved in this is because we're pretty far along in synthesizing the genome of yeast, and with some colleagues, we're aiming much higher now. So we aim with our colleagues to reduce the cost of designing, synthesizing, assembling, and testing genomes, as Nancy said, by over a thousand-fold over the next ten years. And I firmly believe that this is really going to revolutionize how we learn about the biological world. As a basic scientist, this is what drives me and excites me about the project.

So we've come up with a roadmap for what we call GP-write versus GP-read—the original human genome project we now refer to as GP-read, and it's GP versus HGP, Human Genome Project. GP-write is meant to encompass all the genomes. It's not a speciesist approach, if you will. It's very much, as I said, focused on the technology. I'll emphasize the fact that the HGP component of GP-write—so there's a subset that is focused on engineering human genomes, because that's the genome we all care about. And very importantly, we've decided we're only going to do this in cells. We have no interest in producing people with synthetic genomes. We want to do somatic treatments. We want to develop therapies and we want to learn things.

And so everyone asks why, and I hope in the discussion we can talk about why. There's the basic science of how does it all work and, "If I can't build it, I can't understand it." And I'm going to skip over a lot of complicated science that—we've already learned some tremendous things about the three-dimensional of the genome in the yeast and I think we're going to learn much more about the roles of the genome if we move to larger organisms and their genomes.

And then I like to take the Biblical approach to this, because of the plagues, okay? So these are the famous plagues and these are today's plagues, and they almost all have an intense biological component which we think could be tackled on variations of GP-write.

So with that, I'll just mention that one of our science projects we're really excited about is what we call the Dark Matter Project to really dissect all of those thousands of switches that control when and where our genes turn off the control, what each cell turns into, and so on. If you don't know, you can just put it on Amazon, you'll get, "Junk DNA: A Journey Through the Dark Matter

of the Genome." So it's right there on the Internet for you. So with that, maybe we'll start a bigger discussion.

David Duncan: Thank you, guys.

I'm David Ewing Duncan, and I'm very pleased to be moderating this panel. I love it, as a journalist, I often have stories, I hear about things way in advance of other people and they're brand new technologies. It's almost sci-if, it seems and I take them to my editors and they go, "We don't get this," and they have no interest in doing a story. And then suddenly, everybody wants to do a story. So we're not quite there yet with this but I think we're getting pretty close. You all are feeling that happening here.

So we just heard about the meeting last week, and I guess it attracted—it was several hundred people, right?

Kelley: More than 220 people.

Duncan: Yes, so a lot of people, from all over the world. So we just heard a little bit about it, and I wanted to just quickly, because I want Bob to respond—he's our physician ethicist. He's one of these guys who has multiple titles, amazing. I don't know how you guys do all that, but anyway. For those of us who are not scientists, maybe you could give a quick explanation of what exactly you're doing, you know, maybe to a sixth grader or something like that.

[LAUGHTER]

You know, how does this actually work?

Robert Klitzman: Okay, well I think the analogy of reading and writing is relatively straightforward. It's a pretty boring language they're writing. It only has four letters: G, A, T, and C. And it's really the order of those letters and the way they're strung together that forms the genes and the chromosomes that are the blueprint of our organism and all organisms on the planet. And an interesting point about reading versus writing DNA has an analogy in reading and writing a book. When you read a book, it's kind of a straightforward passive exercise. You read it and then you know when you're finished. Writing a book, however, has a very different feel to it. It is fundamentally a creative exercise. You have to decide what to write. There are an infinite number of books one could write, and similarly, there are an infinite number of genomes one could write. And so it really all boils down to something I heard Esther Dyson say earlier today, which is it's not the technology, it's what do you want to do with it. How are you going to use it? And that's the hard part is finding that sweet spot between what's doable and what's worthy of doing, what would make a difference in our world.

Duncan: Just really quickly, how close are we to this?

Klitzman: To what?

Duncan: To having what you guys want to achieve, your vision.

Klitzman: The yeast is a microorganism, but it's a higher organism so it's more closely related to us, and we're very far along on that. I'd say we're about 80% complete. We recently published on—a total of six and a half of the 16 chromosomes are completely signed, sealed, and delivered, analyzed and so on, and the other nine and a half are well on their way, with an international team all over the world.

So there's no question that this can be done. The question now is what other projects are really worthy of doing as we advance this to a larger scale. And in the meantime, we need to reduce the cost dramatically because the costs are just way too high to contemplate right now for something like the human genome. It costs about ten cents a base and it's three billion bases or DNA letters. So that's far too expensive, obviously, so we want to reduce that cost by a factor of a thousand so that we can contemplate this kind of work on the much larger scale.

Duncan: And I think you said we're about five years out—and I know you have something that you want to say, Nancy. But if you could do it right now, and the costs and all these other factors, you've said it's about five years out, or it could be. So what I'm trying to get at here is this could happen fairly quickly, potentially.

Kelley: I think what Jeff is talking about is work in the human genome would be five years out, although there'd be implications on a smaller level earlier while the ethical implications of that project would be being discussed. But we're ready to start in pilot projects now. For example, Harris Wang at Columbia just received a $500,000 dollar grant to study a phototropic human cell line. And so the work is beginning now and we will be seeking additional funding for that.

But what I wanted to say is another analogy that may be more familiar to people is in the digital world, right? So just as the computer code software that we work with consists of infinite permutations of zeroes and ones that are used to drive everything all over the world, and started with enormous computers that were very expensive and now come down to mobile units that are relatively very low cost, it's the same four building blocks that Jeff is talking about, four letters that scientists are using on the computer to design new segments of DNA and to try to understand how they are going to operate in cell lines. So we're at a very similar place right now and I think you're going to see the trajectory of progress be just as intense.

Duncan: Yeah. And I was just trying to set you up, Bob, so we could figure out where we were. And I would love to have you respond any way you like with your various hats, I mean, as a physician, somebody that works that patients, as an ethicist. How do you respond to this project?

Klitzman: I think this is a great project and I think what you've heard here and in the previous panel is that we're in a very exciting period of time in terms of understanding the human genome. Really it was less than 20 years ago that we first did a draft sequence of the human genome and we've learned a lot. There are a lot of benefits, but there are also a lot of risks, and I think like any new novel technology—think understanding the human atom—we can produce cheap nuclear energy or we can produce atomic bombs. And so I think in answer partly to what

David was saying earlier, technology is revolutionizing healthcare. It has been for hundreds of years. It's going at a quicker pace and we need to be careful. And I would say also, we need to think about, getting back to what David was saying earlier, why we in the US pay so much for healthcare and have the worst healthcare among industrialized countries. And a key thing is following the money in a lot of issues, and this included, I'd say.

And I also just want to comment briefly on some of the issues that were relayed in the previous panel. It's estimated that precision medicine will probably help with diagnoses for about 3-5% of people. So 95% of you here will not have useful, actionable diagnoses through precision medicine, at least in your lifetimes most likely. We've done research, giving back, doing whole genome sequencing, finding out how many people have actionable results. It's a small number, it's a great number. The cases we heard earlier of the kid with cancer, that's great, but for diagnoses it's limited, just to put that in context.

The other issue I just wanted to comment on from the previous panel very briefly is genetic discrimination is real. A reason that I'm maybe willing to share my Gmail account, or realize that it may be hacked, but maybe more resistant about my own genome is because the Genetic Information Non-Discrimination Act, which was passed by Congress about ten years ago, covers health insurance. It does not cover life insurance, disability insurance, long-term care insurance. So within a few years, if you apply for disability insurance, life insurance, the insurer will say, "We'd like to have your whole genomic testing done," or "Have you ever had genetic testing done? Have you ever had it done"—through 23andMe or somewhere else—"We'd like to see the results, thank you very much. We see that you have a gene that gives you an increased rate of cancer X, we're going to deny you coverage, or we'll charge you triple the amount."

There's subtle discrimination at the workplace. So people say, "Everyone thought I'd be promoted to be the boss when the boss retired. I mentioned to someone, 'You know, I tested for this breast cancer gene—I'm fine.'" Next thing, when the boss retired, the people are not promoted. They are not fired either. So I just want to present a context that there are things that we need to worry about, about genetic information getting out there.

Hype is an important element of science. It has led to a lot of funding, billions of dollars for genomic research, which is great. I fully support government investment in science. However, we need to be careful about what is realistic as payoff and when. So for instance, human embryonic stem cell research has so far not produced a single approved treatment, despite billions of dollars of investment. We heard about we're going to take skin cells and create induced pluripotent stem cells that could be used for all kinds of things. We've done clinical trials. They have high rates of cancer, for instance.

So I think that the payoff is trying to get good treatment, but we need to be careful about, you know, what's a realistic timeline. Is it two years, is it a hundred years? You know, I often think an analogy is if someone asked Christopher Columbus in 1500, "What did you discover?" he'd say, "I discovered a few islands off the coast of India." And it took several hundred years, 300 years later, Lewis and Clark are still traipsing around trying to figure out what's in the middle of the

country. And I think similarly with genome and genomic research, we're learning how much we don't know.

A friend of mine wrote an article about 20 years ago called, "Why Was the Gene for Alcoholism Discovered Seven Times?" And it turns out, seven times the "New York Times" had headlines, "The Gene for Alcoholism Discovered." And of course, each time, several years later it wasn't replicated, etcetera. And that was 20 years ago that article was written. So I think it's very important to do basic research but we need to be careful.

Another issue, for instance, is we now are using gene editing technologies. They're being used around the world in various countries on human embryos and we're already being able to do genetic testing to choose which embryos we want. Many people are saying, "I don't want my embryo to have the breast cancer gene" and we're not using embryos with the breast cancer gene. There are clinics in the U.S. that say, "We give people male babies." Couples come in, often from south Asia, they say, "I don't want female embryos," we just give them male embryos. The Chinese came to the foreground a few years ago with CRISPR technology, gene editing. When they started to use this on human embryos, the word was that they were trying to find genes for intelligence to put into the embryos. There was then a moratorium that was agreed upon by several countries. But this technology, because we believe it should be in the public sector, spreads. So just as ransomware was developed in the U.S. and is now being used by North Korea or wherever, so too these technologies can spread—

Duncan: Bob, I'm going to jump in.

Klitzman: We just need to be careful, I would say. So I think these are great potentials for great advances. They're important, they're going to help many people, but we do need to be aware of some of the limitations, some of the risks I think, just going forward, just to put that in response.

Duncan: We're a little farther along on a couple things, like actually induced pluripotent stem cell technology is in humans.

Klitzman: But there's no approved treatment. There's no approved treatment using IPS.

Duncan: Well, of course, but it's got to go through clinical trials first.

Klitzman: But they've all failed so far. So there's been IPS sales using the I, for instance, they lead to high rates of cancer. So again, great that we're doing all this. It's the timeframe we need to be careful about.

Duncan: Right. The point is that these technologies take a long time.

Klitzman: And there've been a lot of failures. There's been a lot of hype and hope that's not—

Duncan: Part of what you're talking about is how we integrate this into society.

Klitzman: Yes, absolutely.

Duncan: And GINA, for instance, it actually does—workers are covered, although there is a bill in Congress to take that away, just so you all know that, in your workplace. But let's talk about that for a second. Well, let's talk about, Jef, something that you mentioned about the why. Because that gets us into—and unfortunately, you can see this is a huge topic. I mean, this is really an important topic. And all the topics here are.

Boeke: We just spent two days talking about this last week.

Duncan: Yeah. This is a species, which is us, which is about to be able to essentially write its own evolution and this is extraordinarily complicated and there are hopes and fears and plusses and minuses. But let's talk about the why for a second. Obviously, there are movies about this, there are a lot of fears about it, which we'll get to in a second. But why would you want to do this?

Boeke: So we have spent a lot of time talking about this, and like you, we recognize that all new technologies can be used for good or they can be used in bad ways. And so what we've tried to do in structuring at least the outline of a roadmap for the project is to focus on technology development so that we can become better at writing DNA and assessing the consequences of what we write. And during the first five years of the project, as that technology development accelerates—we're not starting out today writing GATC, you know, those three billion letters, because we don't know what to write yet. We don't have a good enough hype-able killer app at the moment for a full genome. But we have what we think are some pretty darn good ideas for pilot projects that might be something along the lines of 1% of the human genome, which turns out to be about three times the size of the yeast genome, just to put it in perspective.

And so one of my favorites is what we call the ultra-safe cell line that's meant to address some of the issues that you talked about, but maybe not right away in embryonic stem cells. We start with something a little bit more prosaic, but nevertheless very important, which is the biotechnology industry, which produces a lot of medicines in cells called Chinese hamster ovary cells, CHO cells. That's where a lot of biologics are made, and certain orphan drug production facilities have been brought to their knees by virus infections. And it's in principle possible to write the bits of our code that encode proteins in such a way that we literally change what's called the genetic code, which specifies sets of three DNA letters that specify one amino acid in a protein in such a way that we delete some of the codons, as they're called, from the genome altogether. Then we can engineer the machinery of the cell so that it no longer recognizes those codons, and all viruses would be dependent on that machinery and thus, it should be possible to engineer a cell that cannot be infected by a virus and therefore solve this practical problem of the biotech industry.

Duncan: It's kind of a super cell that you could be impervious to lots of different—

Boeke: Yes. And this is just one step. Another very important step would be anything we could do at the genome engineering level to reduce the probability of cancer development. Formation

of somatic mutations in p53, for example, there are very good reasons to think that you could make designer changes that would reduce the incidence of these events.

Kelley: Another practical application is using pigs to grow transplantable organs. So out of George Church's lab, who's another co-leader of the project, comes a company called eGenesis, where they are using gene editing technologies to actually offset some of the adverse consequences of transplantation. And George actually thinks that could be in clinical trials within 12 months.

Duncan: These are essentially growing human-like organs that could be compatible with the people you're donating them to.

Kelley: That's right.

Duncan: Yes. So Nancy, does this worry you at all? I mean, there is a little genie-out of-the-bottle situation here, and I think it was said earlier, and I would say this as a technology writer, these things will happen. If we don't do it, the Chinese will do it, somebody will do it. And it's arguable who should do it, I suppose. But does this worry you, unintended consequences, that sort of thing?

Kelley: So when I first started, as I mentioned, I didn't know about this science or technology at all. So when the Sloan Foundation asked me to take a look at it, I had to wrestle it to the ground first before I could actually begin to communicate about it. And yes, it did worry me a lot. And even two years ago, when Andrew Hessel came and asked me to talk to Jef about doing this project, we both had reservations. Because it does open up so many questions. The truth is, as a society, we're going to have to wrestle with those questions. They are coming and we are going to have to wrestle with the answers. And there aren't any easy answers.

The other thing, as I said to Jef, and I think this is ultimately what convinced us both, is that this technology was developed first in the United States. U.S. scientists have been leaders in this area, and now there are countries like China and the UK and Scotland, all of whom who have roadmaps in this area and are going to be actively pursuing scientific and technology development. This project needs to happen in the U.S., where there are ethical guidelines to oversee a project like this and where there's public disclosure and a commitment to that by the project. And ultimately, I think that notion of, "Somebody's going to do it, it needs to be here" was a big impetus behind the project.

Duncan: You know, it is interesting that—I mean, people are comparing it to splitting the atom, and I think Bob even mentioned that we've had arguably some positive uses possibly of nuclear power, splitting the atom and you have the weapons side. We haven't actually done ourselves in yet. Hopefully never. But this technology is so much cheaper and simpler, at least some of the basic technologies. Even CRISPR-Cas9, I was interacting this morning on email with a high school student at George Church's lab who won the Intel award last year. So this is a very simple and cheap technology, which is why it can be done almost anywhere.

Klitzman: It turns out when you multiply by three billion, it's not so cheap anymore.

Duncan: That's true. Although even one little fix, you can change one letter and cause—anyway, real quick, Bob, and then I want to go to questions because I want to include you all here.

Klitzman: I mean, every day I get emails for do-it-yourself CRISPR kits for a few hundred dollars. I just want to emphasize something you said, which was biosecurity. So a major concern is also making a super Ebola, making a super Zika bacteria. It's the same technology that's used in gene editing, for instance. And so again, I think we need to be aware that it's two sides. I think the fact that this project included ethicists from the beginning is terrific, and I think is a model. But again, this is diffuse stuff and just we need to be aware of that.

Duncan: Well, you can also design antiviruses.

Klitzman: But it's a war. We have resistant bacteria all the time.

Duncan: Yeah. Anyway, we need to move—

Boeke: Can I just have one other thing, and that is I also think it's really, really important that we engage the international community in this effort from the get-go in a big way. Because this has been one of the things that I've been very involved with the yeast project is building a community of like-minded individuals. We have our own ethicist for the yeast project. It's baked in. And if we don't—

[LAUGHTER]

But I think this is actually going to be really critical that we not make it too much that the U.S.A. has to lead.

Kelley: Well, that was what started our conversation, but I think you're absolutely right, Jef, that's not where it ends. And the truth is there were ten countries represented last week, and many of those countries sent governmental representatives to talk about helping to fund the project and to create a very collaborative way of governance and of working together with the scientific teams. So we are really committed to that.

Duncan: And I want to applaud you all on that, actually. As a historian, I've written about the process, which is earlier technology that scared people, and I guess that's a bit of a model. Although that was pretty much only scientists, and I think you all have done a really good job of that. So we have a few minutes here. Any questions? Anybody really excited about this technology or not?

Audience: So last year at TED was the first time I heard about CRISPR. There was a woman on stage that gave a really spectacular talk about this technology and one of the things she talked about is the idea of eliminating all mosquitos that could carry the Zika virus. She said, "Sounds great, right? We get rid of mosquitos, no more Zika virus." She said, "But what about

the birds that are dependent on that particular mosquito?" and she talked about pulling the thread out of the sweater. Those of you may remember the movie "I Am Legend" with Will Smith, where somebody invents the cure for cancer and then two weeks later everyone in New York City is turned into a zombie. It was a very good movie, other than the zombie part.

[LAUGHTER]

But I guess my question is when we're hearing about what's happening now in North Korea, countries that may not be participating in the idea of treating this new technology ethically, hearing about high school students with a kit that can start changing genes, it's pretty terrifying. I guess my question is when the genie is out of the bottle—it sounds like what we're hearing here is bordering on the miraculous, right, to cure all these diseases and to go into our genes and make us into better humans. But what can be done about the other side of this? I know you're having ethical discussions about this. I'm just curious, now that the genie is out of the bottle, and the high school students are playing with this, what next?

Duncan: Can we adapt that just slightly to who do you trust with this?

Klitzman: I think one area is medical journals. So an interesting area, for instance, is should medical journals be publishing genomes of infectious agents? So if we reconstructed the 1918 flu epidemic virus, should they publish that, should they not? And I think that there are institutions that need to be involved, and I think the more international it is—and I think that it speaks to the need for more international cooperation generally in the world today—a little political plug. But I think that there are possibilities and I think just having scientists be very aware of this. I think this project is great, but there's a lot of projects that may or may not pay as much attention to some of these issues.

Kelley: On that score, I would just point to two examples of precautions that are being taken now. One is in the iGEM competition, which is an international competition where students all over the world use these technologies to create new approaches to problems and they come together to demonstrate what they want to do. There's international cooperation amongst all of the teams and precautions that Department of Homeland Security and the FBI is working with these students to make sure that nothing's going on, you know, no releases or anything like that.

Also, on the citizen science side, the FBI has actually convened meetings of citizen laboratories because they want to be close to that community and understand how kids and entrepreneurs in their garages are using these technologies and where there may be danger points. And I think that's the only way you can approach it. You can't put it back in the bottle.

Boeke: Yes, and the FBI has a big program to outreach to student groups and especially the iGEM community and the DIY bio, as it's called, the do-it-yourself bio community. I think the approach is we're here for you, we recognize that there's tremendous potential here, but we want you to come to us if you hear about anybody who's misusing this. That is the FBI's

approach on this. And it was very exciting for me when I got my first call from him and he introduced himself as the weapons of mass destruction directorate.

[LAUGHTER]

Duncan: I've met that guy. They show up everywhere, I don't know.

Kelley: The other important point here is safety engineering, which is going to be a very important part of our project. And that means building mechanisms within the cell that would kill it, for example, under certain circumstances, or prevent it from being released into the general environment.

Duncan: Yeah. It's interesting, because it's a little bit of a line of defense that you're putting up against some of the worst things that can happen.

Audience: Hello, this is Yannis from Deutsch Telekom. To me, it's in between Pandora's box, and the holy grail. And I'm not decided yet which side we are more on in this very moment. And with a great respect for the FBI, but this is only the U.S.

[LAUGHTER]

Do you see any international body to set up some ethical rules that might belong even in China or—I'm very happy to hear about this memorandum that you mentioned. But I'm very skeptical to the fact that we will not be able to set up some international ethics. And this is not only about CRISPR or personalized medicine. This is also about cybersecurity and the questions that arise in this respect. Do you see any institution that might be powerful enough?

Klitzman: There's hope. It needs a lot more work, but I'm optimistic that most of the world's countries can come together. North Korea, who knows? And that's part of the danger. It doesn't mean don't have the technology go forward, but we do need to be very careful.

Kelley: Some of the conventions are outdated right now, and the U.S. isn't even a signatory to some of them. So obviously, there needs to be work done in this area and we have a working group as part of the project that is going to look at policy development from the international level down to the state level to try to make some recommendations and move that forward.

Duncan: So I want to thank the panel. And by the way, we're about to do a sort of Q&A conversation with you all, which I think David is going to come up and do it. So if there's some more questions about this, feel free to ask, and you guys will be around a little bit. So let's give a big hand to the panel. Thank you.