NEWSLETTER

No. 4 - 2018

RSNN
Regulatory Science Netwerk Nederland

Dear Reader,

This is the fourth Regulatory Science Network Netherlands (RSNN) Newsletter. The RSNN, a network for experts from academia, government, the pharmaceutical industry, patient organisations and others involved in regulatory activities related to drug development, aims to facilitate activities in the field of Regulatory Science in the Netherlands by stimulating dialogue and collaboration, and sharing information and methods. The RSNN is aligned with other European platforms active in the field.

The RSNN Newsletter informs participants and stakeholders of activities and developments in the discipline. In this edition, we report on the Regulatory Science session on disease interception (BOX 3) held at the FIGON Dutch Medicines Days on October 2, 2017. In the morning, three excellent academic speakers provided examples of disease interception opportunities. In the afternoon, two speakers shared the industry and regulatory positions on disease interception.

In 2017 the executive board of the RSNN asked Lygature to come up with a plan to support the next steps needed to build a solid basis for the RSNN. We are happy to announce that a partnership agreement will be signed and financial support will be secured. You will find more details in this letter.

SAVE THE DATE:
20 June, 2018

RSNN REGULATORY SCIENCE WORKSHOP

Utrecht,
The Netherlands

CALL FOR AGENDA TOPICS: YOUR INPUT IS NEEDED!

FIGON DUTCH MEDICINES DAYS - REGULATORY SCIENCE MORNING SESSION

Dr. Christine Gispen-de Wied (Medicines Evaluation Board /vice-chair RSNN) welcomed all attendees and in her introduction took them back over the last two RSNN-events. On the agenda of these two meetings were:
1) the use of biomarkers in the diagnostic process or as a surrogate endpoint for treatment outcomes and
2) patient outcome measurements as endpoints that are of value to the patient.

In disease interception both topics play a role: how do we identify the best population (those that will benefit the most) and how do we define the outcome of the interception?

GUT AND MICROBES

As a first example of a potential technique that could be used in disease interception, **Prof. Dr. Ed Kuijper** (LUMC) introduced the attendees to the world of microbiota, the microbiome, and faecal transplantation.

The human gut microbiota has become the subject of extensive research in recent years and rapidly developing sequencing methods and analytical techniques are enhancing our knowledge of the resident gut species and their potential functional capacity [BOX 1]. Not all bacteria have been cultured yet, but a recent new approach, called culturomics,

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You can join by contacting:
Anke Kip
email: anke.kip@lygature.org

We also like to invite you to our LinkedIn group at:
https://www.linkedin.com/groups/8559430

[BOX 1] WHAT IS THE HUMAN MICROBIOTA?

The human microbiota is the collection of all microorganisms (bacterial, viral, or fungal) that live in a particular environment of our body. The human microbiota consists of 10-100 trillion symbiotic microbial cells harboured by each person, primarily bacteria in the gut. Collectively the genes of these microorganisms, that outnumber the genes in the human genome by about 100:1, are called the microbiome.
The study of the diversity of the human microbiome is as old as microbiology itself. In 1680, Antonie van Leeuwenhoek studied his oral and faecal microbiota and noted the striking differences in microbes between these two habitats and between samples from both these sites in healthy individual and patients. Today powerful molecular techniques help us to gain insight into why these differences exist, and how transformations can be made from one state to another (Ursell 2012).

has revealed many new bacterial species in healthy individuals (Greub 2012, Lagier 2016).

Based on new knowledge, it is now believed that bacteria of the gut microbiota are associated with several diseases, such as inflammatory bowel disease, diabetes, neurological diseases, and obesity. They are also thought to be associated with the successful treatment of cancer. A clear causal relationship with the aetiology of a disease has only been found for Clostridium difficile Infection (CDI) which is a serious infectious disease with some 120.000 infections per year in Europe, a mortality of 10-15%, and a recurrence rate of 20%.

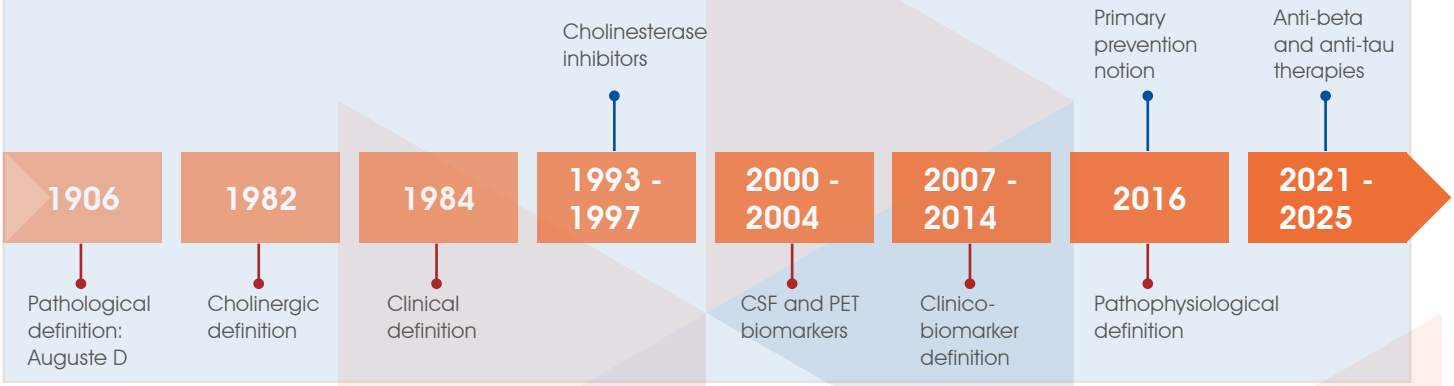
For a long time, managing CDI has been based on antibiotic treatment, although this is associated with frequent recurrences. Knowing that the microbial composition of the gut plays a role in the likelihood of developing CDI has opened the route to new intervention options based on changing the composition of the microbiome. In theory, this can be achieved by administration of beneficial microbes (probiotics) or compounds supporting the growth of beneficial microbes (prebiotics), or by transplantation with faeces from healthy individuals. The first two methods have not been proven effective in the treatment of recurrent CDI. Then five years ago there was a breakthrough when the third option, faecal transplantation, resulted in a cure-rate of 81% for recurrent CDI, and this after only one infusion of donor faeces.

Today, Faecal Microbiota Transplant (FMT) had become the preferred treatment for patients with recurrent CDI (van Nood 2013). To facilitate the use of FMT, the LUMC started the Netherlands Donor Faeces Bank (NDFB, see www.ndfb.nl) in 2016. The NDFB provides ready-to-use faeces samples obtained from a pool of well-screened donors. Patient selection is standardized; they are only eligible for FMT after careful screening of their clinical data by a gastroenterologist, an infectious diseases physician and a medical microbiologist. Up to March 2018, 70 patients have received FMT at several local hospitals; 87% of them were cured.

Clearly the success of FMT in the treatment of recurrent CDI is of high value to patients and society. The success has also inspired clinicians and researchers to look for new targets for treatment and to plan a lot of new studies, some of which are in cooperation with the pharmaceutical industry. Further research is needed into the long-term effects of FMT, the role of viruses and prions, the relationship with immune defence against immune system diseases and malignancies, and how intervention in the microbiota and in particular FMT can play a role in disease interception.



SUMMARY OF DIAGNOSTIC DEFINITIONS AND DEVELOPMENT OF THERAPIES FOR AD



BRAIN AND AMYLOID

The shift to disease interception is also a topic that is relevant in the ongoing efforts to prevent and treat Alzheimer's Disease (AD) [Box 2]. But, as **Prof. dr. Philip Scheltens** (VUmc) noted, the contrast with the previous presentation couldn't be larger: from gut to brain; from a clear success story to one where we have still very little to offer and are still far from disease interception. The need to go in this direction is clear however. Results from clinical trials in the last 10 years have almost all been negative, most probably because treatment started too late. Today's challenge is therefore to diagnose and treat AD earlier, before dementia sets in.

However, for a long time this was not possible since AD could not be diagnosed properly. It was not until 1984 that the criteria for diagnosis were formulated, but still only in the form of clinical symptoms; no biomarkers or signs of what is happening in the brain. But now this has changed enormously. Today we're able to diagnose the disease on the basis of the pathology. We can show the amyloid plaques on a PET-scan and we have biomarkers in the form of pathological changes in the cerebrospinal fluid. This development was picked up by an international group that is now working on a new framework of criteria using only biomarkers: the amyloid biomarkers (A), the tau biomarkers (T) and the neurodegenerative biomarkers (Jack 2016). So the new scheme is solely based on biomarkers (ATN profiles) regardless of the presence of signs and symptoms.

This will help to diagnose Alzheimer disease much earlier because the neuropathological changes of AD precede the symptoms by many years. Moreover, actual knowledge of the disease cascade gives us the opportunity, as we do in oncology and other diseases, to focus on therapies as early as possible. So, dementia research will follow the oncology pathway of earlier detection and personalized/precision medicine. Several recent research projects have adopted this new approach. One concerns a β-secretase inhibitor that prevents the formation of toxic amyloid β. Another one, that Philip Scheltens was particularly excited about, is the development programme for aducanumab, an investigational treatment for early Alzheimer's disease. Data from a recent phase 1 trial with aducanumab showed reductions in amyloid plaque levels and even showed a dose related effect (Sevigny 2016). So, these are very promising results and they underline Philip's main message that in the fight against Alzheimer's disease we have to intervene early.

[BOX 2] ALZHEIMER'S DISEASE

The global impact of AD is huge. In 2015, there were 47 million people with dementia worldwide; every three seconds a new diagnosis is made. We have known the disease for a long time since Alois Alzheimer described in 1907 a patient with memory problems, language problems and behavioural changes. He also described in 1907 the main characteristics of the disease: the amyloid plaques and the neurofibrillary tangles.

BENEFIT-BASED MEDICINE

In her introduction of **Prof. dr. Frank Visseren** (UMCU), Christine Gispen-de Wied indicated that we would now focus on the issue of who to treat and who not. When we know who to treat, prevention and interception can become more effective and cost-efficient. According to Frank Visseren, to answer the 'who question' it is essential to predict the risk of developing a disease and to predict the effect of treatment in individual patients. This could be viewed as benefit-based medicine. As an example, he referred to the risk of a cardiovascular (CV) event. Not all patients who have had a CV event have the same risk for a new one. The recently developed SMART-risk score can now be downloaded in Appstores ('vaatrisico') and calculates the 10-year risk of a recurrent vascular event based on reliable predictive criteria, such as age, cholesterol level, blood pressure etc. So, no fancy biomarkers are needed. Secondly, we have to predict the effectiveness of treatment for each individual patient. We know that not all patients will benefit equally from the same drug, although the drug will have been proven effective on average. And that's the point: "You are not average" as the voice-over says in the video clip for U-prevent, a tool to determine someone's individual health profile (U-prevent app). So, we must continue to perform randomized controlled trials, but afterwards we should try to translate the results of these clinical trials into gain of disease-free life for individual patients at risk. Then the patient and doctor know what they may expect as a return on the investment of taking medication every day. To researchers, industry and regulators, Frank made a passionate plea for individualizing the results of large trials and for the use of more appropriate and simple ways of expressing the effects of new medicines, instead of only average (relative) effects on large groups of patients: "Help doctors to translate the results of large trials and cohort to individual patients. That will accelerate Precision Medicine. The right treatment for the right patient!"

Someone in the audience was very pleased with his point of view on prediction, because she saw it as an intermediate step towards personalized medicine. After all, it comes down to shared decision making. For that, precise and individual information is needed on risks and expected individual benefit of drug treatment. It is important that a patient can make an informed decision on whether or not to start certain treatment.

During the short plenary discussion that followed, Christine Gispen-de Wied noted that all speakers had focussed on the importance of what is relevant for the patient. For regulators, this is a new way of thinking. Another notable trend within academia and the clinic seems to be the shift from treating disease towards prevention of disease. Both conclusions formed an ideal warming-up for the afternoon session in which industry and regulators commented on the topic from their perspective.

FIGON DUTCH MEDICINES DAYS - REGULATORY SCIENCE AFTERNOON SESSION

The afternoon session was introduced by **Just Weemers** (Pfizer Netherlands). His take on the three morning academic presentations and the discussion was that we have to make sure that patients' treatment is based on their risk profile and their prospect of benefitting from the drug. In the afternoon session, two other speakers shared their industry and regulatory views on this and the role of disease interception.

Starting-off was **Paul McCleverty** (Head of Oncology Johnson & Johnson). To Paul, disease interception is the right-time-component of personalized medicine and he prefers to talk of early therapies based on a biomarker diagnosis before the start of symptomatic disease (early detection). If we look at oncology, diabetes, and dementia, there is a huge need, both from the patient perspective and the healthcare provider perspective to get involved in disease interception. But the development pathway is data-driven and takes many years. In the 1950s cholesterol was identified as a risk factor for cardiovascular disease, in the 70s the first statins were given to humans, and in 2009 the first guideline on cholesterol "interception" in CVD was produced. So, we need to go faster and engage all stakeholders to ensure that the challenges of developing, approving and conducting HTA assessments of novel medicines in this new disease interception setting are in place. Also we need to develop tools and guidance on the identification of the right individuals eligible for disease interception. This guidance should also address why early interception is needed, and why one should not wait. What is the clinical and pharmacological rationale? What are the legal questions? Is the interception reimbursed? What is the evidence that the interception is better than a later intervention? How does all this balance out with the benefit/risk of the interception and most importantly the needs of the individual/patient? Also, how do we design interception studies? For this we first of all need to identify risk factors/mutations that are specific and biomarkers and surrogates that are specific, sensitive, validated, cost-effective, and practical. We also need new modelling techniques, statistical analysis, and other

[BOX 3] DISEASE INTERCEPTION

In disease interception one is focused on the root cause of disease, and on intervention before diagnosis with the aim of stopping, reversing, or inhibiting the progression to disease. Generally, the definition of interception relies on three key factors (McCleverty 2017):

1. Ideally the individual should have no symptoms of disease. If they do have symptoms it may well be too late for disease interception.
2. You should be able to detect a medical marker that can be seen before the patient develops disease symptoms.
3. You should then be able to treat medically and stop the individual from having disease symptoms based on the detection of this marker.

Based on this disease interception can be defined as:

A therapeutic intervention in the asymptomatic phase of a disease based on the detection of markers of early disease.

An example would be if you detected high cholesterol in someone following a blood test. There are no symptoms as you cannot see or feel high cholesterol. However, if left untreated, this would be a contributor to future cardiovascular disease, leading possibly to heart attack or stroke. If you gave this person a drug that reduces their cholesterol before a CV event, this treatment would be called disease interception. In this example, the patient has no symptoms, cholesterol is the medical marker and the treatment is intercepting the cardiovascular disease before it can develop. This meets the three key factors mentioned earlier.

One area of common confusion is the difference between disease prevention and interception. It may be useful to refer to the three key factors. If a person's disease is prevented, they would have no symptoms and so would meet one of the key factors. But there are no medical markers or medical treatments and, as such, prevention does not meet these same definitions.

ways of including subjects in studies. Clearly these are all very challenging issues! So, there is a lot to do and it will not be easy, but it is worth working on.

Then **Prof. dr. Bert Leufkens** (UU/ chair RSNN) was given the floor to address the regulatory perspective. In line with Paul McCleverty, he also highlighted the enormous challenge for regulators.

Everyone aims at prevention; it is very cost-effective to prevent serious diseases. Who could possibly object to early detection, early intervention, or early interception? In his view the interception concept is really new and everything comes down to four important issues:

1. Can we identify the right population that will benefit?
2. What type of outcome measure is acceptable?
3. Who may benefit? and
4. What is the comparison?

In conclusion, Bert stated that in his view it is not only a scientific discussion; it also concerns society at large. We have to show that these new concepts may be the answer to some current medical needs and should not forget the lessons learned from earlier experiences in the treatment of diabetes and cardiovascular diseases (statins).

During the plenary discussion, all the perspectives presented during the day were examined further. Just Weemers stated that the long list of questions to answer isn't for him depressing at all; it is something that has to grow and RSNN is the right place to discuss this and to create more awareness where needed. Bert Leufkens noted that at the moment there is a big gap between what science can deliver and the needs of regulators. Christine Gispen-de Wied stated that the Medicines Evaluation Board (MEB) can also learn from internal discussions in the past in an attempt to close this gap.

To put it back to the context of the Regulatory Science Network Netherlands, Just Weemers stated that today's topic fits in very well: "We don't have the science yet to answer most of the questions mentioned today, but we have the network as created two years ago to discuss these with a multi-stakeholder approach. And that is where it starts."

SAVE THE DATE: REGULATORY SCIENCE WORKSHOP 2018

This summer, the RSNN will again organise a Regulatory Science Workshop. The aim of the meeting is to provide a platform for information, sharing of knowledge and discussion. The central topic of this workshop will be the role of Summary of Product Characteristics: who should participate in its development and updates; patients as well? And should data be added that are not collected in a traditional manner (e.g., real-world data, off-label information), and if so how?

As always the day will start with several lectures, followed by breakout sessions and a plenary discussion. The sessions are interesting for various disciplines. There will be ample opportunity for both formal and informal networking during the workshop, drinks, and a dinner.

Date: June 20, 2018
Location: Utrecht, The Netherlands

Further details will follow!

PARTNERSHIP AGREEMENT

In 2017, the Executive Committee of the RSNN asked Lygature to develop a plan for the next steps needed to build a solid foundation for the RSNN, by extending collaborations with partners (academia, the government, pharmaceutical industry, patient organisations, and other disciplines) that are involved in regulatory activities related to drug development, and by making these relationships sustainable; and then together with these partners sharing the responsibility for the further (financial) support of the RSNN.

In October last year, Lygature presented the draft strategic plan and the organisational structure of the RSNN. The draft plan was approved by the Executive Committee. In the following 3 months, Lygature was instrumental in securing the financial support needed and also in finalising the legal framework of RSNN. The outcome of that work was presented at an RSNN Executive Committee meeting held in February 2018. A partnership agreement between Lygature, the MEB, the University of Utrecht, and the Vereniging Innovatieve Geneesmiddelen will be signed that will secure the funding and the needed management support. The latter will be the responsibility of Lygature. To open it up for the wider community involved in the regulatory sciences, the agreement is set-up in such a way that other stakeholder representatives and academic partners will be able to join by signing an accession form.

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WEB LINKS

- AETIONOMY 2017. www.aetionomy.eu
- DIRECT 2017. http://www.direct-diabetes.org/project/
- EPAD 2017. http://ep-ad.org/
- IMI 2017. http://www.imi.europa.eu/projects-results/success-stories-projects/btcure-project-insights-connect-bone-cells-rheumatoid
- U-prevent app. www.youtube.com/watch?v=D5HdXNp6iaI
- Lygature. www.lygature.nl
- Medicines Evaluation Board. www.cbg-meb.nl
- Vereniging Innovatieve Geneesmiddelen. www.verenigginnovatievegeneesmiddelen.nl

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