Round table discussion

The 2nd round table discussion on development of new medicines for neglected tropical diseases: From bench to bed, achievements and challenges*1

— Partnerships, treatments and NTDs: 2005 to 2018, 13 years of change —

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(Saturday, May 12, 2018, IDEC Inc. conference room, Tokyo, Japan)

*1 This article is the extract of "Part 1" of the round table discussion composed of Part 1: mainly Prof. Croft's lecture in English and Part 2: discussion in Japanese. Full version in Japanese is included in *Clinical Evaluation.* 2018; 46(2).

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Abstract

Just a little over a decade ago, research and development (R&D) for neglected diseases was stagnant. Since then, neglected tropical diseases (NTDs) have been defined, product development partnerships (PDPs) have been established, and private and academic sectors have been mobilized to work together. This has brought about a huge movement that has grown around NTDs. PDPs have acted as an effective catalyst in encouraging Pharma and academia to engage in these diseases, various forms of innovative public private partnerships have been developed, and new treatments are in the pipeline.

Much has been achieved over the past 13 years, but we have still got work to do. Sustaining not just the funding but sustaining the expertise is a real issue. Involving disease endemic countries in drug R&D is also an important challenge. PDPs, government, Pharma, academia will all remain responsible for ensuring that developed drugs are used effectively in the settings of poverty or broken health systems. All drugs created and approved need nurturing.

In the middle of these huge changes globally, Japan has demonstrated great potential with its government's commitment and the dedicated efforts by top-level scientists. As global R&D into NTDs and other neglected diseases is advancing, increased efforts are needed to secure funding for further innovation, ensure effective use of developed drugs, and promote partnership-based R&D models. Japan is expected to continue making significant contributions as one of the key players.

Key words

product development partnerships (PDPs), neglected tropical diseases (NTDs), research funding, research and development (R&D), innovation

Rinsho Hyoka（*Clinical Evaluation*）. 2018；46：W55-W73.

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Simon L Croft has worked on the discovery and development of anti-infective drugs for over 35 years in academia, industry and public-private partnerships (PPPs). Recent funding from WHO, EU, MRC, UK DFID, Medicines for Malaria Venture and the Bill & Melinda Gates Foundation has given Simon the opportunity to engage in research from the discovery and development of novel drugs and formulations for the treatment of leishmaniasis, malaria, human African trypanosomiasis (sleeping sickness) and American trypanosomiasis (Chagas disease), to operational research on disease control and implementation. Projects on miltefosine, AmBisome® and topical paromomycin, reached clinical trials for the treatment of leishmaniasis. Current research interests include PK PD relationships, predictive models for drugs and vaccines, topical formulations and drug resistance. From 2004 to 2007 Simon was the first R & D Director of the Drugs for Neglected Diseases *initiative* (DND*i*), Geneva and from 2008 to 2014 he was Dean of Faculty of Infectious and Tropical Diseases at the LSHTM.

Source: https://www.lshtm.ac.uk/aboutus/people/croft.simon

1. Introduction

Hirabayashi Today we are very happy to be able to have a round-table discussion, titled "The 2nd round table discussion on development of new medicines for neglected tropical diseases: From bench to bed, achievements and challenges", with Prof. Simon L Croft, taking this precious opportunity as he was invited by Nagasaki University, and with our colleagues engaged in activities concerning Neglected Tropical Diseases (NTDs) (Table 1).

The reason why we say "the 2nd" is because we previously in 2005 hold a round-table discussion of the same title, which was published in *Clinical Evaluation* (*Rinsho Hyoka*)*9.

Today's discussants are mostly the same as the previous time: Prof. Haruki Yamada, Prof. Kiyoshi Kita, Dr. Chris Brünger, and this time Mr. Daisuke Imoto attends. As we wish to make publication in Japanese, so some part discussed in Japanese is published only in Japanese version but presentation by Prof. Croft and some part discussed in English is to be published through the journal web-site.

We look forward to fruitful discussion. So, Simon, please start your presentation, after brief self-introduction.

2. Six significant changes

Croft I am at the London School of Hygiene and Tropical Medicine. I have now been working on drug discovery, drug mechanisms of action,

*9 Croft SL, Yamada H, Otoguro K, Kita K, Hirabayashi F, Brünger C. Development of new medicines for neglected diseases. *Clinical Evaluation*. 2005; 33(1): 109-35.

Table 1　"Neglected Tropical Diseases (NTDs)" in the WHO's web-site

"Neglected tropical diseases (NTDs)" is explained in the web-site of the World Health Organization (WHO): "a diverse group of communicable diseases that prevail in tropical and subtropical conditions in 149 countries – affect more than one billion people and cost developing economies billions of dollars every year. Populations living in poverty, without adequate sanitation and in close contact with infectious vectors and domestic animals and livestock are those worst affected." The following 20 diseases are listed by the WHO.

- Buruli ulcer
- Chagas disease
- Dengue and Chikungunya
- Dracunculiasis (guinea-worm disease)
- Echinococcosis
- Foodborne trematodiases
- Human African trypanosomiasis (sleeping sickness)
- Leishmaniasis
- Leprosy (Hansen's disease)
- Lymphatic filariasis
- Mycetoma, chromoblastomycosis and other deep mycoses
- Onchocerciasis (river blindness)
- Rabies
- Scabies and other ectoparasites
- Schistosomiasis
- Soil-transmitted helminthiases
- Snakebite envenoming
- Taeniasis/Cysticercosis
- Trachoma
- Yaws (Endemic treponematoses)

Source: http://www.who.int/neglected_diseases/diseases/en/

drug development for diseases for malaria, trypanosomiasis, fungal infection, Chagas diseases and leishmaniasis for 38 years. I have also had experience in other areas of parasitology working overseas in Africa. My time with DND*i* (Drugs for Neglected Diseases *initiative*. https://www.dndi.org/) from 2004 to 2007 was as the R&D director, but I had previously been involved in the preparation of DND*i*, called DND from 2002 to 2004, and I have continued as a Scientific Advisory Committee member from 2011 to now 2018.

After leaving DND*i*, I had 6 years as the Dean of the Faculty of Infectious and Tropical Diseases at the London School of Hygiene and Tropical Medicine. After 10 years of management and administration, I decided return to research, and focusing drug development for a specific disease, cutaneous leishmaniasis, and I think we now have made some really significant advances and understanding of how to develop both topical and oral drugs for this disease. I also am engaged in control projects for visceral leishmaniasis in Asia and East Africa. I have also had the pleasure of rediscovering that my scientific brain is still there and I can do it. I have been fortunate to work closely with colleagues in Japan since 2005, including Kiyoshi, even being invited to his retirement party in 2016 which was the wonderful event, with Haruki since we first started working in 2005 the Kitasato institute where we first met, and Chris in 2004 in Kuala Lumpur before I was appointed actually to DND*i*; I also met Fumiko for the first time in 2005, and I met Kurihara-san, Saio-san, in 2005 as well.

It is wonderful to be here again, and also to know Chris is now in this wonderful office with the view which we cannot quite see. So thank you Chris, and thank you both Kiyoshi and Fumiko for organizing me and getting me here with various airplane/air-flight changes - we have managed to do it. So, I was asked by Fumiko in an email last week to reflect on these 13 years and I thought that at this meeting we would probably be talking about specific DND*i* changes, what has been coming through the pipeline, what significant impact we think DND*i* has made, and perhaps what we think is slightly overblown. So, what I was thinking

Table 2 Patterns of Changes

- The NTD movement – advocacy and funding
- Increasing numbers and types of NTDs and demands
- The number of Players
- The roles of PDPs, academia, biotech and pharma
- Revision of clinical targets and profiles
- Integration of diagnostics/biomarkers

about, was reflecting on, was that DND*i* is not alone and it is operating within a world of change. And I have listed here what I think have been six really significant changes over the past 13 years in the world in which DND*i* lives and has to exist, which is important because DND*i* like all organizations can think it is the only player in the world, but it's not, it is inter-acting with many other organisations (Table 2). I think there are six areas that made a big impact on neglected tropical diseases, to which DND*i* has exploited in some ways but could do better in.

3. The NTD movement

Although NTDs were put on the research agenda at beginning of 2000's when DND*i* being established in 2003, we first met in Japan in 2005 and talked about the role of Japan in neglected diseases. Since then a huge movement has grown around NTDs; it is both an advocacy and a public health movement called the NTDs*[10]. There have been backing with large funding from the Bill & Melinda Gates Foundation; this and other support is recorded each year in the G-Finder Report*[11] published by a group called Policy Cures Research*[12]. It's interesting to note that the title of this latest report is "reflecting on a decade of global investment". There has led to the commitment by 10 pharmaceutical companies and others who actually engaged not necessary in discovery, but in a major donation of drugs (London Declaration)*[13]. There have been key advocates - Peter Hotez in USA, David Molyneux and others from UK- who have really ensured the new leadership and from other organisations like Sightsavers and many others have become involved.

Since then a huge movement has grown around NTDs; it is both an advocacy and a public health movement called the NTDs.

4. Increasing numbers and types of NTDs and demands

During this growth of the NTD movement, two different types of neglected tropical diseases have been defined: There is Preventative Chemotherapy and Transmission Control NTDs (PCTs)*[14], really the neglected diseases for which there are already drugs, vaccines or diagnostics. So this mass drug administration (MDA) has been the lead for many soil transmitted helminths - STHs. There is also a clearly defined number of innovative and intensified disease management NTDs (IDM)*[15]. These are the NTDs for which new tools are required –

*10 See Table 1.

*11 g-finder. http://www.policycuresresearch.org/g-finder/

*12 Policy Cures Research. http://www.policycuresresearch.org/

*13 Uniting To Combat Neglected Tropical Diseases. London Declaration. http://unitingtocombatntds.org/

*14 World Health Organization. Neglected Tropical Diseases, Preventive Chemotherapy and Transmission Control (PCT). http://www.who.int/neglected_diseases/preventive_chemotherapy/information/en/

*15 World Health Organization. Neglected Tropical Diseases, Innovative and Intensified Disease Management (IDM). http://www.who.int/neglected_diseases/disease_management/Innovative_Intensified_Disease_Management/en/

human African trypanosomiasis, leishmaniasis, Chagas disease and Dengue. There are other diseases, like the fungal infections Mycetoma, recently added to the WHO NTD list*[16], Cryptococcus and others, for which, for which new tools, drugs, vaccines and diagnostics are also required. There is a bit of spit in the camp actually about where the priority should lie and people like David Molyneux insist that we have all that is needed and we don't need to invest in new research just focus on applying what we have. This is not my view, not the view of many others.

5. Landscape of Players and Roles

5.1 PDPs as catalyst

Over the past 15 years, since 2003 when DND*i* was established and to some extent before since Medicines for Maria Venture was established by in 1999, a key strategic objective for any organization is to understand the landscape of players (Fig. 1) – there is the private sector, the funders, the evaluators, and academic groups, who have transformed their activities, as well as PDPs (Product Development Partnerships).

PDPs have taken a central role in building interactions and leadership. Unless you understand who to work with, what strengths and weaknesses each organization has, and how to work with them, and working with them is essential, then you are missing a trick and you could become isolated. For example, you know that WHO provides an important role to enable engagement with endemic countries so we work with them for that. We know that the private sector has a profit motive, but we have to work with them and we have to work with them effectively and we have to adapt our culture to their culture.

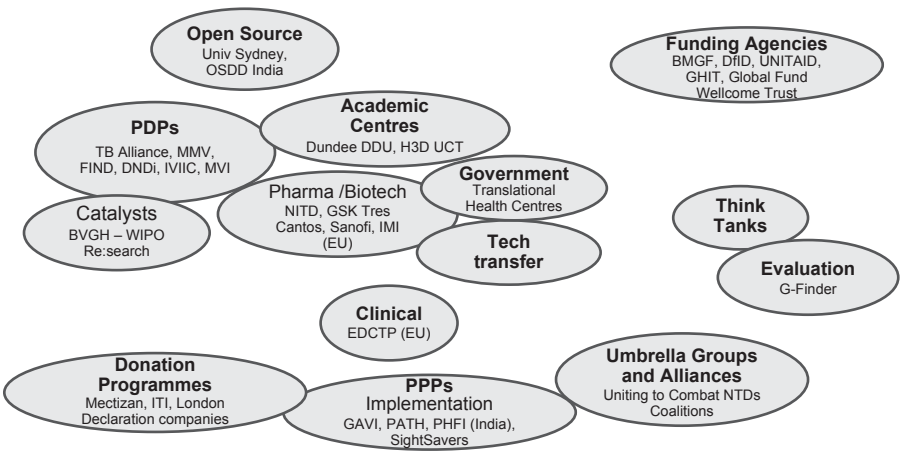
What actually are these PDPs like DND*i* and MMV (Medicines for Malaria Venture) ? and what have they done? In the past 13 years the portfolios of discovery and development projects have really grown. Initially, both MMV and DND*i* took on projects which were "low-hanging fruits", for example, drug combinations and re-purposing drugs from one indication to another. A number of

*16 World Health Organization. Buruli ulcer, Mycetoma. http://www.who.int/buruli/mycetoma/en/

functions of PDPs are listed on the box (Fig. 2); I consider one of the most important jobs that MMV and DND*i* have done is to act as a catalyst.

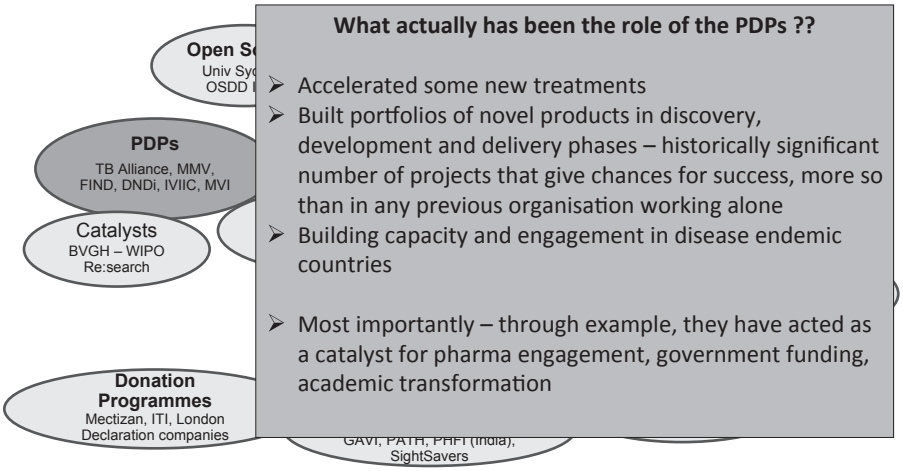
They have shown by example what can be done. They have encouraged academic groups to reshape themselves to be involved actually in drug discovery. But most importantly, they have encouraged the biotech and Pharma sector to re-engage in this whole area, additional funding from governments, like the UK government, and other philanthropic

Fig. 1 Academic - private sector - public partnerships need to understand the Landscape of Players (1)



The nature of relationships and how/where/when collaborations and partnerships are required is built around an understanding of who is in the relationships

Fig. 2 Academic - private sector - public partnerships need to understand the Landscape of Players (2)



The nature of relationships and how/where/when collaborations and partnerships are required is built around an understanding of who is in the relationships

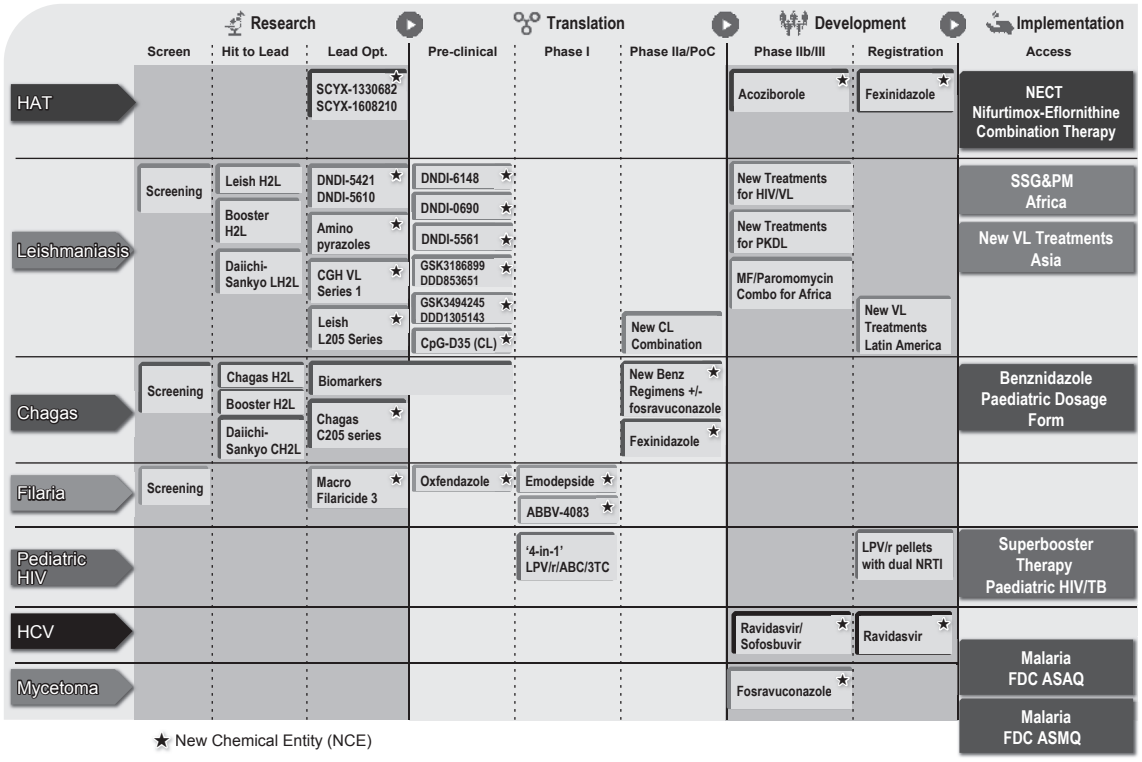
organizations, and shown the way for new organizations like GHIT(Global Health Innovative Technology (GHIT) Fund). They have acted as a catalyst. I think that role is often ignored. People recognize what PDPs have done when they look at the portfolio but their role as a catalyst has been ignored, and I think there should be more emphasis on that role.

5.2 PDP portfolio and clinical targets

As far as the number of players, I would like to consider some other aspects of it. 13 years ago we could never have envisaged - I think we had hopes, we had plans, we had dreams, but we could have never envisaged the scale and impacts of the PDPs. I have just used the example of MMV, which is an easy example, because this PDP is focused on one disease, has a lot of funding and a clarity around strategy and objectives.

Just looking at the portfolio of the number of projects now in the pipeline, never in a history of drug discovery and drug development, has there been such a focus and concentration to enable such a comprehensive portfolio to be built*17. The importance of a portfolio for MMV and DND*i* (Fig. 3)*18 is that it enables choice around which projects to progress, and which ones to drop, it encourages decision making which is supported through target product profiles and clinical candidate profiles. For drug development malaria is not one disease.

Fig. 3　DND*i* R&D Portfolio June 2018



Source: DND*i*

*17 MMV-supported projects. https://www.mmv.org/research-development/mmv-supported-projects

*18 DND*i*. PORTFOLIO. https://www.dndi.org/diseases-projects/portfolio/

Malaria, needs drugs for prophylaxis as well as treatment, and for eradication it needs novel drugs to kill gametocytes and act on liver stages.

This is the same with DND*i*. We can consider the demands for new treatments for leishmaniasis – there is not just visceral and cutaneous disease, we also need treatments for HIV-visceral leishmaniasis co-infections and PKDL (Post Kala-azar Dermal Leishmaniasis). For Chagas disease, it is important to understand that a drug is not just for treatment or cure, but should actually be effective to prevent the disease progression, from the indeterminant asymptomatic stage to the chronic debilitating stage. The sophistication relating to disease complexity has to be considered within the structure of the portfolio, so when we talk about the portfolio in relation to choice we are actually considering choices. This extends to also enabling the more sophisticated thinking about which combinations of the drugs might be suitable for specific forms of diseases. And that's important when we consider not just treatment but also disease control, elimination and eradication.

5.3 New models of partnership

So this changing world has also involved not just the development of PDP portfolios also given encouragement to Pharma to be engaged. It has encouraged development of other forms of public private partnership. It was the GHIT Fund*[19] which I have just illustrated which is really the first successful public private partnership for which government and Pharma have taken a major role in creation, compared to DND*i* which was created by MSF (Médecins Sans Frontières), and MMV which came from WHO/TDR.

And there are also what I call NTD dating agencies, if you understand how "dating agency" translates into Japanese.

The BVGH*[20], bio-ventures for global health partnership which acts as a dating agency to enables Pharma, biotech and academics to come

*19 GHIT Fund. https://www.ghitfund.org/
*20 BIO Ventures for Global Health. https://bvgh.org/

together around compound libraries and disease models; BVGH success is in the hundred and nine, collaborations agreements that they have arranged over the past year (2017).

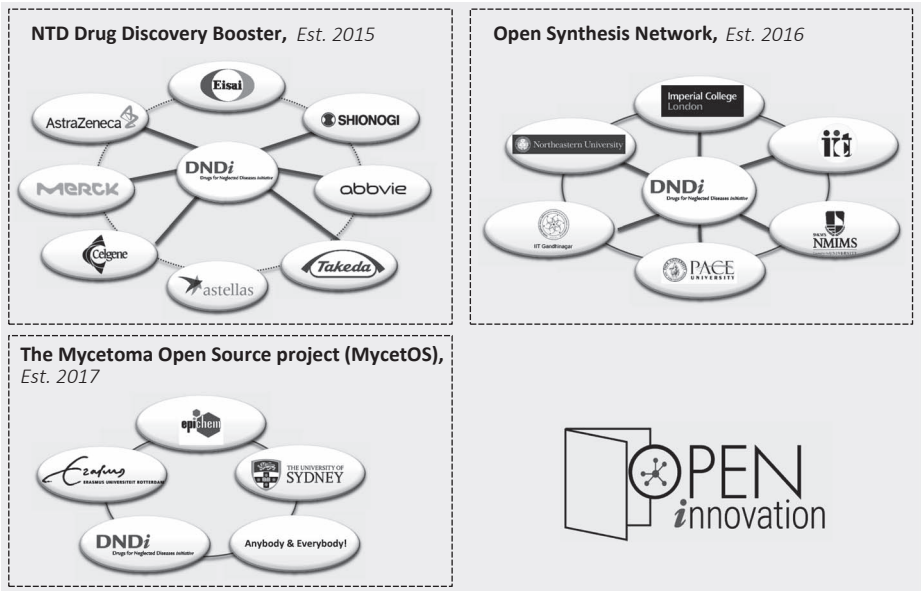
There are other models which have been developed. GSK has developed an open lab at Tres Cantos for interaction with the private sector in a precompetitive setting. TB drug development remains a very big challenge, unfortunately. I think the public private partnership set up originally also 14 years ago, TB Alliance*[21], has not been so successful in terms of its output. The Bill & Melinda Gates Foundation has supported a TB drug Accelerator, led by Ken Duncan (ex-GW), which is another form of bringing together people and projects from the biotech, Pharma, academic and clinicians from endemic countries, to accelerate the R & D process. It is a different form of partnership. A similar "accelerator" model is now in place in DND*i* (Fig. 4).

5.4 Pharma impact

If when Chris, Fumiko and I were sitting together in 2005, and we had said that 10 years later over 5 million compounds would have been screened against leishmanias and trypanosomes others might have thought we were not just dreaming but lying. This was such an outrageous idea but it actually has happened.

The past 13 years has seen advances in technology to enable such high through put and content screening (HTS/HCS). We actually engaged, in 2006, with the Pasteur Institute in Seoul to start and HCS project. Now it's not just DND*i* but also two European Pharma companies, GSK and Novartis, that have really turned on the tap. GSK Tres Cantos also led another initiative, when in 2010 they published all the data on their anti-malarial compounds and made their library an open source – the first company who has done that. In 2015 they published all the data on their screening against try-

Fig. 4　Some of DND*i*'s Open Innovation Projects



*[21] TB ALLIANCE. Engaging Civil Society at the UN. https://www.tballiance.org/

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panosomes and leishmanias. So this openness is a welcome additional change. They have obviously been doing some cherry-picking and working with the drug discovery unit at Dundee University (UK). They now have two pre-clinical candidates for leishmaniasis and are also working on Chagas disease. Novartis, through the GNF laboratories in San Diego, have screened 1.5 million compounds against some of these parasites and identified some novel leads which they worked on further. But they not only have found an interesting compound which is shown in one of the figures, they also identified the parasite proteasome, as the primary drug target. This is the first time in any parasite that proteasomes have been identified as a key target which enabled them to search for other compounds against that target.

DND*i*, working with SCYNEXIS, have also identified a novel compound, an oxoborole, which is now in the Phase II clinical trials for human African trypanosomiasis. Initially this came about, through the close interactions DND*i* had with MMV in the period from 2004 to 2007, with frequent meetings to exchange ideas about drug development. During one meeting, Carl Craft who was the MMV CSO - Chief Scientific Officer (now DND*i* SAC) mentioned that one company he knew, Anacor, had some interesting compounds; Anacor was set up by some of Carl's ex-colleagues. Through that contact with MMV, DND*i* gained access to the Anacor boron-based compounds. Regular exchange, both formal and informal, enhances interaction between organizations with benefit to all.

5.5 Rules and structures for the academic private sector partnership

With these changes, developments and interactions, there are some rules and behaviours to be observed not related to health.

In all sorts of sectors where PDPs operate, from metreology, to education and transport, there are rules. Now most academics and most Pharma companies and biotechs understand that rules of col-

Chris Brünger, Daisuke Imoto

laboration, of agreements, recognizing the importance of concepts of licensing and a concept of confidentiality, that publication is important for Pharma companies, PDPs and academics - when the time is right. This is all been a part of the real change in the interactions and has been formalized. I remember when I worked for DND*i* spending many afternoons with the lawyer, trying to understand how royalty-free license agreements could be reached with partners. There are only some organizations like European Union, WHO where bureaucracy makes it difficult, where academia does not understand; in some way working with Pharma can be easier as the endpoint is clearer.

5.6 Different understandings of "Innovation"

So, the other change which links all this that word "innovation" and what it means. Innovation has become one of the keywords that has been so used in the past decade, everyone wants to innovate. But again, it is important to understand concept of innovation means different things to different groups, that an understanding the language of innovation is essential.

If you are talking to government you need to show that your innovation is going to be positive for economic development. So for the UK government as a donor, research on leishmaniasis is also something that ensures better relations with India and Japan, which would benefit the country through economic links, and give value for money. When working with the WHO, we have to adapt our language to show that the aim is to solve a public health problem which will help to lift people out of poverty. Whereas, for industry and the private sector, we aim to work within the pre-competitive space and we understand that beyond that stage involves a different negotiation and endpoint. So this blanket term called "innovation" has to be subtly adapted for each purpose.

5.7 Changes for academics

And with this change of language, academics, like Pharma people, have had to adapt to and has made some changes.

One of the changes, not mentioned so far, is that there are now groups in academia who have actu-

ally recruited ex-pharmaceutical industry researchers, because companies like Pfizer and Astra Zeneca have closed their infectious disease units; these highly-skilled ex-Pharma scientists have been a bonus for academia and PDPs including DND*i*. One of the most successful units is within a biomedical research institute at the University of Dundee, with one anti-malarial candidate and two anti-leishmanial candidates. So, it can work, but requires a different form of leadership, and working with academics having to adapt.

6. Outstanding issues and the future

6.1 Sustaining the expertise

But we are not at an end by any means. There are still some challenges (Table 3).

The main challenge I think that worries people is funding, because success can mean, like for human African trypanosomiasis, a tick in a box that the disease is now controlled and no more research is needed. 15 years ago, leprosy was so called eliminated, a tick was put in the box, all funds research were withdrawn. Yet today we have increasing transmission of leprosy in India, Brazil, the Philippines. There are all these issues that, in English we call "taking your eye off the ball", it's a cricket term, take your eye off the ball, then you know the disease will come back. Most infectious disease will be eliminated (that means reduced to a very low level of transmission), but not eradicated.

So sustaining this, sustaining not just the funding but sustaining the expertise. In India now, because they think that leishmaniasis is going to be eliminated, there might possibility be no new generation of scientists working on Kala Azar. Many of my generation are retiring and there are fewer new people coming through. I think this a real issue, not just sustaining the funding but the sustaining the expertise, sustaining the excitement of working across the Pharma – biotech - academia sectors. There's also still the important challenge of involving disease Endemic countries in drug R & D. There are some good examples. India and Brazil that have set up their own translational health institutes which is good; ASEAN countries have developed a program for neglected disease, which has as yet not moved off the drawing board; commendably DND*i* has set up a drug discovery accelerator in Latin America. And Prof. Kelly

Table 3 Outstanding issues and the future

1. Sustainable Models for Academia and the Private Sector Beyond "donation" and government intervention, is there a sustainable model for private and public sectors, given commitments to R & D of some pharma, eg Novartis, GSK, Novartis, and Biotech, and Biotechs, eg AnaCor, SCYNEXIS
2. Involvement of disease endemic countries Do disease endemic countries have the capacity for drug R & D and centres of excellence ?
3. Sustaining elimination and control eg HAT and VL Do we have TPPs for safer drugs ? Do we have process to integrate them with diagnostics into surveillance/outbreak systems ? Or should we focus on Vaccines ?

Haruki Yamada, Kiyoshi Kita

Chibale, a Zambian chemist, has set up a centre in Cape Town, South Africa working on TB and malaria; he has the first anti-malarial drug to come out of an African laboratory. So, it can be done but more effort needs to be made.

Sustainability is the issue, and we know that, linking in with this sustainability, there has to be the possibility with many of the diseases, a rapid response. Nothing has shown it more clearly than the Ebola crisis three years ago. It does not have to take so many years for a drug or a vaccine to be implemented in a clinical crisis.

Actually when it came to this major crisis they thought this disease might affect the West as well as, not just some west African countries.

It's got to be people who have the ability and knowledge to be able to rapidly transfer that industry pharma skill into public health. And again, I fear that if there are too many ticks in the boxes and with that we are going to lose the connections and expertise. We have been fortunate having people like, Profs. Kita and Yamada who have worked across the sector who have also worked in Africa and South America - who have that experience.

6.2 Connect development to implementation

Then the last point, as we have to always remember and understand that all the drugs we are developing have to be used in the settings where there is poverty or broken health systems, for example, Afghanistan, Syria, and some central American countries. What we as scientists have been doing and what we still do is we try to develop efficacious drugs - we focus on efficacy. But this difference between efficacy and effectiveness has to be clearly understood - what works not in the clinical trials Phase III and Phase IV, but what works in the village.

We know that there are examples from India for Lymphatic Filariasis. There is a donated drug, albendazole from GSK, - 700 millions tablets a year are sent to endemic countries for MDA. But when it came to the analysis of lymphatic filariasis areas an eastern state of India, only 40% of the vil-

lages are receiving the drug, because their health systems are not good enough. And of 40% who received the drug, only about 40% of the people were taking the drug for a whole variety of reasons. It is always important for all of us to consider that we are trying to make not just efficacious treatments but think how new drugs will be used, along with the new vaccines and new diagnostics, and we should not leave it too late. This was one of two important lessons I learnt from DND*i* linked to the target product profile. The second lesson, also emphasized by an ex-GSK colleague, was always to look at the whole process, the whole system, from compound to the patient and community, for what you need has to be appropriate. So that is really my view of the context.

So my view, within the context of 13 years on is that we have still got work to do as well as reflecting upon the huge changes that have occurred. With DND*i*, I think the success of DND*i* is having two new drugs for human African trypanosomiasis, that two drugs reached the clinic for Chagas disease, that a number of successful drug combinations have been identified for visceral leishmaniaisis. For VL, the success is also to have three pre-clinical candidates to move into clinic in the next years and to work with Novartis and GSK-Dundee to support their novel drugs through for this disease, a real boost for collaboration for NTDs. So, there have been significant changes, but there are still big challenges: how to use vaccines, diagnostics, drugs, how to integrate meta-surveillances and response systems.

＜Discussion＞

Impact of new HAT-specific treatments in DND*i*

Yamada So, we would like to ask your opinion how is the impact of the outcome of research and development by activities you have mentioned.

Croft Regarding the impact of new treatments, ASAQ (Artesunate/amodiaquine) and NECT (Nifurtimox-Eflornithine Combination Therapy) combination for are established treatment for sleeping sickness. The impact of SSG/PM (Sodium Stibogluconate and Paromomycin) is limited. It has been approved in Sudan but has a mixed impact. Pediatric benznidazole has not taken off in its implementation in South America, because of difficulties with production and delivery of benznidazole. For new treatments, there is a claim that DND*i* was involved at single-dose AmBisome where possible and with the combinations. Hence, there is a mixed picture of impact.

Brünger We understand this level of detail, but that is not enough. I want to know how many tablets of ASAQ and ASMQ were produced, where they were delivered, how many patients were reached, and what the impact was. There was a video of the launch of ASMQ in Brazil, which showed in flashy images the impact on children, workers, etc. I put together a proposal to track this, because ASMQ was supposed to be introduced into the healthcare system. The healthcare system in any country is about counting things – counting how many tablets were delivered, how many workers, schools, and patients were reached and what the difference was in terms of the number of malaria attacks over a 1-year period and so on.

DND*i* should insist that partners produce these data and publish them. There are many different mechanisms for collecting, reviewing, and assessing the data. There is a word in Japanese "*ikuyaku*" （育薬） which means that after you've created a drug and it's approved, you need to nurture it, collect more data, and improve its usage. But there is no nurturing team for DND*i*'s new drugs that I am

aware of.

I don't think that department needs to be within DND*i*. If, for example, the government of Brazil is one of the key users of one of the combination therapies, something should be set up with that government function.

Drug delivery and community involvement

Clinical Evaluation　In view of ethics, the 2016 revision of the CIOMS guideline has a strong argument about the community engagement[*22]. At the time of planning the clinical trial in developing countries, you should clarify planning of community engagement focusing how this developed product should become affordable for the people. From the time of decision about which compound and community that you start the clinical development until the approval, this community should be involved. As you mentioned, we should track whether this developmental strategy is successful or not. There should be a statistical program to count the tablet how much it was sold to the market and/or the government.

Brünger　DND*i* drugs are not sold; they are just distributed. It's not about affordability but about the mechanisms for delivering the drugs to patients who need them ensuring that drugs are being used appropriately.

Croft　A prime example of what could be done is the NECT combination for sleeping sickness, because the procurement is all done through MSF. They can count what comes in and what goes out. The distribution is also organized with WHO, so it's a narrow channel. Yes and the countries using them are limited. MSF's have their procurement group in Bordeaux who has the numbers. MSF's job is not to do the evaluation.

[*22] CIOMS (Council for International Organizations of Medical Sciences). International Ethical Guidelines for Biomedical Research Involving Human Subjects. 2002.

Closing remarks

Croft I am interested in the topic about ensuring that when drugs or new treatments do come through, that an organization has the responsibility to ensure that they are used effectively whether that is following up with pharmaceutical companies like Sanofi that is taking on fexinidazole. They have a responsibility, especially when public money from Japan, from UK, or from the Gates Foundation has been used to get that far. If you are not doing it yourself, ensure that the delivering organization is going to do that.

It's good to hear that there is an increasing awareness of NTDs in Japan. The G8 has been a wonderful motivator. I do review frequently for G8. One of the things I always look at is the inclusion of the Japanese group. There is coherent possibility of working as a proper partnership. There are honorable activities in Japan e.g. by BT Slingsby who led the launch of the Global Health Innovative Technology (GHIT) Fund. He also led global strategy for the developing world at Eisai & Co, for their new business models of R&D and market access.

Imoto DND*i* might be able to receive a grant from the World Bank shortly for the first time for a project in the Democratic Republic of Congo. If the current negotiation goes well, the Bank would provide a grant of approximately 3 Million USD to DND*i* to support community-based activities that will reinforce health system capacity for detection, diagnosis and treatment of sleeping sickness (HAT) at the community level and strengthen the community's engagement in HAT control. It will take advantage of a new oral treatment already having completed phase 3 clinical trials and the screening tests that are more rapid. The grant, however, will not be used for conducting clinical trials. The World Bank is a financial institution that always puts an emphasis on the outcome that is achieved from the investment it makes. If the project was materialized, the Bank would closely look at its achievement to see if DND*i* can be perceived as a partner going forward. The conclusion of the Bank would be dependent upon the ability of DND*i* to report the development impact with concrete numbers - the Bank would possibly conclude that it is not worth working with DND*i* if there was no clear ex-post data.

Yamada Today, we had a very fruitful discussion for NTDs drug development - what we could achieve and what we could not achieve during last 13 years, and what we have to do next. I am convinced that PDPs have a special role for this drug development, and we have to make further efforts for the construction of the systems to overcome several barriers to the partnerships among the public, private sector and academia players through better understanding of our mission. These include sustainable research funding systems such as GHIT Fund, and the improved role of academia that can contribute to the fundamental research such as natural product research, mode of actions of the NTD drugs and finding new drug targets. To realize these, I expect certain screening centers to be established to evaluate compounds against NTDs in Japan as contact points to accommodate the requests from the academia and private sectors who wish to contribute to NTDs drug development, and also research collaboration between academia and private sectors, as we have already experienced (Table 4). To gain wider understanding of the partners, we also need to make a system returning the data to the partners on how many patients could benefit from the use of the developed dugs and treatments.

Kita Thirteen years have passed since the previous round-table discussion[*9]. Although situation

Table 4　Collaborations with Japanese partners

Year Started	Projects	Partners in Japan	Diseases
2005	Kitasato Screening project (natural products)	Kitasato Institute	HAT
	Ravconazole project	Eisai	Chagas disease
	Ascofuranone project	University of Tokyo	HAT
	Nitroimidazoles－1 project	Tokushima University	HAT
2006	Pan-Asian Screening Network	Kitasato Institute	HAT, Leishmaniasis
2009	E1224 Clinical development project (South America)	Eisai	Chagas disease
2010	Kala-azar Research Centre collaboration (Bangladesh)	University of Tokyo, JICA, JST	Visceral Leishmaniasis
	Microscopes donation project (Leismaniasis East Africa Platform)	Kyorin University, University of Tokyo, Olympus, Warehouse TERRADA	Leishmaniasis
2012	Drug Discovery Research collaboration （re-purposing)	Astellas	Chagas disease, Leishmaniasis, HAT
2013	Emodepside project	Astellas	Filariasis
	NTDs Drug Discovery Consortium research support	Astellas, Nagasaki Univeristy, University of Tokyo, National Institute of Advanced Industrial Science and Technology, Tokyo Instiute of Technology, High Energy Accelerator Research Organization	Chagas disease, Leishmaniasis
	GHIT Screening program*	Eisai,Takeda, Kitasato University, Institute of Microbial Chemistry	Chagas disease, Leishmaniasis
2014	CpG-D35 project (* started in 2016)	Osaka University, GeneDesign, Nagasaki University	Cutaneous Leishmaniasis
2015	NTDs Drug Discovery Booster*	Eisai, Shionogi, Takeda	Chagas disease, Leishmaniasis
	Aminopyrazole project*	Takeda	Visceral Leishmaniasis
	Fosravuconazole clinical development (Sudan) (*started in 2017)	Eisai	Mycetoma (Eumycetoma)
2016	Screening program*	Daiichi Sankyo	Chagas disease, Leishmaniasis
	Screening program (natural products) (* started in 2018)	Daiichi Sankyo RD Novare	Chagas disease, Leishmaniasis
	Preclinical efficacy of CpG D35 combination therapy*	GeneDesign	Cutaneous Leishmaniasis
	Identification of new drug targets*	RIKEN	Chagas disease, Leishmaniasis
2017	NTDs Drug Discovery Booster II*	Eisai, Shionogi, Takeda	Chagas disease, Leishmaniasis
	Preclinical study of CpG D35 combination therapy*	GeneDesign	Cutaneous Leishmaniasis
2018	NTDs Drug Discovery Booster III*	Eisai, Shionogi, Takeda, Astellas	Chagas disease, Leishmaniasis

* Funded by GHIT　　HAT: Human African Trypanosomiasis

has become better, products are not sufficiently provided. We must seriously think about how to speed up further and improve efficiency. I think we should not be satisfied with current situation.

It is said that Japanese young people are inward, but it is not really true. So I think people will join more and more in this area if we create a place where young people can be active and have a successful experience. Although it is not NTDs, for example, discovery of EML4-ALK causative gene of lung cancer by Dr. Hiroyuki Mano (National Cancer Center Japan) and drug discovery based on it was launched in a very short time. I think we can do it, too. I'd like to speed up to a couple of times in the next 5 years and make use of the experience accumulated so far. Looking back on the 13 years at this point, having such a discussion is very important. I would like to further strengthen and promote partnership so that further efforts in various fields will be fruitful and further development

will be promising.

Hirabayashi There have been the really significant changes over the past 13 years since the previous publication of round-table discussion[*9], as well as past 15 years since the establishment of DND*i*, which include major movements made by governments, international organizations, funders and pharma, and partnerships initiated by academia. All of these changes have led to substantial advances in R&D in to NTDs and other neglected diseases. As new drugs are being created and approved, ensuring fair access to the drugs and nurturing them is expected to become an increasing challenge. Building on the collaborations with diverse patners, we need to continue mobilizing efforts to develop drugs that are efficacious and work effectively in the resource-poor settings often with broken health systems.

We had fruitful discussions today and hope to have another roundtable in future to review achievements.

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