CHRISTIAN BRÉCHOT

President of the Institut Pasteur, France

John ANDREWS

Now it is my pleasure to ask Christian Bréchot from the Pasteur Institute to join us.

Christian BRÉCHOT

Thank you very much, Mr Andrews, and thank you, Thierry de Montbrial, for the invitation and for setting up this session. I will start with a quote from a Nobel Prize winner, Sydney Brenner, who stated that progress in science depends on new techniques, new discoveries and new ideas, probably in that order. This statement may be too strong, but it illustrates that technology is at the heart of progress in biomedical research.

Now, before moving forward, it is important to emphasise that scientists in the field of biomedical research do need infrastructures, equipment and technological platforms. This is at several levels. There is sequencing, for example, and Dr Zhu from the Beijing Genome Institute will introduce this topic. There is now bench-side equipment, and in fact, a lot of it is outsourced in centres such as the Beijing Genome Institute. The key is bioinformatics and integrative biologics.

However, life science and biomedical research has moved to a status which was previously devoted to physics or to chemistry. This is the need for large equipment, such as cryo-electron microscopy, which is at the national level through the synchrotron. It is interesting to see that about 35% of the activity of SOLEIL Synchrotron in France is devoted to life science. It is a complete redistribution of the needs, and this is obviously in the context of connectivity and sharing information. This is the major point about automation and about the blend between the individual creative energy of scientists and automation.

It is very relevant for the Pasteur Institute. I will not go into the details, but it is a large research French institute. It is multidisciplinary, with 2,500 people. They are also very much involved in public health, in teaching and in public-private partnerships. This is in the context of an international network. In addition to this, and it is really my pleasure, we have initiated very interesting collaborations with Qatar.

In this context, this is an example of what we call the Titan Krios electron microscopy. This is the new generation of electron microscopy and it costs EUR 10 million. It needs a special building and it cannot be decentralised. It can give us invaluable information. For example: information on antibodies, which bind to the Ebola viral protein. It makes it possible to design new treatments, new diagnostic tests and new vaccines. Felix Rey in our institute has recently shown that antibodies for the dengue virus cross-react with antibodies for the Zika virus. This opens up very interesting perspectives for prevention and treatment. Another example is that you can directly visualise the viral particle of HIV as we have never been able to do before.

Regarding governance, we have really come to a point where each worldwide research institutes cannot have all the large infrastructures. We need to have networks and distributed infrastructure. I have an example of the European molecular biology laboratory. It has facilities in Heidelberg, with many platforms: in Grenoble for structural biology, in the UK for bioinformatics and in Italy for marine biology. There are other examples and the number is increasing.

Coming to the sequencing, we all know that it is a revolution and the cost has very much declined. This has actually led to a new appraisal of the human genome and the implication of disorders of the human genome. However, it is always important to remind you that we have other technologies, which I am not going to detail. This is what we call micro-fluidic at the Pasteur Agency. This has allowed us to set up new immune-assays, which are 100-1,000 times more sensitive than the current assays.

All this progress has led to the concretisation over the past 15 years of what we call personalised medicine, precision medicine. We are able to identify the parameters of a single individual among the population and to design biomarkers for prediction of treatment, efficacy of treatment and side effects. Many analyses show that all this can only increase in the future. Already, 42% of the new drugs from the companies are amenable to be targeted on a personalised basis, and this comes to 73% for cancer. We foresee a very significant increase in the future, and it is a topic of large investment for the companies.

We need to put this in the context of the global and One Health perspective, and we have outlined a very important move. In the UK, we have Genomic England and in the US, we have the precision medicine initiative. There is a move to have hundreds of thousands of individuals followed up on a prospective basis, with all their genome analyses determined. This will allow us to have a new insight into global health.

The resilience project is particularly interesting. The idea is that you follow up a cohort of individuals who have mutations. They should have the disease but they do not have the disease. The question, which is the reverse, is why, and which are the components which modulate the impact on the genome of mutations. This is a major turn and this is very demanding, but we need to have this large cohort.

We need to share this information worldwide, and clearly, we have entered an era where technology has allowed us to move beyond goodwill and talking. This has been shown in our session. We are mining electronic records for better research application and clinical care. As we are all aware of, it is about coming from the data obtained from individuals and data which are obtained in the laboratory. Then integrate the data, and this is the key word in the database, and then transfer this to a number of institutions and doctors.

Now we have entered the era of large networks that encompass for example different hospitals, and research institutions which can share this data. This is in the US, and we also have this in Europe and in Asia. Obviously, this raises a number of questions which can be addressed later. Now we have also entered the era where large companies are becoming new players. They provide new software frameworks which have now helped us to empower people to take a more active role in their health. This is for example with Apple and this is with Microsoft with respiratory illness. There is another one in oncology, but I could have obviously cited other companies. There is a major move in which the patient is a more active partner in his or her health through these technologies.

We have entered the era of artificial intelligence and deep learning. Facebook is an example and I could cite others. Again, it is about the individual being part of the whole process. Finally, a Rapid Diagnostic Test (RDT) is a key point of care. There are now disposable ones, which will completely overhaul the way we regulate our tests and the health system. It goes beyond the diagnostic tests. We have shown the evolution of the stethoscope over the years, from it was first set up by Laennec. We have such sophisticated disposals that again, we can use them in a very different way.

It is about what Leroy Hood calls a predictive, personalised, preventive and participatory approach to medicine, the famous 4 Ps. However, we have to be realistic. It is also about personalised, problematic and promising medicine, because we know that we have several challenges. Reproducibility of the data is a key point. If we share and if we

transfer data which are not reproducible, this obviously has no value. There are economic questions with regulatory agencies and ethics, confidentiality of the data and so on.

The question, especially for an institute such as the Pasteur Institute, is about how to integrate all this progress into the global and One Health perspective. It is clear that the Pasteur Institute is very much focused on its international network. It now has 33 institutes in 26 countries, and we are currently setting up one in Guinea, in Conakry. Again, Rapid Diagnostic Tests are very important for countries where we are working, and they are completely changing the pattern of diagnostic. This allows us to have this connection test onsite, to communicate and then to act.

At the Pasteur Institute, we have been working very hard on next-generation diagnostic tests. There is an example of a taskforce that we have set up following the Ebola crisis. Obviously, I do not want to go into the details, but we have several examples of immune-assays and assays based on molecular biology. They share the same concepts and they can be performed very rapidly, and again and again, they can be performed on site.

I am very proud of what our students have recently won at Pasteur. This is the gold medal at what is called the International Genetic Engineering Competition or iGEM. It is an engineering competition in Boston. They have designed a tool that allows us, using the same apparatus, to trap a mosquito, test the presence of a virus and share the results throughout the world. This is how it will stand out in the field. We have a bulk of technologies which allow us to work on centralised organisation and also to work on decentralised organisation.

I will just illustrate again that we provide infrastructure, teaching and onsite capacities in many countries. However, the point I want to make is about new technologies and the capacity to generate data on site and to share the data. This allows to design a regional and global approach worldwide. Again, I do not want to go into detail, but there are several scientific consortia which are run globally. They deal with malaria, resistance to antibiotics and a number of pathogens and clinical conditions.

We have entered the era of the molecular epidemiologic map of a disease. A *New England Journal of Medicine* paper has been published by 10 Pasteur Institutes, working with several partners in many countries. This provides the first molecular map of resistance to treatment of malaria with what we call artemisinin. This would not have been feasible only five years ago. The Pasteur Institute is at the heart of the reaction to the sanitation crisis. Again, all the technologies for sequencing and for sharing information are at the heart of the coordination we can set up, in order to deal with all these sanitation emergencies and crises, which I have indicated.

We need to have networks between various countries, and I have given an example of a network that has been supported by the European Commission. This is about One Health, and that means merging the efforts of clinical medicine and veterinary medicine to produce a survey of infections and emerging infections in different countries. This is a good example, because you want to establish this network, but then you need the correct technologies to do so. There is another example, performed in partnership with the United States. This is with the assistant secretary for preparedness and reaction, and it is again on the setting up of networks to prevent and react against sanitation crises. For example, these include avian flu and influenza.

Within the international network, we have set up an example in Cameroon of novel system architectures and features of platforms. These are platforms to generate the data and platforms to share the data and provide early-warning systems. Again, the organisation is the same, and it is easy to describe but very difficult to set up. You generate the data on site, you merge the data and you integrate the data, and this is where it becomes difficult, and then you are able to transfer the data. The point I want to make with this information is this. What has been perceived initially only a few years ago as something which will only be possible for so-called developed countries is now absolutely amenable to emerging and developing countries.

Finally, there is an important action which again illustrates the potential of this innovation. This is what we call the Pasteur Health Genomic Centre. It means that selected institutes of the network provide bio-banking capacities that deal with regulatory constraints, ethics and economics. Then we provide these selected institutes with the capacity to generate data on site instead of transferring the samples to France, to the US and to other countries. Then they must share the data with a computer biology based information system.

We cannot do this by ourselves. We are in the era of partnerships and this is a clear example of the need for governance rules. We are interacting with the Gates Foundation on this, with the Sage Bionetworks and also with industrial partners. This is a case where we have to share the information but also to meet with constraints, with confidentiality, with intellectual property and with overall security.

To close, I would like to shift the topic for a moment. I believe we need to remain very humble with regard to technologies. There is a very interesting topic, which is intestinal microbiota. That means we actually have two genomes, which are the human genome and what we call the bacteria genome. There is about 1.5kg of bacteria in our intestines, and the interplay between these two genomes is really shaping our personality and our features. They are very important for a number of diseases, including so-called non-communicable diseases such as diabetes, obesity, cancer and neurological disorders.

Sequencing of the intestinal bacteria was impossible about 10 years ago. The progress of technology in sequencing has led to detailed analysis of these populations and it has contributed to a medical revolution which is ongoing. This is the capacity to transfer the gut microbiota from one animal to the other and to transfer a given phenotype. This is now possible in humans. There is a very impressive *New England Journal of Medicine* paper.

This shows what happens when you have patients with *clostridium difficile*, which is very difficult to treat. You can compare those who have received a faecal microbiota transplantation from patients who have recovered from *clostridium difficile*. You can compare them with those who were treated with antibiotics. There is a huge difference, and those who received faecal microbiota from recovered patients recovered themselves.

The point I want to make is that this is excellent, but if you look at this, this is an old concept that has been revisited. It was well known in veterinary medicine and it was well known by the Chinese during several Chinese dynasties. The point is that in some cases, what technology really allows us to do is to make a reappraisal of old concepts, but this is not a problem. This is to the benefit of the patient.

To close, again, we speak of technology and we speak of automation, but we should never forget that individuals will be at the heart of creativity. When we recruit young scientists, we want them to be modern, but we want them to keep the ideas of the founder, Louis Pasteur. There is a painting from Magritte which is called ‘La Clairvoyance’, and I like it because it really shows that technology has made huge progress. It is a real revolution, and obviously, I have only shown a part of it. We have seen the applications, and we are paining the bird, but we are still looking at the egg. What we hope for the coming years is to be able to have this transition from the egg to the bird, and this is what the Pasteur Institute is very committed to, with its partners.