Dr. Iida

Ladies and gentlemen, thank you very much for coming to the Legal Issues in Medical Activities and Drug Innovation Symposium. This is part of the event co-hosted by Tokyo Medical and Dental University, Waseda University Research Center for the Legal System of Intellectual Property, and University of Washington, Center for Advanced Study and Research on Intellectual Property. Opening remarks by Professor Morita, please.
Ikuo Morita

Thank you for your kind introduction. I am Morita. Thank you very much indeed for being with us out of your very busy schedules. Thank you for such a large turnout. On behalf of the organizer, allow me to extend a few words of welcome.

We have the Legal Issues in Medical Activities and Drug Innovation Symposium. It’s been materialized by kind cooperation by Professor Toshiko Takenaka, the Washington School of Law Professor and also Waseda University visiting professor, and Professor Takabayashi of the Waseda University, faculty of law. Three universities have organized it with great experts and speakers.

We are medical university and this meeting is a fusion of science and fine liberal arts. From the viewpoint of social science, we are having this symposium addressing industry-academia cooperation. It’s indeed a great opportunity. We hope that this is going to have a broad discussion.

In the pharmaceutical industry here in Japan from 2008 to 2012, one after another, blockbuster products will see the patent expiry to address unmet medical needs and blockbusters – as a challenge to those issues I think demand for the cooperation among business, government and academia will be ever higher. To develop pharmaceutical products, we would like to capitalize on or make a contribution by our great high-quality basic research that we have in our universities as well as translational capability at university hospital, but at the same time we need to pay attention to relevant laws and regulations and ethics.

In the first part, we will address legal issues surrounding clinical trials experts in health law from Washington University Law School, Professor Patricia Kuszler and Associate Professor Beth Rivin. We also have from our school Professor Hagiwara, who is from School of Bioscience. He has been very active in this cooperation as well as he has launched a bio-venture. Now, this Medical Act and related legal issues are important issues for us to address. We look forward to listen to their stories.

In the second part, protecting medical advancement with patent and venture-business incentive, Medical Doctor and Patent Attorney Andrew Serafini, and also Professor Jan Krauss, Patent Attorney in Europe, as well as Dr. Ryo Kubota, the CEO of Acucela who has been going ahead with research and development activities.

I hope that we can make what little contribution we can make to the development of medical area research as well as technology. I’d like to thank all of you who complied with our request and traveled long distances to be with us. And our special thanks must go to Professor Takabayashi and Takenaka who cooperated with us in organizing and operating this symposium. I also would like to wish you all further development and exciting career. Thank you very much for your kind attention.

Dr. Iida

Thank you, Professor Morita. We would like to now begin the program.

First, there will be a presentation by Professor Hagiwara of the Medical Research Institute of TMD and Graduate School of Biomedical Sciences. Then, there would be a presentation from Professor Kuszler of the UW School of Law and Professor Rivin on clinical trials as well as ownership and entrepreneurship issues. And thereafter, there will be a panel discussion moderated by Professor Takenaka.

Now, I hand over the microphone to Professor Takenaka.
Toshiko Takenaka

Thank you very much for the kind introduction. My name is Takenaka of the University of Washington. Despite the heat, I very much appreciate the heavy turnout. It’s hot outside but we expect that the discussion will be heated up and the temperature within this room will go up.

LLM Program for Medical Law has been created at University of Washington since last year. This is not only for the legal profession but for the medical profession, for example, those involved in medical error related issues or hospital management or ethical issues. This is a program to take up the US legal framework from a broad perspective and conduct comparative studies as well.

Now, let us begin Part 1. We have Professor Hagiwara speak about the healthcare provision issues on global health and what kind of assistance is being done on the global front. And after we have his report then we could talk about the ethical standards in clinical trials and other issues pertaining to clinical trials, ownership of samples used for research. We thought that it would be better for those presentations by Beth Rivin and Pat Kuszler. And then, we would like to entertain questions from the audience.

Now, without further ado, I would like to give the microphone to Professor Hagiwara.

Hagiwara Masatoshi

Thank you very much for the kind introduction. In fact, as indicated by Professor Morita, I will be moving on to Kyoto University from 1st of July, so, the last Tuesday lecture was my final lecture. Because my last lecture last Tuesday focused on the science, I thought it would be best to talk about more down-to-earth primitive issues.

The reason I thought so is because most recently I started up this new NPO with a friend. Mekong Medical Aid is what MMA stands for, and we focus on Vietnam, Laos, Cambodia, Myanmar and Southern China along the Mekong River and some parts of Thailand along the Mekong River. The objective of the NPO is to provide for medical aid and assistance to those areas. The Secretariat is located at Arisawa hospital. This is not an NPO to make only economic contributions. We also provide medical equipments and drugs and pharmaceuticals as well as technology on pro bono basis. And we’ve been able to discover many things through our activities as such and that is going to be the subject of my presentation this afternoon.

Beth and Patricia will probably talk about clinical trials but I’m often requested CROs of Japanese companies to conduct clinical trials in Vietnam. They complained that the cost in China is becoming expensive so they want to establish clinical trial networks in Vietnam and they seek my cooperation. But I am still hesitating and I haven’t accepted. After my presentation, you may realize why I’ve been hesitating and have not nodded yet to those approaches.

As you know, Vietnam has a population of 85 million. The total area is 329,000 square kilometers, slightly smaller than Japan. Japan’s total area is 370,000 and it’s close to 90 million. This is rather outdated. In 15 or 20 years the population of Vietnam will surpass the population of Japan according to statistics. So, it’s not necessarily a small country.

They have their own language, but basically it’s part of the Chinese cultural zone. When you go to an old temple, you see Chinese characters on the walls. It’s difficult to read the names of Vietnamese people but the reason why those Vietnamese names are difficult is because they are basically Chinese names. So, when they are written in Chinese character then it’s easier for the Japanese to get the names. But after
the French occupation, they tried to read the Chinese characters in the French way. And after their independence from France, they switched to English expression of what used to be the French expression of the Chinese names. So, today the English expression of the Vietnamese names is so complicated that no one can read. But the cuisine is great because of the influence from French and Chinese cuisine.

When you land at the airport, this is what you see on the streets. Those of you who have traveled to China 20 years ago, you might have seen this kind of scene. It’s completely different at least in Beijing and Shanghai. So, once you get into the city, crowds on bicycles would surround the cars. So, it’s very close to what China used to be 15, 20 years ago. I am not an expert, but the level of development of hospitals or infrastructure is quite close to China 15 years ago. Bicycles are the main means of transport. They’re carrying swine and carrying a cow.

Today, foot-and-mouth disease has become a big issue in Southern Japan, in the Miyazaki Prefecture and the farmers there are troubled. How – with the contagion spread and infections spread. But no one is worried about that kind of veterinary disease in Vietnam. So, is this cow infected with mouth-and-foot? No. No one knows. There is a high probability that this cow might be infected, but this is the kind of country it is. So, even if Japan alone takes various measures to solve the issue, unless the level of science is uplifted in surrounding countries, it would be difficult to seclude us from these diseases.

And this is how they transport birds, hen and rooster. There is no guarantee that these aren’t infected from avian flu. When I asked my joint researcher, my colleague - when we say we want to test a new drug from avian flu; oh, okay, catch 10 birds and you are likely to have at least one who is infected. So, amongst these birds that are being carried on bikes, there might be some infected. And so naturally, this driver is exposed to the threat of avian flu.

In fact, this is rather outdated statistics. More than 100 people had died from avian flu. It’s only Indonesia and Vietnam who has caused more than 100 deaths from avian flu. Vietnam’s population is a third of Indonesia. So, in terms of ratio against total population, the concentration of deaths caused by avian flu is the highest in Vietnam. And, as I said, if avian flu comes into Japan and a bird is infected, and there were such incidents like that, it becomes a big scandal and all the birds in the surrounding will be slaughtered, that’s how serious we try to tackle. But in Vietnam, there is constant avian flu, and at a certain probability, it’s a normal state for people to be infected by avian flu at a certain level. There are viral infectious diseases other than that, and dengue fever is one, and this represents the spread and outbreak. Mekong Greater region and Vietnam are some of the areas where there is high concentration of dengue fever patients.

We wanted to do something about these infectious diseases. So, we began a joint research with Vietnam. Hanoi Medical University runs a hospital called Bach Mai Hospital. And I came to know this hospital, I had a personal friend, and we were offering dialysis equipments. It cost about more than 10 million per unit. But after 5 years of operation, when a new patient emerges, the equipment is replaced. The Japanese patients want to receive dialysis with state-of-the-art medical equipment. So, every year there are a certain number of second-handed used equipments that are retired. So, we maintain those medical equipments and offer to Hanoi Medical University free of charge. We began that activity with my friend and Bach Mai Hospital was the recipient institution of those equipments. This is a photo of the activities back then. These equipments for dialysis are brought in and this is being used locally. This activity is still ongoing and continues today.
That served as an opportunity for me to begin to visit Vietnam frequently and I observed various buildings. This is within the premise of the hospital. There are crowds of people, patients and patient families, and they can’t fit into the hospital. The capacity is too small. So, on the premise they would sit down and eat. I also went to the Department of Infectious Disease. This is the hospital building for infectious disease and there would be two or at most three patients per bed. And the families, like you see, they would be sleeping on the floor and you see children running around the infectious disease department. And you see this window left open. When you are asked by pharma companies to do clinical trials at this kind of location, would you be willing to do it? Yes, there is the wealth of patients, but can you really control these people and obtain clinical trial data? This is Bach Mai Hospital, which is the biggest general hospital in Vietnam and this is the reality of such hospital.

Dr. Roy, the Deputy President of Hanoi Medical University is a friend of mine. So, I asked him, are you satisfied with this? He said if the hospital offers a bed only for one patient, what would happen to all these people? Only a handful of these people would be eligible to be registered to the hospital. So, they say it’s not ideal, but the capacity is in shortage and the equipments and infrastructure is in shortage and that’s reality of Vietnam and other areas in the Mekong region.

So, with Hanoi Medical University and with Research Institute of Vaccination and Microbiological Studies, we began to do a trial, a project, on joint development of new pharma. Japan’s JST is supporting us. It’s not just about transporting something but to jointly develop a new drug that they need. And through this program, we receive exchange students in Japan to educate them properly in Japan. They would participate in this kind of technological development. In the future we are hoping that the country can be able to host clinical trials at global standards and we wish to foster human resources towards that aim.

Ministry of Health of Vietnam, we visited the Ministry of Health. This is a young person, Professor Tien, who is a Medical Doctor, Vice Minister. It’s the counterpart of Ministry of Health, Labor, and Welfare of Japan. This person will probably become the top official of the Ministry of Health. So, it’s not just the ODA to develop infrastructure such as hospital buildings is required from donor countries but technological transfer or jointly developing drugs for infectious disease, these are some of the proposals being made from Vietnam to Japan to conduct such activities. This is a doctor of Hanoi Medical University and we received her in my course of the Graduate School and she is studying anti-viral medicine.

We also do projects with Cambodia. After we began our activities in Hanoi, we began our projects in Cambodia. Takatsuki is in the suburbs of Osaka and the Rotary Club took the initiative to launch this project. Cambodia is next to Vietnam and the population is smaller at 13 million, but even more than Vietnam they are underdeveloped in terms of medical infrastructure.

You only have the image of Cambodia being a country of culture heritages like Angkor Wat. But there are 13 million people and the level of development is very much behind. The ruins of war still remain and there hasn’t been complete reconstruction after the war. So, you see all these ruins that had been caused by war still on the streets. What you need to be careful of, you go the toilets, and there are so many toilets without paper and I’m sure Beth knows this well. When you go to these places, you would be troubled but I wonder why these government buildings are so grand.

For example, in Southeast Asia there are many people who die from these diseases but they aren’t any statistics so you don’t know the actual number. And if there is vaccination then you know that they would be saved and vaccination is obligatory in Japan so there aren’t many patients but there is no vaccination.
in Cambodia. So, the Rotary Club cooperated and we decided to provide them with vaccination of Japanese encephalitis.

But even if you have vaccination, you have to obtain the cooperation of them to receive the vaccination. Sen Sok International University is the first private medical university that has been ever established in Cambodia and they are now receiving vaccination of the encephalitis. Even if the Rotary Club pays, we discovered that the price of vaccine is extremely expensive in Japan because of various reasons. So, the vaccines for Japanese encephalitis purchased in Japan, you send it locally, you can only give it to 1000 but if you buy it in China, it’s half the price so you can vaccinate 2500 people. We also discovered that if the vaccine is made in Thailand, you can cater to 5000 people. So, we are purchasing from Thailand and bringing it into the next-door country Cambodia.

So, along the Mekong region, when I was involved in various activities, I discover many things that I would never have discovered if I had just stayed in the university. I didn’t know vaccines were so expensive in Japan in comparison to other countries. That’s a big question. It’s been paid by our taxes that we pay. It may be that the Japanese Government is suffering from huge amount of deficit. But if the Ministry of Health, Labor and Welfare offers vaccination, safe vaccines, at a lower price, if they have more reason, may be the medical cost could be reduced quite significantly.

Bach Mai University, as I said, the new building was built through ODA given by the Japanese Government, but no one knows. There is a small panel, and when you really read it, there is a small sentence saying that it was built by Japanese Official Development Aid, but no one knows that. I’ll be moving to Kyoto, but I am trying to cure the diseases that current pharmaceuticals cannot cure. Then this is the kind of design of drug that we want to develop, and then the NPO can distribute a drug labeled as such. If we can finance this through Japanese Official Development Aid, this could be much more effective than building buildings. At the time of the Gulf War, Mr. Armitage of the United States said that this shows the flag. I think this is a typical example of ‘show the flag’ and we want to show our flag as such. Thank you very much.

**Toshiko Takenaka**

Professor Hagiwara, thank you very much. Let me now introduce the next speaker. Clinical trials in developing nations were a major issue. Companies want to do clinical trials but they can’t. It’s not just the problem of lack of facility. There could be legal risks if clinical trials are to be done in developing countries. There could be legal risks as well as facility risks. And also, the provider of medical services may be doing something on goodwill, but sometimes those clinical trials could be criticized as being experiments on human body. So, application of global standard will become necessary. As one such major endeavor, my colleague, Beth Rivin will speak about such subject matter.

Both Beth Rivin and Pat Kuszler before coming to law school were medical doctors who had actually been involved in provision of medical services. And so, they have experience as practitioners and at the same time they’ve studied theory. So, they put practice and theory together to tackle the challenging topics on the market. Beth Rivin, please.

**Beth Rivin**

Good afternoon. Today, I’ll be speaking about our research ethics, and focusing my comments on re-
source-poor settings and the leading issues of justice.

So, I will briefly make a few comments in a global context, the history and some standards that we should look at and a case in the United States that I will discuss again briefly Abdullahi versus Pfizer looking at the Kano-Nigeria situation in 1996; and then justice in resource-poor settings.

Looking at the Global Forum for Health Research 2008 data, of course, they analyzed data from years before than we see the nice graph that shows the exponential increase in dollars of our research funds. And we see that equally increased are the private sources, the public and not-for-profit sources. So, it’s actually increased significantly from then as well. Just to mention, when we talk about global health research, it is not just clinical research. We are talking about public health research, including epidemiology. So that term ‘global health’ is very broad.

The disparities that exist in the world are quite large. When we talk about research, we must understand the context within which we are doing, and our colleagues are doing that research. The “10/90 gap” is often quoted that language of the gap for disparities relates back to 1986 data with the publication in 1990 of that language of the gap, which says that less than 10% of the health research funding is devoted to health problems that account for 90% of the global disease burden. This data still exists. When you look at the new study that the Commission on Health Research has done, it’s now called Global Forum, in 2003 and 2004, we see that that gap continues to exist and there is movement towards correcting this, but it is only small movement at this point.

The origins of our standards for research ethics frankly come from exploitation. We have emerged into a world where there are standards. But before World War II, both in Europe and in the Pacific, we did not have these standards. The world had not come together to understand that we had to have new norms and standards that exist for all research.

The Nuremberg Code was created. It is the foundational document for all research ethics. It has 10 foundational ethics guidelines, the first of which is the most prominent and one could argue certainly from the American perspective the most important, and that is that the voluntary consent of the human subject is absolutely essential. And I say the American perspective because we are so individually focused. But the voluntary consent and the informed consent is so essential for the ethics of any research.

Here are the 10 guidelines. Of course, the first voluntary consent is so important. Number two, scientific rigor and on and on. Let me mention again number six; risks must be weighed against the importance of the problem, and we’ll get to that a bit later.

The standards for bioethics or research ethics have gone through an evolution and this evolution has been marked by some landmarks as you see in the slide. Beyond the Nuremberg code, we’ve seen many more documents that have come forth from the World Medical Association, the Declaration of Helsinki with revisions, actually, the last one in 2008, we see CIOMS and we’ll get to a number of these today.

Let me point out that in addition to the emergence of a new understanding of research ethics from World War II and the experience around the world, we have seen also a movement in human rights. And they have the same roots and so the Universal Declaration of Human Rights one could argue has many commonalities with our research ethics standards today.

The 1979 Belmont Report that came out of the United States National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research is a document that stands out as a document that not only articulates some of the principles that are foundational for research ethics, but also starts to
talk about justice in a way that had not been spoken about before. There is a focus on autonomy, respect and dignity for the individual language that you see in human rights, and this is embodied in informed consent in the process.

And of course, you see justice as well which we could argue was a bit more undeveloped in research ethics until more recently where we see a more focused understanding of what justice is. But the Belmont Report actually has an interesting quote that I would like to give you, which is that, it’s says that “Research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.” And so, in fact, you see it stand out as a document that actually starts to focus on the issue of distributive justice.

Now, what populations are vulnerable and what populations may need special protections, and what are those special protections? This is a big question. I have listed some of the populations that have been spoken of in terms of vulnerable. Sometimes the context of the society makes certain populations more vulnerable than others. Vulnerable to what, vulnerable to exploitation in research. Are children vulnerable? Absolutely. By nature, most children, especially below a certain age, cannot speak for themselves and so we look to the parents. Are the parents actually articulating what the child might want, right? And so, we speak about assent, getting some kind of informed consent in the age-appropriate language from the child.

The Council for International Organizations of Medical Sciences (CIOMS) was established in 1949 and offers a comprehensive guideline. And again, it keeps getting updated, the last one in 2002. What does it say about research on vulnerable populations was it has specific guidelines, and the research should have the intention of benefiting the group to which the vulnerable population belongs. It should be therapeutic, or if non-therapeutic, should pose minimal risk. For instance, in children, we should focus on whether the therapeutic research would be providing potential benefits in relationship to the risks. And so, we have to look at that risk-benefit ratio, especially in these vulnerable populations.

Now, in terms of analyzing global health research, justice has historically focused on exploitation, the recruitment of subjects and the conducting of the trial. Flawed or cursory procedures have been focused on in terms of getting informed consent; nonexistent local or national ethical review of proposed research has been another issue in justice; and the lack of proper skills on the part of the local researchers can be a big issue in terms of justice.

What do we mean by exploitation? A leading scholar who has been a prolific writer in the area of research ethics defines exploitation in the following way, and it’s a very broad definition. “Exploitation occurs when wealthy or powerful individuals or agencies take advantage of the poverty, powerlessness or dependency of others, by using the latter to serve their own ends, without adequate compensating benefits for the less-powerful or disadvantaged individuals or groups.”

This brings me to the case of Rabi Abdullahi, the Pfizer in the United States. I would be remiss if I didn’t mention this case in terms of exploitation. This case is one that is actually on the docket for the US Supreme Court. So, it’s been appealed by the Second Circuit Court of Appeals, and we are now waiting to see if the Supreme Court will hear this case. The case currently is about whether under the Alien Tort Act this case will be moved forward and be heard in the court system in the United States. As we look at the facts, we see that there is alleged exploitation.

Pfizer allegedly went into a situation in Kano, Nigeria, where there was an epidemic of bacterial men-
ingitis, with a number of physicians in Nigeria. And Pfizer researchers did a randomized controlled study on children. They allegedly got consent from the Infectious Disease Hospital in Kano, Nigeria. The government officials did write to Pfizer and gave their approval for this study. There is a lot of controversy of whether there was actually an ethical review at the hospital. Apparently, there was no ethical review committee that signed the form that said there was a review. And so, there are a lot of disturbing features of this case.

What happened here was that Pfizer wanted to study Trovan, which is an antibacterial drug. They designed this study to be two-armed, one having this not an FDA-approved drug for children in the one arm, and the other arm was a lower dose that was not FDA-approved for this particular purpose, ceftriaxone, which is a great drug for bacterial meningitis, but the arm for the study was a lower dose than what was normally given to children. The result was that 11 children died and many had serious permanent neurologic deficits; paralyzed, death, blind, brain injured. There were five deaths in one arm, six deaths in the other.

So, this case was brought to the US against Pfizer, and so, we will have to wait and see if this can go forward. But there is serious research ethics issues raised and the case is about violating international legal norms, which are the issue of informed consent and some other issues. So, we’ll have to watch. But, again, research ethics standards are not consistent today with what is alleged to have happened at this time. And of course, if this does go forward, I have to say and if there is a decision against Pfizer, this will certainly be a wakeup call for companies or researchers that are doing research in resource-poor settings that they can move forward and try these cases in wealthy countries.

So, as we strive for justice, what is justice required when wealthy-country researchers are conducting research in resource-poor countries? What do sponsors and researchers owe to clinical-study participants, and to the community, and broadly to the country? When we talk about distributive justice, what are the burdens that are being placed on the participants and what are the benefits to that participant population, to the community, to the country? Now, of course these inequities exist around the world between countries and within countries. So, there are disparities within populations, within a country, including resource-poor settings.

There is a controversy and a debate about what should be done in the setting. One point of view would argue that medical and pharmaceutical products are just one more commodity that is distributed inequitably around the world, and what’s the big deal? There are already inequities it’s just part of it. The other contrasting view that one could say is extreme, is that medical and pharmaceutical products are necessary to maintain and improve human health, and they should be taken out of the market system. This kind of thinking is consistent with the human rights analysis of obligations regarding public health that this isn’t just a widget, it’s not just an auto product, that this has a special category.

There are many challenges to attaining justice and to doing the right thing in clinical research when we are working in resource-poor settings, not only language and culture which includes the understanding of what health and disease are, how do you explain what this disease process is in an informed consent if the people don’t understand disease to be the way diseases that we – germ theory, if there is no understanding of basic germ theory in the population. So, there are those challenges.

In addition, what does it mean to aim for justice and strive for justice in research when the setting is so difficult? The health infrastructure, it doesn’t exist. It’s inadequate. Many people do not have justice in
their own country. They don’t have access to adequate services. So, what does that mean for a researcher to go into that setting and do a clinical trial? Again, the benefits and burdens of the research, what is fair to provide in a post-trial setting for the participants that provided you with a vaccine or a medical device product that is going to make your company billions of dollars? And of course, the ethics review system may be very inadequate, if it exists at all. And this again, puts the burden on the wealthy country ethical review process, doesn’t it?

So, what are the implications for ethical review and should there be more of a focus on distributive justice and the fair benefits of research rather than what generally exists today, which is that ethics review committees focus on informed consent and the risk benefit analysis.

Let me just say that our US National Advisory Commission states that researchers and sponsors of clinical trials should make reasonable good faith efforts before the initiation of a trial to secure continued access to all the participants to the needed experimental interventions. It goes on to say that when no arrangements have been negotiated that the researcher should justify to the ethics review committee why this is the case.

Our US Code says there is no requirement for post-trial access to research products. The Declaration of Helsinki is a bit more robust as all international guidelines tend to be in terms of post-trial access, I have to say, in the US we are a bit more minimalistic when it has to do with law regarding or guidelines regarding post-trial access. So, Helsinki says, yes, we need to inform about the outcome of the study and to share any benefits with those who are involved in the study make post-study access by the subject part of what is a standard.

The CIOMS says any products developed will be made reasonably available to that population or community. What is the community, is it the whole country? How do we define community? And of course, the UNAIDS Guidance is the strongest in terms of distributive justice, in terms of post-trial access, and it says any HIV-preventive vaccine demonstrated to be safe and effective should be made available as soon as possible to all participants in the trials in which it was tested as well as to other populations at high risk of HIV infection. There was a lot of civil society organization involvement in this language.

So, very briefly, let me be provocative and ask what is the role of the IRB in this context in wealthy countries? What is the role of researchers when we are trying to attain distributive justice standards? Maybe the role of researchers in wealthy countries that are doing research in resource-poor settings has to be expanded and maybe researchers need to learn some skills that they already don’t know, add-on another thing they have to learn. But maybe that’s true if they are the negotiator with the developing country - population in the developing country government actually, and they have to also negotiate with their own IRBs. So, thank you very much.

Toshiko Takenaka

The next speaker is also my colleague, Director of the LLM Program, Patricia Kuszler. She will touch upon IP and will talk about the ownership of cells and ethics as well.

Patricia Kuszler

Introduction and I’ll be sort of continuing the theme that both Professor Hagiwara and Professor Rivin have begun, in looking at some of the justice and rights issues that come up in research. My topic today
is to look at what is a very hot issue in the United States and around the world, the issue of research using cells, genes and tissues, many of which may be have been banked for many years and are incredibly valuable resources as we seek to develop new drugs and therapies.

So, today, I'll be covering a few specific issues and we are going to focus primarily on sort of the rights issue. Who has rights to these substances and what is the robustness of that right and how much power goes with that right? What rights are held by the individual who originally contributed or donated or has taken away from them the cells or the tissues or the genes? How about the researcher, who has worked the substance, perhaps changed it, perhaps not, but is engaged in doing hopefully productive research to develop new therapies and technologies? What about the university or the funder, the research sponsor, what rights do they have in this ownership issue?

There are some special challenges with genetic research that we'll be talking about, a very big issue around the world, but particularly in the United States and the UK right now. Where should we look at the rights that evolved a society? What are the rights that should be given to society at large for the global good? And whoever holds these rights, what kind of rights are they? Are they rights of consent, classical property, buy and sell, intellectual property, patenting, or some new kind of property, informational property as one scholar has referred to it?

First of all, as we take a look at the idea of what if the rights are held by an individual, does it matter what the nature of the contribution is? If the individual is a patient, it's likely that that tissue issue or gene or cell was retrieved during necessary surgery or treatment to rid the individual of an illness or malady. Does it matter that the patient's tissues were co-opted into a tissue bank for later research, does the patient need to know that? Sometimes the individual is a subject who actually knows they are engaged in a research trial. Then, do they have any unique special rights to benefits as Professor Rivin talked about? Suppose the individual isn't a subject, isn't a patient, but wants to donate tissue for the greater good or wants to donate tissue for a specific aim, does that change the nature of the contribution?

Suppose it's a community – in the United States and around the world we are experiencing the issue of DNA cells, tissues that have been retrieved from various unique indigenous populations, tribes, and this has given rise to the issue of a community-concentric community approach. In some cases those communities argue they should be collaborators in the research holding the same standing as the actual researcher. If we go with the idea that there is some kind of consent that would be obtained from the subject, the patient, the donor, what is the function and power of that kind of consent process?

We already know that consent is different when we have a regular doctor-patient interaction than it is in a researcher-human subject interaction. And indeed, if we are working with communities, the concept of community consent where you may be getting consent from the tribal elders as well as the individuals, and if the individual has rights, this patient, this donor, how long do they last? Do they last after life, after death, and what about these community rights? So, as we think about this, we have already had some legal cases are beginning to chart this difficult course.

Of course, the golden case that everyone always hears about is Moore v. University of California. This is a case involving the “stolen spleen”. This gentleman was a patient at the University of California. He was there because he had a very bad leukemia. It’s called hairy cell leukemia. And at the time he was seen, it had less than a 5% 5-year survival rate. In the course of his treatment, his spleen was removed and it was a very large, very interesting spleen. His doctor was also doing research and used the spleen
in his research, creating a cell line. Some years later, Mr. Moore became concerned about this. He thought it was my spleen and they have developed a valuable cell line, surely I should get a piece of the action, some compensation for what I contributed.

The court held that Mr. Moore didn’t own his spleen once it was removed from his body, there was no classical property interest, and that he didn’t have any right to any specific compensation from the actual remuneration that was derived from the cell line. The researchers had however violated the standards of informed consent and fiduciary duty by failing to tell Mr. Moore that they were going to use his spleen for research.

We have another situation that came up just a few years ago in the Greenberg v. Miami Children's Research University case. Here we had some families who were seeking to find a cure for their children's disease. Their children had been born with Canavan's disease, a severe genetic mouth malady that causes death. It’s common in the Ashkenazi Jewish population. These families banded together and they approached a researcher and said we would like you to do research on this disease to find the mutation that causes it and to develop a test that would be useful to families with this disorder in their family group so that we could test beforehand and know if our child was going to be affected with this terrible disease.

The researcher took the money and he also took samples that they gave him freely. In the fullness of time, he did discover the gene and he went on to patent a test. The families were very angry because they said we did this so that the families who are suffering from this genetic malady would have an opportunity to have a test, an inexpensive test, and now it’s being turned into a commercial product, and they also sued. And once again the court said that mere donation of genetic material doesn’t give the donor any rights to that material after the fact. Now, the court did go onto say however that the fact that the families had given the researcher money was significant. That amounted to an unjust enrichment, and since they had invested in the research, they should get some money back.

So, you see already we have some difficult situations arising with respect to that own the tissue, the genes. In terms of community rights, we have had a recent big case in the United States with the Havasupai tribe. This tribe resides in the bottom of the Grand Canyon and they have a lot of diabetes in the tribe. Back in the mid-1990s, they approached a researcher who agreed to do some research on diabetes and genetics using their samples. They freely gave their samples. They consented to research on diabetes. Time goes by and at many research centers blood and tissue gets moved around to researcher, other researchers who might be interested and sure enough another researcher who was interested in schizophrenia got hold of these samples and did some research on them. Another one was doing research on alcoholism. And then last but not least, there was an ethnography researcher who was doing research on Migration Theory; where this unique tribe had come from originally? The Havasupai didn’t consent to any of those latter three. They only consented to research on diabetes.

In the fullness of time, they found out that the researchers had been researching things other than what they had consented to. This angered them greatly. They believed that mental illness and alcoholism have negative connotations. And more importantly, they have a deep spiritual belief that their ancestral and spiritual home where they sprang from is at the foot of the Grand Canyon, not having migrated across the Bering Sea. In a long complicated case which just settled a month or so ago, Arizona State University was required to give the tribe back all of the samples and had to pay $70 million, a significant hunk of damages.
Lest you think this sort of community rights, tribal rights thing, is only in the United States, just a couple of weeks ago researchers were forced to release collections of blood samples taken from the Yanomamo tribe in Brazil and Venezuela during field work in the 60s and 70s, and these samples were also given back to the tribe, the argument being that the tribe had not consented to the research purposes that had been later undertaken. So, now we have issues of what rights do the donors have, what rights do the subjects have, what rights do the patients have, what rights do the communities have.

Then if they are rights, the next question is they time-limited? We saw in the Yanomamo case, those tissues had been present in research labs since the 60s and 70s. Many of the contributors were now deceased, yet the tribe asserted that they all had tribal DNA and therefore they were owned by the tribe.

We recently have a big bestselling book called ‘The Immortal Life of Henrietta Lacks’ and it traces the origin of the HeLa cells, one of the most common, most prolific cell cultures we have in the world, it is literally all over the world. These cells were derived from a cancer patient in the 1950s, Henrietta Lacks, a very poor woman in Baltimore, and of course she did not consent to have her cells used immortally forever by researchers for many different kinds of research ranging from polio vaccine to cancer to flu. But then, the standards of informed consent weren’t very developed in 1951. The researcher who harvested the cells and successfully cultured them gave them freely to other researchers. He did not profit, create any intellectual property, and did not really derive any fame from the research.

The story talks about the survivors of this woman, also very poor, generally not well educated people who believe to this day that they have some ownership rights in the cells of their mother and grandmother; that those cells are also resident in them and that they should have some ownership given the advances that were derived from their relative’s cells. So, you see this is percolating along as a never-ending problem. Rights held by the researcher who has worked on the tissues, what impact does work and transformation have on rights of ownership?

The very famous case of Diamond v. Chakrabarty said that you can take a naturally occurring cell and you can’t patent it. But if you do work on it and change it to something else, then you can patent that cell and it’s become something else. How much work is enough? How much displacement is enough? What impact does the relationship between the researcher and the subject have? History would suggest that the relationship between researcher and subject is transient, not very substantial, and even baldly opportunistic. So, surely, the researcher can’t have any ongoing interest in cells they have harvested.

This came up in a case just a couple of years ago where Washington University employed a researcher named Dr. Catalona. Dr. Catalona did research on prostate cancer. He had gotten cells from many prostate cancer victims. They donated their cells willingly for prostate cancer research. He had put them into a tissue bank at Washington University, continued to research on them for several years; then moved onto another job at another university and he wanted to take those cells with him so that he could continue his research.

Washington University said those are ours. They’re sitting in our refrigerator. They’ve been in our custody. We’ve maintained them. We’ve controlled them. We possess them. They are not yours. They belong to us, the research sponsor. And the court agreed with them. The court said neither the original donors of the cells nor the researcher who had gotten the donation had any continuing ongoing ownership rights. The ownership vested in Washington University. And that sort of speaks to, I am sure we’ll hear more about technology transfer laws this afternoon, but technology transfer laws would also provide a
university with a level of ownership.

It gets really dicey when we get into genetic information and genetics and genes. In a classical medical model, genetic information would belong to the patient who you drew the sample from or whose DNA you just sequenced. But in the classical research model, the information would belong to the research enterprise. And then there is a new model, the Genetic Alliance model. Here we have, not unlike our family in Greenburg, we have a family that has a severe genetic disorder that afflicted their children and they got the bright idea of banding together with other families with this disorder, and holding their DNA and their samples in their own possession and cutting a contract deal with researchers which would allow them to share in any intellectual property that came up before the research was done.

This model has proven to be very popular. And Genetic Alliance is now a group that has several different genetic disorders involved. They maintain their own tissue bank. They maintain control over their samples. And in order to use their samples to do research, you will, if you are a researcher, have to engage in a contract which will give them a part of the patent, if there is anything and indeed part of the proceeds, if there are any profit down the line.

In genetics, we have this issue of genetic information is at once the most personal and the least personal of information. Because of course all of our family members also share our genetic information and some of our genes. This was highlighted in Iceland where Iceland legislated a health-sector database, argued that the legislation was seeking to collect specimens from every Icelander in the course of their normal healthcare using presumed consent. These samples would be sent to decode a corporation that was working on genetic research to find cures and therapies for common disease, including those that affected the people of Iceland.

The idea was that they would get this very unique database from this very interesting population that is quite homogeneous and valuable from a genetic perspective, and the payback would be that Iceland would get a good deal on any drugs that were derived from this genetic research. All is well until a 16-year-old girl says you’ve got my dad’s DNA, that’s my DNA too and it violets my constitutional rights to privacy. She brought suit against the Republic of Iceland and she won, thus overturning the Health Sector Database Law completely in the nation of Iceland.

Such sort of the dynamics of this idea of personal rights to privacy and the greater good of what we can get from genetic research, we’ve also seen that come up in the States recently. We had two big cases, Minnesota and Texas. Neither has gone to – has actually been fully litigated. One is still in the early phases. But both involved parents who argued that the newborn blood spot samples - I’m sure it is also true here in Japan. We test all newborns for common inborn errors of metabolism like phenylketonuria. Those samples are stored forever.

Researchers have learned that that’s a wonderful database to be able to get a lot of genetic samples very quickly. They’re valuable database. However, parents made the argument that those are their children’s DNA and that researchers shouldn’t be able to use those databases even anonymized to do research unless they get explicit consent. The Texas courts look like they were going to probably go that way and it was resolved by settlement that led to the destruction of 5 million newborns spot samples in the state of Texas a few months ago.

One could make the argument that it violates the idea of societal good that these sorts of big databases are vital to new drug research, new therapy research, new understanding of how genetics works. One
could argue that such scientific resources are so valuable to research and to society at large that surely individuals shouldn’t have that much power to overturn this valuable research. Historically, tumor registries are the example. It gets very difficult as governments especially in the US seek to compile big databases. We’re currently doing a genome-wide association study database that is supposed to collect gene samples from all over our country and it’s receiving some really interesting scrutiny.

Proponents of research argue that such big databases shouldn’t be wasted, that they should be exploited with appropriate protections for individuals like anonymization to provide us with an opportunity to derive better good for the globe, better global good, better goods for society. But the fact of the matter is that these issues are still unresolved. If we look at research and its role as global societal good, how can entrepreneurial activity lead to new drugs, innovations, treatments, how can it be fostered and promoted if we maintain this tremendous dedication to an individual tribe’s right to unravel an entire huge biobank or database. Subjects, donors and indigenous populations, how can their rights to privacy, their rights of ownership, and their rights to perhaps even control research, how can those rights be recognized? Genetic Alliance advocates for inclusion in IP rights.

Others, notably the tribes, and some of the parents of newborns argue that they should have even greater dispositive control. Some of the tribes that we work with at the University of Washington make the argument that they should not only have intellectually property rights, but should also have the right to control what’s published, that they have veto power over what the researcher publishes. How does that square with our ideas of scientific integrity and academic freedom?

So, as we take a look at our current rights regime and ask ourselves if it’s equal to the task, it seems highly unlikely that it is. Can consent address the issues? Can consent be set up to address not only our current research but our future research we may want to do with these samples? Can you do it with tiered consent forms where an individual would say it’s okay for you to use it for this research, and it’s okay if you want to use it for future research that deals with cancer, and it’s okay if you want to use it for future research on flu, but it’s not okay if you’re going to be looking at migration theory, so those sorts of tiered consent forms.

Should it be classical property? Should subjects, donors, patients, be accorded ownership of their tissues and be able to make the argument that they can buy and sell them at will in the marketplace, would that further research or would it further exploitation? Intellectual property, is it elastic enough to address all of the alleged rights that are at play here?

Sharon Terry who runs Genetic Alliance would say, sure it is, we’ve used intellectual property contracts, contracts about intellectual property to further our cause. But is it true that researchers in universities are always going to be willing and able to incorporate the subjects, the tissue donors, into the intellectual property club? Is it fair? Is it functional? Do we need a new property scheme? One scholar argued that we should have copyright-type approach where the right of personal information would be controlled by individuals who could license the use of that information.

Obviously, the transaction cost would be enormous. There would be several different layers of licensure. There would be an opportunity for gaining around the individual in terms of genetic research. It could tie in with a tiered consent, some problems in terms of the fair use issue. But the upshot is that if science increasingly uses cells, tissues, genes, DNA, including samples that are stored in longstanding databanks and repositories, we have clearly conflicting rights between researchers, entrepreneurs and
the original donors, subjects or patients who contributed those cells, and potentially between the universi-
ties and sponsors who are currently storing those particular substances within their walls.

Obviously, genetic data race and samples race increasingly are complex issues and there is lots of ten-
sion here. And I think that we - it's a challenge for all of us to try to figure out how to figure this out be-
cause it seems clear that none of the current rights regimes provide us with an answer that will solve all
of these problems. It is an issue that is likely to be devils even more in the future, as we really explore
the powers of biobanks, genebanks and tissue repositories to solve global health problems. Okay, let me
conclude there.

**Toshiko Takenaka**

We'd like to begin the panel discussion. Professor Hagiwara, do you have any questions because you
said you were hesitating to host clinical trials in developing countries?

**Hagiwara Masatoshi**

I want to show one example. In Vietnam, they produce most of membranes for blood dialysis, but most
of them cannot use. It's a kind of exploitation. That's why I started donation of blood dialyzer to Vietnam.
It's one way to reduce the exploitation by volunteers. My major fear is RNA splicing. So, we use a lot of
DNA information. And recently, high-speed DNA sequencing appeared. So, that means personally we can
determine all of the genome sequence in near future and we use such kind of information. But at that
time, we don't know the owner's name. So, we don't care their personal right because we don't know the
name of the personal genomic information. So, it's very complicated problem for researchers. I have no
idea to take care such kind of right. Thank you.

**Patricia Kuszler**

It's an interesting point that Dr. Hagiwara makes in the sense that one of the arguments says that if we
just simply anonymize these cells, tissues or genes that all is well, that what one does not know, it does
not matter and that the altruistic approach can be honored in this way that when people donate they
truly donate. However, advocates on the other side of the equation say with high-speed sequencing that
increasingly particularly genetic information can never be anonymized because it will always be able to be
tied to your family members. And as high-speed sequencing enters not only the laboratory but Internet
sales, it will be very easy to establish what DNA goes with what person or what family. And so, there are
a lot of questions as to whether DNA and genetic samples can ever be anonymized, which of course opens
up an enormous issue in terms of genetic research.

**Beth Rivin**

Just my comment is that there are no international standards.

**Toshiko Takenaka**

So, Pat and Beth do you have any comment to Professor Hagiwara's presentation?
Patricia Kuszler

Yes. I do have a comment particularly with your addendum at the end. It’s an excellent example of providing a benefit to a population that has contributed something to societies that have used it to better their own population’s health where the originators of the tissue would typically never have access to the dialysis therapies. And it’s a really wonderful thing to hear about Professor Hagiwara’s research where rather than having to be shamed into providing just benefit he has derived a way to provide some benefit to the very individuals who contributed the materials for the membranes. And that sort of example of sort of the novel ways that some governments, researchers, research sponsors and even pharmaceutical firms are looking at how they can give back to the populations that they work with some sort of a benefit that will compensate them for the contribution that they are making to the world.

Hagiwara Masatoshi

Yeah. So, I think point is not the legal regulation. I think point is the goodwill of us so that’s why I started originally NPO. I’m a scientist so my wish is I want to develop our science. But we need many support from society, not only our own but also other society. So, I think legal matter cannot take care of everything, but our goodwill will contribute much. So, we should grow up all the goodwill. That’s my personal opinion.

Beth Rivin

Yeah. Just not to be controversial although I tend to make these provocative statements, but in fact, Professor Hagiwara, you bring up the issue of justice versus charity and there is a whole dialog about whether what we do is justice or is it just charitable? And so, I would argue based on human rights as well as research ethics that there is a justice that we should strive for, a distributive justice. Certainly, there should be charitable acts. I would never stop charitable acts, but that it’s really we’re striving for justice that is about distribution of burdens and benefits and wealth.

Toshiko Takenaka

I think for Japanese, distinction between charity versus the justice can be a kind of difficult and there is no clear sort of definition for each concept. As well as the majority of Japanese people when they hear like a global health or justice more like a wealthy country giving something out and just one-sidedly helping them however, could you explain a little bit more about justice versus charity?

Beth Rivin

So, charity is derived from sort of a moral understanding of what a person or what an organization or perhaps what a government might do – it’s usually not governments, but an entity might do for someone else or a group because of some moral basis driving that action. Although that’s the foundation for justice as well, there are laws such as international human rights laws that we have sort of come together as a world understanding as the basis for action. That part of – there is equity that we should strive for and that actually governments have obligations to within their own populations strive for equity and justice for individuals and populations, and that there is sort of a bigger world order. And of course, this is an ongoing debate in an evolution of understanding of what justice is.
So, justice in the 1800s was very different, wasn't it, with colonialism and that’s part of perhaps the history of that we bring with us to try to perhaps redistribute some of that. It’s not only wealth really that I’m talking about but it’s access to information and services. And when we’re talking about health, it’s trying to improve everyone’s population health.

**Patricia Kuszler**

Of course justice is a coat of many colors. We have a kind of justice that Beth and we have been talking about is what’s called distributive justice where the idea is that people who contribute to the research endeavor should have some distribution back of good services, perhaps return of results so they could act on them. But this idea of distributive justice is just one facet of justice. We also have to think about compensatory justice. And when we take a look at the Havasupai tribe for instance, you noticed they got a big chunk of money. This is some form of compensatory justice. Getting their samples back is compensatory justice as well. It’s giving them compensation for what has been taken from them in sort of the compensatory idea.

Then there is also procedural justice where people have a way to make their argument that they should get some return of results, return of drugs, some distributive justice where they have some way get at that. In the United States, that usually goes through the court systems, but in many other countries that doesn’t. There may be some other administrative methodology by which they can procedurally seek justice for themselves.

As we take a look at this idea of what – I’m trying to differentiate between charity and justice. One of the ways that we see this happening I think around the world is this greater movement towards collaboration between the subject populations and the researchers. In some of the – this is often termed community-based participatory research. We have seen a lot of it go on with tribes and indigenous populations in the US as well as our researchers in the US going and working in unique areas where the subjects or their leaders become partners in the research. And some of these justice issues get sort of negotiated and indeed contracted to ahead of the game. That is actually proving to be an increasingly popular model for doing research in resource-poor countries.

Now the problem of course is if the country is too resource-poor, they will not have the leaders that are capable of engaging in the transaction. But it is one of the models that’s out there in terms of trying to deliver a more just outcome to research where research subjects and indigenous populations who may have contributed something like the membranes for dialysis ahead of time know they’re going to get something in return rather than having to try to figure it out after the fact which is kind of where we are all at right now.

**Beth Rivin**

Just a very quick comment. The concept of actually the core principle of participation is one of the core principles of human rights. And in fact, going back to the roots of bioethics and human rights, the idea of participation of the populations of the individuals that are actually affected by the decision should be critical in human rights and it’s sort of more and more the case in research ethics.
Toshiko Takenaka

Thank you very much. I think the time is pretty much up but could we just have 5 minutes because I am sure that there are those in the audience who wish to ask questions. So, let’s allow for comments and questions from the audience, anyone?

Many of you work for Japanese hospitals or universities, what do they do about samples they get from patients? Do they really control and manage those resources well in an orderly manner? We are not as litigious as the United States, so, maybe you’re not so worried about litigation, but there is a potential problem with regards to possible litigation in the future. That’s my impression I have after having heard the presentation.

Once again, let us appreciate the presenters with a round of applause. Thank you very much.