SCIENTIFIC ADVISORY BOARD

Report of the Fifth Meeting

Virtual Teams session, December 14, 2021

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(Approved by the SAB on 25 January 2022)

Introduction

This document details Lygature's Scientific Advisory Board (SAB) discussions on December 14, 2021, regarding trends and developments that impact the scientific strategy of Lygature. It comprises two parts:

PAGE 3-4:
Details the task and composition of the Lygature Scientific Advisory Board and the agenda of the meeting.

PAGE 5-9:
Provides a write-up of the discussion session and summarizes the board's conclusions.

This report is made publicly available through the Lygature website to inform all Lygature stakeholders.

Task and composition

On Tuesday, December 14, 2021, the fifth meeting of the Lygature Scientific Advisory Board (SAB or 'the committee') was held. Due to the ongoing COVID-19 pandemic, this meeting was held virtually via a Teams meeting with an adapted agenda.

The SAB is appointed by the Lygature Board of Directors. Its task is threefold:

1. On an annual basis, to advise on the coherence of Lygature's project portfolio, provide feedback, and identify opportunities for cross-fertilization between projects in the various domains
2. To provide input on the development of new public-private initiatives from an international perspective, building on the strengths of the Dutch Life Sciences & Health sector
3. On an ad hoc basis, to review project proposals that will be submitted by Lygature to various consortia funders (e.g. Bill & Melinda Gates Foundation, Japanese GHIT fund)

The members of the SAB together span all dimensions of Lygature's activity: scientific discipline (medtech, pharma), geographic scope (national, international), organizational structure (public, private), etc.

The members of the SAB present in the meeting were:

- **TON RIJNDERS** PhD (Chair), former General Director Oncode Institute, former Scientific Director Lygature and TI Pharma
- **ROB WILLIAMS** PhD, Chief Drug Development Scientist at the Centre for Drug Development, Cancer Research UK
- **LAURENT DEGOS** MD PhD, Professor Emeritus of Hematology at University of Paris, Diderot Hospital Saint Louis, Paris, founder and first President of Haute Autorité de Santé, and past Vice President of the Pasteur Institute and Curie Institute
- **SJAAK DECKERS** PhD, Venture Partner at NLC Health and CEO of Microsure
- **TOMAS SALMONSON** PhD, partner at Consilium Salmonson & Hemmings, former chair of the Committee for Human Medicinal Products at the European Medicines Agency

Agenda

The meeting was divided into two discussion sessions:

1. Update on the highlights and progress since the last meeting
2. Outside-in discussion on scientific and societal trends

Bert Leufkens (Scientific Leader), Jon de Vlieger (Business Development Director), Alexander Duyndam (Director Communications & External Affairs) and Jorg Janssen (Managing Director) from Lygature participated in the Scientific Advisory Board meeting. For the discussion on the Unite4TB project, Lygature Program Managers Janneke Boere and Remco de Vrueh joined the meeting.

1. Highlights and progress since last year's meeting

The meeting started with an update on the progress made since the last meeting on October 14, 2020.

First, the impact of the discussion topics in the 2020 meeting on Lygature's progress was reflected on. The first topic was the observed positive effect of the pandemic on public-private collaboration and global health issues. This is illustrated, for example, by a change in sentiment in the Dutch parliament towards public-private collaboration, potentially large investments via the Dutch National Growth Fund, and new projects in the global health portfolio such as Unite4TB (see below for details). Another topic discussed last year was patient engagement the further involvement of people with direct experience of health challenges. This has been made tangible in various research projects for example, with the Patient Advisory Board in RADAR-AD and a publication on how to make the patient voice heard based on experiences in the APPROACH project.

Other topics discussed at the 2020 meeting were the need for regulatory innovation in advanced therapy areas. This topic was on the agenda in various sessions of the Regulatory Science Network Netherlands (RSNN), including 'The route for ATMPs from bench to bedside' expert meeting. Artificial Intelligence (AI) was another topic of discussion that is now a crucial element in various new projects (BigPicture, Unite4TB and AI4NTD). AI was again discussed in this year's meeting (see Part 2 of this report). The importance of inter-institutional data sharing was also stressed in the 2020 meeting, and projects such as FAIRplus, EOSC-Life and BY-COVID are good examples. The National Growth Fund investment in the Dutch data infrastructure through Health-RI is a great step forward.

Since the 2020 SAB meeting, various new projects have been started, some already mentioned above. In the Data Infrastructure portfolio, the BigPicture IMI project was started to establish a large database of pathology images to accelerate the development of artificial intelligence in medicine. With Horizon Europe funding, the BY-COVID project was initiated to tackle data challenges that can hinder effective pandemic responses. Within the Strategic Asset Sharing portfolio, two new IMI projects started: PERSIST-SEQ, a research project aiming to build a reproducible single-cell sequencing workflow to capture tumour drug persistence, and EPND (European Platform for Neurodegenerative Diseases), which aims to change the future of neurodegenerative disease by removing barriers to data sharing and collaboration.

In the Global Health portfolio, a great result has been achieved with the successful completion of a Phase III trial of arpraziquantel. New consortia included the AI4NTD (Artificial Intelligence for Neglected Tropical Diseases) project, funded by partners and the Johnson & Johnson Foundation, which aims to develop an integrated AI-driven digital pathology platform that is affordable, accessible, and scalable in low resource settings for the diagnosis and surveillance of neglected tropical diseases. Another new project in this portfolio that was discussed in detail in the 2021 SAB meeting is Unite4TB, which is part of the IMI AMR Accelerator program.

New project: Unite4TB

Unite4TB is a public-private partnership with representation from academic institutions, small- and medium-sized enterprises (SMEs), public organizations, and pharmaceutical companies. Over the next 7 years, the consortium will be active in approximately 40 trial sites on four continents (Europe, Asia, Africa, and South America), with the goal of delivering novel phase 2 clinical trials that will accelerate the development of new Tuberculosis (TB) drugs and regimens. Achieving this goal will facilitate fulfilment of

one of the main unmet needs in the TB field: better-tolerated drug regimens of shorter duration that can be deployed to tackle tuberculosis across various drug-resistance patterns and co-morbidities.

The goals and organization of this large project, which has a total budget of EUR 185 million, were presented. The most innovative therapeutic TB compounds will be incorporated in new treatment regimens and these regimens will be included in the clinical trial platform. Selecting the right compounds for specific regimens is of strategic importance for the success of the project and a task where Lygature will facilitate discussions.

Biomarkers are an important element of the research and artificial intelligence (AI) will be used to find patterns in order to obtain better predictions of potentially successful treatments. Via this route, the chances phase 3 trials failing after successful phase 2 trials should be reduced. Early dialogue with the regulatory agencies on adaptive trial designs and how to implement AI techniques in such a way that they can be included in the dossier will be crucial.

The committee pointed to the importance of connecting with regulatory leaders in the TB field in Europe's national agencies given their insights into historical failures in TB treatment. In addition, the Unite4TB initiative will develop its relationships with other initiatives such as the PAN-TB collaboration. The committee congratulated Lygature on its role in this large and important endeavor.

2. Outside-in discussion on scientific and societal trends

As part of its preparation for the meeting, the committee was asked to think about scientific and societal trends that will have an impact on public-private collaboration and the Life Sciences & Health sector in particular. A range of topics was discussed, with the main points presented below grouped in five areas.

The first focuses on the funding landscape and the innovation climate in general. The second focuses on major trends seen from a content perspective, with the third and fourth focusing on two major topics emerging from these trends that merit additional attention: artificial intelligence and clinical trials. The fifth and last area covers learnings from the COVID-19 pandemic.

The main conclusions drawn by the SAB in these five areas are listed below. Each one is discussed in more detail later in this report.

- The dynamics in the funding landscape, combined with the COVID-19 impact and other factors, is creating a challenging innovation climate
- Societal impact and patient centricity, together with a noticeable shift to preventative care, will be important elements influencing the direction of future research areas
- Artificial intelligence is in vogue, with both strong as well as hyped examples – managing data sources is key
- COVID-19 has had an enormous impact on executing clinical trials – new forms of trials may offer solutions, but progress is slow
- Learnings from COVID-19 should be assessed internationally and public engagement used to rebuild trust in science and governments

2.1 The dynamics in the funding landscape, combined with the COVID-19 impact and other factors, is creating a challenging innovation climate

Looking at general trends, there are large dynamics in the funding of innovation. In terms of private finance, it is becoming increasingly difficult to raise money from investors. In an attempt to protect their portfolios, private investors are decreasing their investments in new innovations to reduce their exposure to risk. At the same time, demonstrating proof-of-concept through clinical trials has become challenging because hospitals are currently overloaded (see also section 2.4). The combined direct and indirect impact of the COVID-19 pandemic on clinical trials is enormous, hampering progress. This is especially true for international studies, which are now extremely difficult to run due to the changing COVID measures in different countries.

Despite this, international collaboration is very much needed. This can be seen, for example, in cancer research, which is increasing in scale, funding (typically 20 million British pounds for 5 years), and scope. The Cancer Research UK Grand Challenges, executed jointly with the US National Cancer Institute, are a clear example. International collaboration is also needed because the donation landscape is becoming much more competitive.

The discussion also alluded the difference between the funding of institutions versus the funding of partnerships. Different trends are visible. In France, charities in areas such as cancer and AIDS have not

changed their policies. In other areas there is clearly consolidation, leading to larger funding initiatives with a clear focus on collaboration. It was concluded that for the moment there is no clear trend in how this will evolve further.

Another factor that is creating challenges for innovation in Europe is the new European Union Medical Device Regulation (EU MDR). There is a huge backlog in approvals, primarily caused by the requirement for re-approval of existing medical technology devices. This is resulting in companies choosing the U.S. as a market for first entry instead of Europe.

2.2 Societal impact and patient centricity, together with a noticeable shift to preventative care, will be important elements influencing the direction of future research areas

With respect to content, the main trend is greater emphasis on societal impact. This trend dominates the political agenda, which might hampers focus on scientific progress itself. Patient centricity is on the other hand a key positive element in this.

New strategies in different organisations and in various countries put much more emphasis on early diagnosis and disease prevention. The questions of how to reach the poorer population and how to address lifestyle issues such as obesity, smoking, and alcohol abuse are a high priority on the agenda. The ethical implications of these priority changes and their impact on research agendas need further discussion.

This overall trend clearly moves beyond the traditional life sciences disciplines. It requires the social sciences to become much more involved. The need for interaction is evident and making the connect between these various disciplines is a challenge in itself. Translating patient priorities and preferences is also an important element, in which public and private players need help.

Another contributing factor is the point-of-care transition from hospitals and general practitioners towards home-based environments. This puts the question mentioned above, about how to reach the various population groups, on this agenda as well.

2.3 Artificial intelligence is in vogue, with both strong as well as hyped examples – managing data sources is key

An area which merits special attention is artificial intelligence (AI), which was also extensively discussed in the 2020 SAB meeting. Its importance has been recognized in various projects started over the past year that Lygature is involved in, as illustrated in section 1 of this report.

In general terms, AI is currently in vogue and has become such a buzzword that it is hard to distinguish between hope, hype, and hysteria. However, there are clearly good examples of putting AI to use. AI can help to identify patterns in medical images, a strong example being the use of AI by start-ups to find patterns in tissue images without the requirement to use contrast agents. Considering the toxicity of many contrast agents, this benefit could have a huge impact on patients, and from a business perspective a sizeable impact on the imaging market.

Another area where AI is being put to use is model-informed drug development. There is clearly progress in this area and step-by-step it is becoming accepted by regulatory bodies such as the EMA, the FDA, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). In addition, AI and deep learning are having, and will have, an impact on digital health.

One of the keys to using AI is the availability of data. However, access to appropriate data raises complex issues, especially when its commercial use is part of the equation. A good way to translate pre-competitive and competitive use in research could be to distinguish between developing algorithms resulting from research (pre-competitive) and using these for validation in industrial or commercial settings (competitive).

This could be much better organized for the advantage of European research. Understanding the nuances and explaining them will be key to moving beyond today's polarisation in the AI debate. This could be an area of interest for Lygature.

2.4 COVID-19 has had an enormous impact on executing clinical trials – new forms of trials may offer solutions, but progress is slow

Some of the trends mentioned above are also noticeable in the area of clinical trials. Firstly, the negative impact of COVID-19 on the healthcare system is affecting these trials enormously, especially international trials as noted earlier. It goes without saying that for a range of diseases patients are waiting.

In line with the observed general trend, patient centricity is top of the agenda. Various factors contribute to this, such as the development of personal devices to acquire clinical endpoints and other digital health developments. Patient reported outcomes have also increased in importance and are now a key element. In all these areas, expert handling of (real world) data is crucial to building the dossiers and ensuring the trust of participating patients. Regulators are still conservative on this topic, although steps are being taken to make progress in this area.

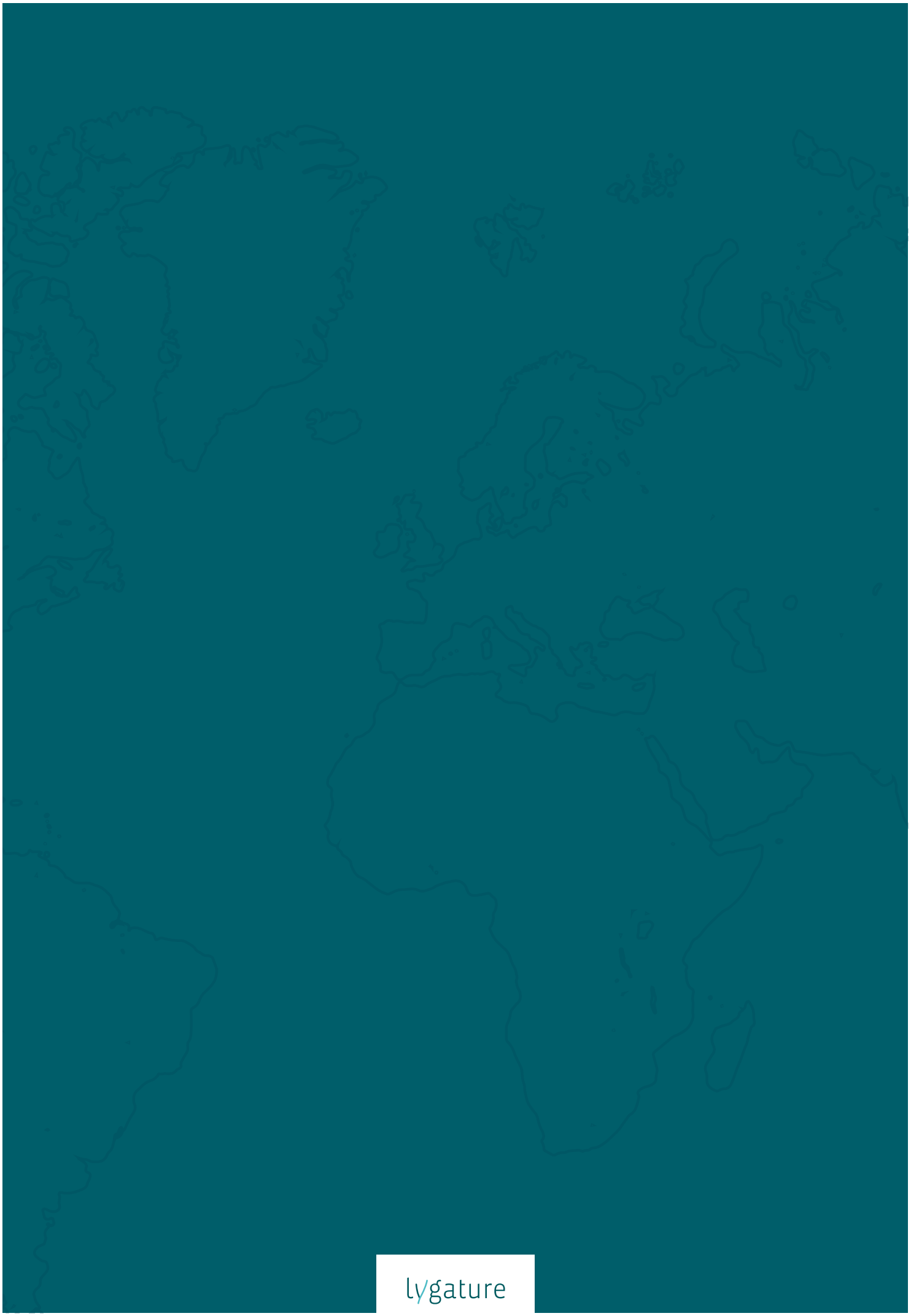
In addition, there is increased interest in new forms of trials such as decentralized clinical trials, hybrid trials, and augmented trials, to name a few. In augmented trials, for example, computer simulations are used alongside physical trials to reduce the amount of time spent testing treatments, the number of patients involved, and ultimately the cost. These new forms of trials could help solve some of the challenges affecting clinical trials.

2.5 Learnings from COVID-19 should be assessed internationally and public engagement used to rebuild trust in science and governments

International discussion and alignment on strategies has become more difficult, for example, in regulatory committees as each country is taking its own approach to tackling COVID-19. As a society at large, we should learn from the pandemic. We must assess where we were successful and where we failed, preferably including an open comparison between countries.

An already apparent societal need that has been emphasized by the pandemic and where there is need for improvement is patient information. COVID-19 has had the positive effect of better educating the general public on virology, immunology, and health in general. However, public distrust in governments remains, and this trust needs to be rebuilt after the pandemic, primarily via public engagement.

The 2021 SAB meeting concluded by expressing the hope that next year's meeting can be held face-to-face again. In addition, it is hoped that new members can add to improve the gender balance of the committee.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