MEDICINES

#1
Volume 11
October
2020

Independent magazine for drug research

Medicines is
the news magazine
of Figon

Regenerative pharmacology

Taking organs-on-a-chip to the next level

In this issue

The FIGON Dutch Medicines Days (DMD) are held online this year, throughout the fall of 2020. Check out the webinars at figondmd.nl. Keynote speakers are presenting their topics in this issue.
▶ Page 10-27

Clémence Ross-van Dorp

This former Dutch State Secretary, and keynote speaker at the DMD, was appointed Ambassador for the Dutch life sciences and health sector. She is strengthening national networks.
▶ Page 10

Towards humans-on-a-chip

Regenerative pharmacology allows an entirely new perspective on human physiology, health and disease. ‘These new methods are more closely related to the intact human body.’
▶ Page 20

Single-Use Event

Register via single-use.nu/event/register

Single-Use Event 2020

CORPUS | Leiden | November 10

On November 10th at location CORPUS in Leiden suppliers and users will meet at the ultimate networking event in the world of bioprocessing, biotechnology and (bio)pharmaceutical manufacturing. You are welcome to view and test new products, network with key suppliers in the single-use industry, and attend presentations about the latest developments in single-use.

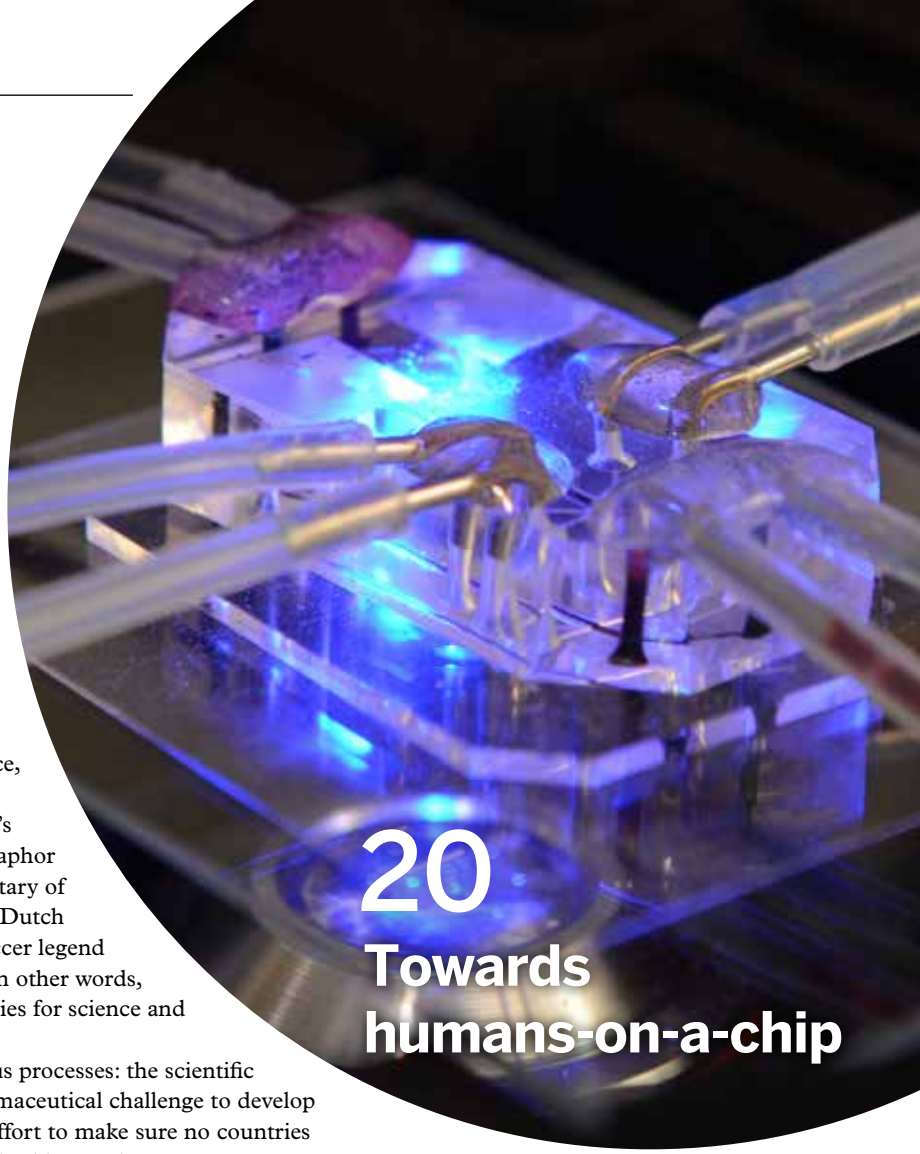
[C2W] MENS MOLECULE MEDICINES

3M ELSCOLAB ondis HAMILTON Parker VAISALA cytiva CPC ANSERS

SARTORIUS PALL Biotech avantor FLOWMEISTER PHCbi M·FILTER

SOLARIS ESI Cell-tainer CerCell greiner I.LABEL WATSON MARLOW Endress+Hauser YPSO FACTO

It takes an entire team



The battle against COVID-19 is like the Olympics: a gargantuan international effort with high personal, economic and emotional stakes. In fact, since the Olympics were cancelled this year, COVID-19 seems to have taken their place. It keeps us addicted to our news sources. It is the talk of the day. And it brings together science, policy, business and societal organisations.

Clémence Ross-van Dorp, keynote speaker at this year's Dutch Medicines Days, frequently uses the sports metaphor (see the interview on page 10). The former State Secretary of Health, Welfare and Sport, currently ambassador for a Dutch action programme on life sciences and health, cites soccer legend Johan Cruijff: 'Every disadvantage has its advantage.' In other words, there are opportunities in this global crisis. Opportunities for science and pharma, and for international policy and cooperation.

The current global pandemic seems to speed up various processes: the scientific effort to understand the virus and its effects. The pharmaceutical challenge to develop a vaccine and optimal treatment. And the diplomatic effort to make sure no countries are left behind. It strengthens the feeling that we're all in this together. Ross-van Dorp: 'It takes an entire team. You can't do it on your own.'

These are the silver linings to the cloud that could in fact be very dark. After all, this is only the beginning, as virologist Ab Osterhaus cautions on page 28. This pandemic has only just started – and it is mild, with a virus that is not particularly deadly nor infectious. It is only a matter of time until the world experiences an outbreak of a virus that is as deadly as Ebola and as infectious as the common cold.

Against this gloomy background, it crucial to recognise today's golden opportunities – and use them. The organisers of the Figon Dutch Medicines Days 2020 have taken this task to heart. With their ambitious programme – online, of course, in the form of webinars throughout the fall – they offer an inspiring glimpse into the developments in the field. Not only into the scientific and pharmaceutical advances, but also into the growing cooperation worldwide.

A great deal of optimism comes from the presentations by the younger generation of scientists: the candidates in the Figon PhD Student Competition (pages 14-17). Optimism also surfaces throughout the talks on regenerative pharmacology (page 20) and physiologically-based pharmacokinetics by nestor Malcolm Rowland (page 24).

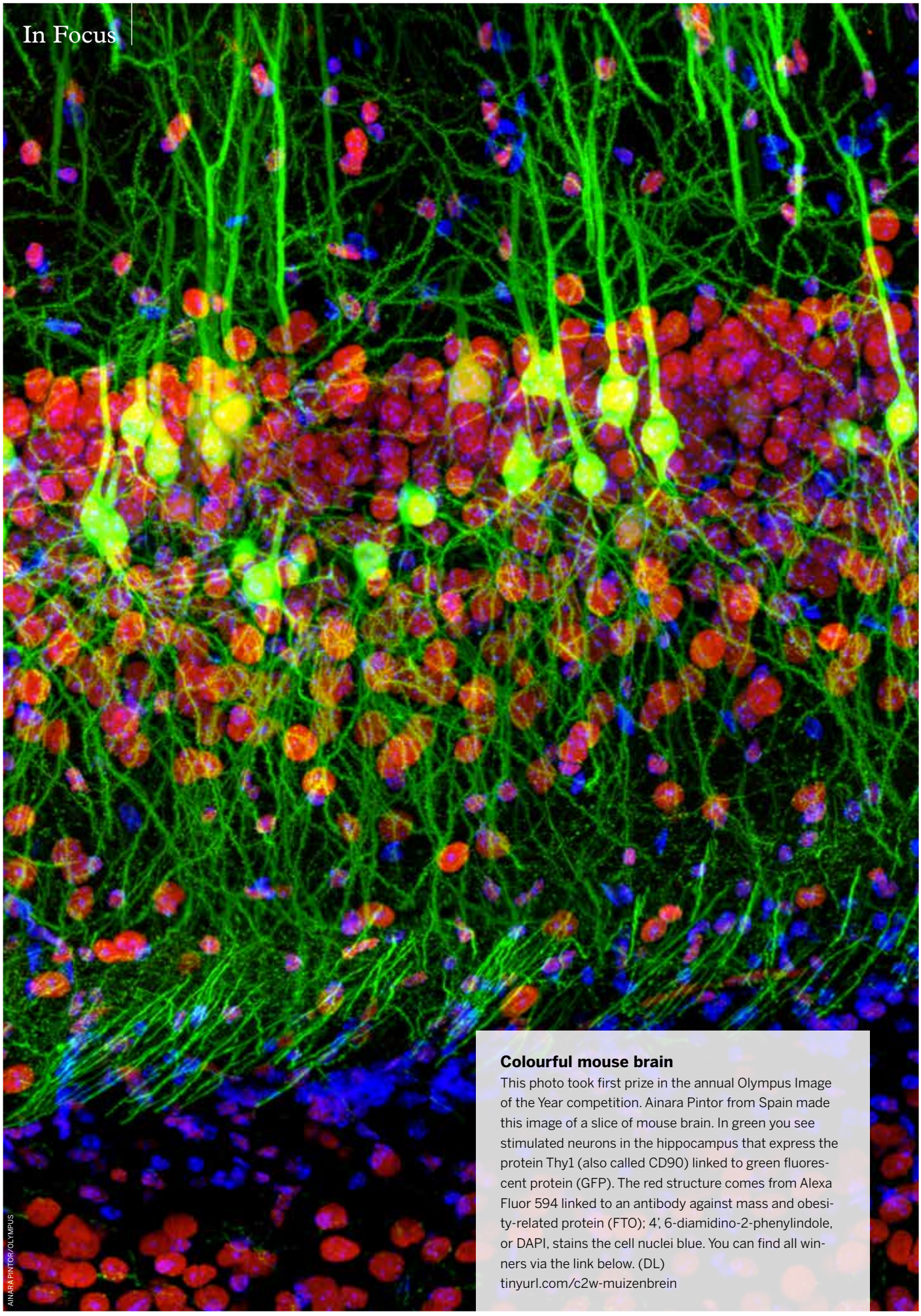
It remains to be seen when there will be an effective vaccine – and when we'll see Olympic silver and gold again. But in the meantime, there is a world of silver linings and golden opportunities. ●

Nienke Beintema, coordinator *Medicines*

n.beintema@vakbladen.com

Questions, comments or story ideas?

Please email us at redactie@vakbladmedicines.nl



AINARA PINTOR/OLYMPUS

Colourful mouse brain

This photo took first prize in the annual Olympus Image of the Year competition. Ainara Pintor from Spain made this image of a slice of mouse brain. In green you see stimulated neurons in the hippocampus that express the protein Thy1 (also called CD90) linked to green fluorescent protein (GFP). The red structure comes from Alexa Fluor 594 linked to an antibody against mass and obesity-related protein (FTO); 4', 6-diamidino-2-phenylindole, or DAPI, stains the cell nuclei blue. You can find all winners via the link below. (DL)
tinyurl.com/c2w-muizenbrein

The illusion of knowledge

The greatest enemy of knowledge is not ignorance but the illusion of knowledge. The current pandemic only emphasizes the importance of Stephen Hawking's famous quote.

Apart from all the misery it causes, you could define the corona crisis as a triumph for science. The public suddenly knows something about epidemiology, virology and medical research in general. Of course that's also a danger because this knowledge irrevocably promotes the idea that you can join in the discussion. But not everyone realises that following the news about COVID-19 for a few months does not equal a scientific education. 'The greatest enemy of knowledge is not ignorance but the illusion of knowledge', as has been written by Stephen Hawking and others.

This was illustrated perfectly by Donald Trump who, during a press conference in April, suggested injecting disinfectant. 'I see the disinfectant that knocks [SARS-CoV-2] out in a minute, one minute. And is there a way we can do something like that by injection inside or almost a cleaning? As you see, it gets in the lungs, it does a tremendous number on the lungs, so it would be interesting to check that.' That's according to the man who has a self-proclaimed 'natural instinct for science'. There was hardly enough space on social media for the panic among the real experts who begged people expressly not to do that.

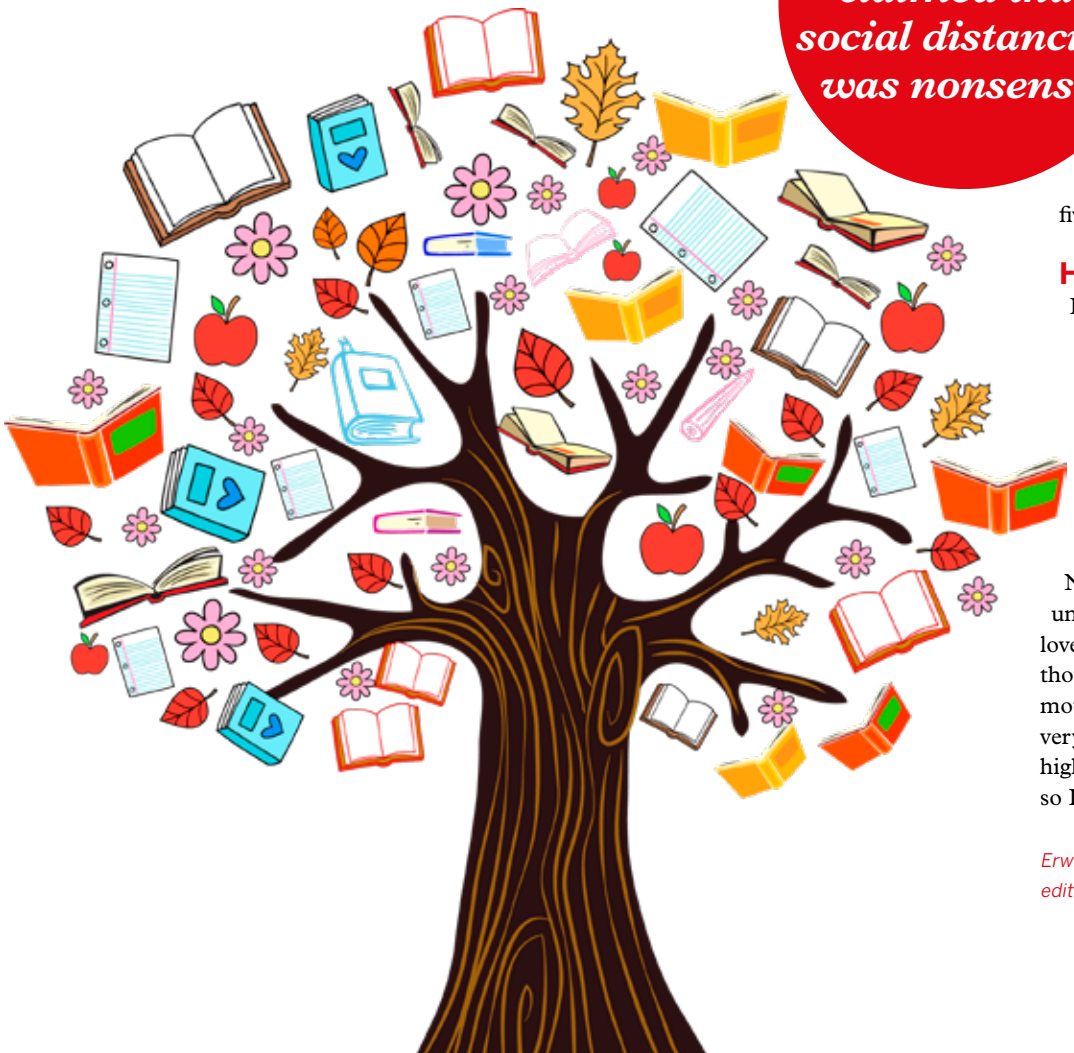
Interpretations

The illusion of knowledge is dangerous. Healthcare, which at that time was already overstretched in the United States, was inundated in the weeks after Trump's statement with patients with toxicological complaints after having injected themselves with bleach.

I see the same happening closer to home. I am unable to convince an acquaintance of mine – who firmly believes, based on chiefly right-wing media, that hydroxychloroquine is the solution to COVID-19 infections – that you cannot simply prescribe an unsubstantiated medicine. My arguments regarding double-blind randomised research, anecdotal evidence, medical ethics and statistics have fallen on deaf ears. He 'has read a great deal on the subject' and is now in possession of the dangerous illusion of knowledge.

And he is not alone. Also other friends and acquaintances make what I feel are far too authoritative statements on COVID-19 based on what they have read in the media, or on the basis of 'their own research'. They conclude that the government's guidelines are excessive and subsequently live by their own interpretations. Early on in the pandemic, a doctor friend of mine, who recently recovered from COVID-19 himself, claimed that social distancing was nonsense; and in the middle of the lockdown suggested meeting up with five of his friends for drinks.

'A doctor friend of mine claimed that social distancing was nonsense'



Hobby

I am therefore somewhat sceptical about this revival of science among the public. Apparently the desire to understand something is deeply rooted in the human brain, even if you only have half the picture. 'I can't say, because I know too little about it' is a heavily underestimated and far too little used statement.

Nevertheless, I continue to fight against unscientific waffle out of moral duty and love of science. Call it a hobby. Even though Fallacy Man wrote on his anonymous blog *The Logic Of Science*: 'It's not a very rewarding hobby, and it comes with high stress levels and periodic fits of rage, so I don't particularly recommend it.' ●

Erwin Boutsma,
editor-in-chief of chemistry magazine C2W

Galapagos rejected

Dutch-Belgian clinical-stage biotechnology company Galapagos says it has been given the hardest slap in the face in its 22 years of existence. The American Food & Drug Administration has for the time being rejected its drug filgotinib, for the treatment of rheumatoid arthritis, because it has issues concerning the side-effects at higher dosages. The Galapagos stock-market price plunged considerably and it will probably take at least a year before the company is given a new chance. The European Medicines Agency is less worried and probably intends to bring filgotinib to the European market later this year.

French-Belgian lab merger

In one of the largest deals made in Belgium this year, the entrepreneurial family De Raedt-Verheyden's clinical laboratory group, CMA-Medina, is entering into a merger with the French Biogroup. The latter is engaged in clinical blood analyses. Through the transaction, the Belgian family holds a majority of shares and the French-Belgian combination immediately becomes one of Europe's bigger market players.

Millions for cleaner laboratories

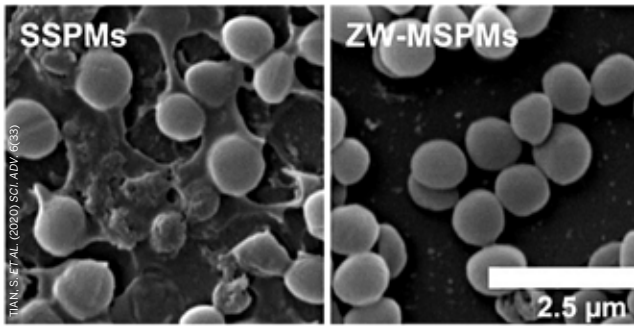
The Vrije Universiteit Brussel (VUB) is injecting € 11.3 million into the sustainability of the chemical laboratories on its campus. The university will use the money to install a highly energy-efficient heating, air-conditioning and ventilation system. Last year, the VUB reduced its CO_2 emissions by 674 tonnes per year by installing solar panels, heat pumps and the re-use of warm air. Additionally, the new laboratories must make chemical experiments more efficient in order to be able to achieve a reduction of CO_2 there too. Renovations will probably start in the spring of 2021.

Metabolomics research in Leiden

The Medical Delta Fieldlab has been opened in the Leiden Bio Science Park. Businesses, care institutions and scientists will carry out research here into metabolic products such as amino acids, hormones, glucose or adrenalin. If you collect these data from a patient you create a metabolic profile, thus making it possible to develop a more patient-specific treatment.

Micelles with a mission

Bacterial biofilms form an almost impenetrable barrier for most antibiotics and consequently contribute to the resistance problem. Henk Buscher, Linqi Shi and colleagues from Groningen and Tianjin, China, looked for a solution to this problem. They found it in micelles that automatically seek out the biofilm, break it up and disperse it so that the bacteria – in this case, *Staphylococcus aureus* – become an easier target for antibiotics and the immune system.



On the left is the biofilm unaffected by control micelles, on the right with the ZW-MSPM there is nothing left.

These are zwitterionic mixed-shell polymer micelles (ZW-MSPMs). Previous research had demonstrated that positively charged micelles can break up biofilms but do not automatically go to the right place. Other research had shown that MSPMs can carry effective antibiotics and, thanks to the composition of the mixed shell, are automatically drawn to the negative charge of the bacterial infection. In this case, the researchers combined these two properties with a zwitterion (a positively and negatively charged molecule) that took on the task of breaking up the biofilm.

The innovative part of this research is probably how the team succeeded in visualising the automatic target selection. They did this by constructing a transparent 'window' in live mice that enabled them to show the disappearance of the biofilm by means of fluorescence. (DL) ●

▶ Tian, S. *et al.* (2020) *Sci. Adv.* 6(33)

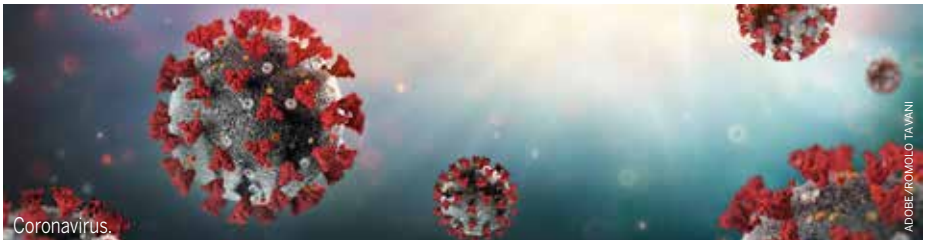
Sugar acts as gatekeeper for coronavirus

Without the help of heparan sulfate SARS-CoV-2 cannot get into your cells. Jeffrey Esko and colleagues at the University of California San Diego School of Medicine discovered that this sugar pulls open the protein fragment so that the cell's ACE-2 receptor fits into it.

It was already known that heparan sulfate, which naturally occurs on cell surfaces, and the chemically related sugar chain heparin attach to the spikes of coronaviruses. That this also is the case regarding SARS-CoV-2 was revealed a few months ago in the journal *Antiviral Research*. However, at the time, Robert Linhardt and his co-authors at the Rensselaer Polytechnic Institute still presumed that heparan sulfate only served as a sort of anchor. They even suggested that the ACE2 receptor protein, known as the 'doorknob' of the virus, would subsequently not necessarily need to be bound by the same spike.

In *Cell*, Esko now makes it plausible that it works slightly less simply. Like Linhardt, he points out a spot on the spikes on which such a sugar fits, but he used a different software package to simulate the structures. Compared with the original SARS virus, there are two differing amino acids in the protein chain on the bonding spot suggested by Esko that would make the bond much stronger. This implies that, a little further, the 3D structure of the spike proteins becomes deformed and will thus fit better on the ACE2 receptor.

By experimenting, first with synthetic spikes and then with real SRS-CoV-2 virus particles, Esko and colleagues later confirmed that heparan sulfate is essential. When they switched off the genes in their cell cultivations for the enzymes that shape the sugar chains, then there was no infection. (AD) ●

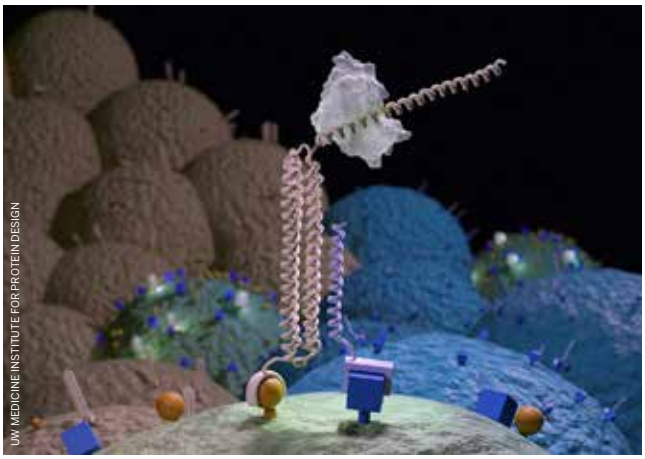


Coronavirus.

Protein logic against cancer

With the aid of self-designed proteins, you can assess cells on two or more properties simultaneously and ensure that immunotherapy really does attack tumour cells only.

Using present-day immunotherapy based on antibodies that target only a single biomarker you cannot always distinguish between healthy and tumour cells. Researchers at the University of Washington report in *Science* a higher degree of selectivity with a new variant of the LOCKR system they presented in *Nature* last year. LOCKR stands for Latching Orthogonal Cage/Key pRoteins. The cage consists of six parallel spiral structures, one of which (the latch) can spring outwards. An active spot on the latch can then bond to an effector structure that is part of your therapy. But this only happens when a third protein, the key, pushes aside the latch by bonding more strongly to the key. These proteins can be designed on a computer with the help of Rosetta software and then produced by *E. coli* cultures.



Quick switch on a cell surface.

The new variant is called Colocalization-dependant LOCKR, in short: CoLOCKR. The cage selectively attaches to one of the targeted biomarkers, the key attaches to a second one. The latch is released if both are coincidently positioned side by side. Experts in Boolean operations will recognise this as an AND operation.

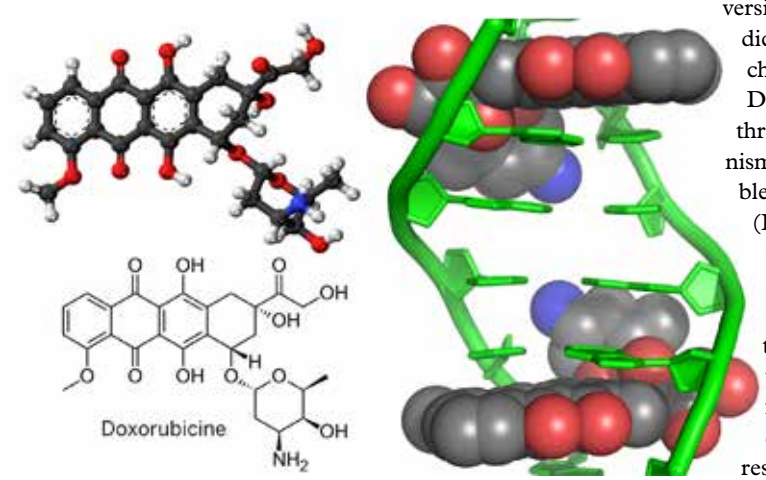
By adding different keys, you get an AND-OR operation that reacts to two biomarkers from a larger collection. To protect healthy cells there is the NOT operation with a decoy protein that attaches to a biomarker that is not found on tumours. The decoy bonds so strongly to the keys that the cages are left out in the cold. The researchers want to combine this principle with CAR-T cell therapy, a recent alternative for antibodies. The combination is highly promising in vitro, although clinical applications are still far off. (AD) ●

▶ Lajoie, M.J. *et al.* (2020) *Science*

Combating anticancer drug's side effects

If you put two methyl groups on the anticancer drug doxorubicin, then the cardiotoxicity is eliminated and the drug becomes much safer.

Doxorubicin (illustration left) is an anticancer drug belonging to the anthracyclines. The drug has been used to treat cancer for some decades now. Despite the efficacy of doxorubicin, this and other allied drugs still have some nasty side effects, especially cardiotoxicity. For young children or elderly people with heart conditions you have to choose between two evils. Researchers at the Leiden University Medical Center, Leiden University, the Netherlands Cancer Institute and the Shanghai Jiao Tong University School of Medicine discovered a chemical solution.



Doxorubicin (left) causes double-strand breaks (right).

Doxorubicin works through two mechanisms, DNA double-strand breaks (DSBs, see illustration right) and chromatin damage, which together ensure the anticancer effect but also cardiotoxicity. The researchers have discovered that if you attach two methyl groups (diMe-Doxo) to the amino group of doxorubicin, the cardiotoxicity disappears without affecting the anticancer effects. The exact mechanism is unknown, but it is clear that diMe-Doxo does not cause DSBs but only chromatin damage.

This idea is new and goes against the established order. Nevertheless, it certainly does work in mice. The researchers compared diMe-Doxo and aclarubicin – a drug that is similar to doxorubicin and only causes chromatin damage – with doxorubicin. Whereas mice die after eight doses of doxorubicin, those given aclarubicin or diMe-Doxo remained healthy, even after fifteen doses, with no weight loss or discomfort.

The authors suggest there may be similar possibilities to avoid the toxic effects of other 'forgotten' anthracyclines. (DL) ●

▶ Qiao, H. *et al.* (2020). *PNAS*

New life in Living Labs

Medical Delta gives a new lease of life – in the form of € 800,000 – to four new living labs focused on healthcare, says the foundation in a press report. The four laboratories will focus on current healthcare topics by creating an environment in which you can test innovations in realistic surroundings. The Zuid-Holland Universities of Applied Sciences in Rotterdam, Leiden, The Hague and InHolland will manage the labs while businesses and universities will also make practical contributions. In addition to research, education will also have its place in the labs.

Organon makes a comeback

Medicines giant MSD has announced that part of its portfolio is to become an autonomous listed company: Organon & Co. Among other locations, Organon will be established in Oss where it was first started almost a hundred years ago. Some 1,100 MSD Nederland employees will work in the company. When the demerger is completed in 2021, Organon will focus on women's health as well as on biosimilars, oncology and inflammatory diseases. The company will also continue to produce drugs.

€ 20 Million for UMCG Projects

The University Medical Center Groningen (UMCG) is to manage five large-scale international projects in the field of life sciences. These projects include proton therapy, to achieve more precise irradiation; research into the cause of diabetes and cardiovascular diseases, specifically the role of the endolysosomal network; medically unexplained conditions such as fibromyalgia and irritable bowel syndrome and the causes thereof; improved tests for the visually impaired; and the optimisation of the effects of rehabilitation.

Largest stem cell facility in the Netherlands

Leiden University Medical Center (LUMC) is to make a start on the construction of Europe's largest stem cell facility this year. The facility will bear the name of NECSTGEN, standing for Netherlands Center for the Clinical advancement of Stemcell and Gene Therapies and will be open to international researchers and start-ups. Research will mainly be focused on regenerative medicine.

Mega takeover in medicines

In September biopharma gigant Gilead closed the biggest deal in its existence. For $ 21 billion it bought the company Immunomedics and its antibody-drug conjugate (ADC) Trodelvy, that was approved April this year. With this acquisition Gilead enters the market for solid tumor therapy.

Slow vaccine release

Package vaccines in a hydrogel that you inject under the skin and you give the immune system ample time to react. It works on mice, claim Eric Appel and colleagues of Stanford University in *ACS Central Science*. They suspect that the effect is twofold. The vaccine components are slowly released from the hydrogel to migrate to the lymph nodes where they activate the T and B cells of the immune system. Simultaneously, the immune system sees the globule of hydrogel as a local infection: immune cells attempt to penetrate the globule to activate themselves by means of any remaining vaccine particles.

It goes without saying that by working in this way, a stronger immune response is generated than when the vaccine is injected in a single shot into the bodily fluids. The authors point out that vaccines normally disappear from the bloodstream within a couple of days, whereas a real infection can last a few weeks. There are indications that adjuvants, such as aluminium hydroxide, bolster the working of a vaccine because vaccine particles stick to them and are consequently broken down less quickly.

It is essential that the hydrogel can be squeezed through a hypodermic needle. To achieve this it must be shear thinning: when pressure is exerted the viscosity temporarily becomes lower. When it coagulates again under the skin it must provide enough space for the vaccine particles and immune cells.

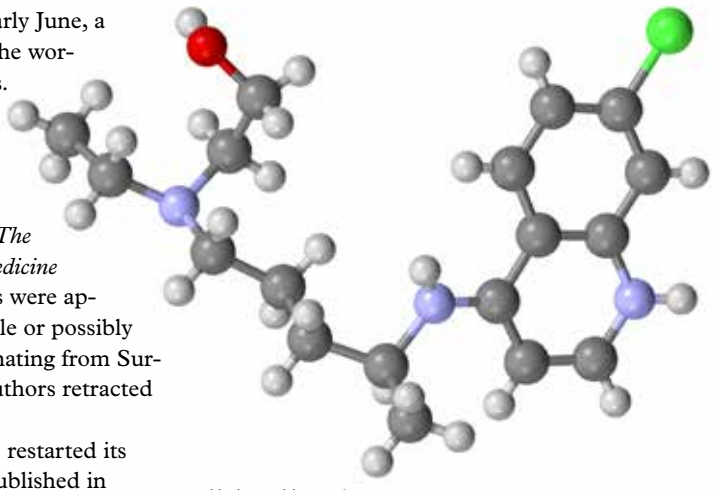
Appel has not yet tried it with a real vaccine but with the protein ovalbumin and poly I:C, an RNA analogue used for research purposes. He did observe a considerable increase in the immune response in mice compared with traditional injections. One measurement method showed that the antibodies were more effective by a factor of 1,000. As a matter of fact, the hydrogel later showed to be full of immune cells. (AD) ●

Hydroxychloroquine blocks immune system

Around the end of May, early June, a strange situation arose in the world of scientific publications. The WHO put its large-scale study into hydroxychloroquine on hold because of two studies published in *The Lancet* and *The New England Journal of Medicine* (*NEJM*). But those studies were apparently based on unreliable or possibly even fraudulent data originating from Surgisphere. Hence various authors retracted their studies.

On the date that the WHO restarted its study another study was published in *NEJM* (without Surgisphere data) which demonstrates that hydroxychloroquine has no anti-coronavirus properties. In addition we now see a new Radboudumc study that really throws a spanner in the works regarding the anti-malaria drug.

On preprint server *MedRxiv* Raphaël Duivenvoorden *et al.* show that hydroxychloroquine inhibits the trained immunity at the functional and epigenetic level. Also, changes take place in the cellular lipidome, which results in a lower expression of interferon-stimulated genes. The researchers therefore suspect that the drug does not have the anticipated antiviral role expected by the proponents of hydroxychloroquine. (DL) ●



Hydroxychloroquine.

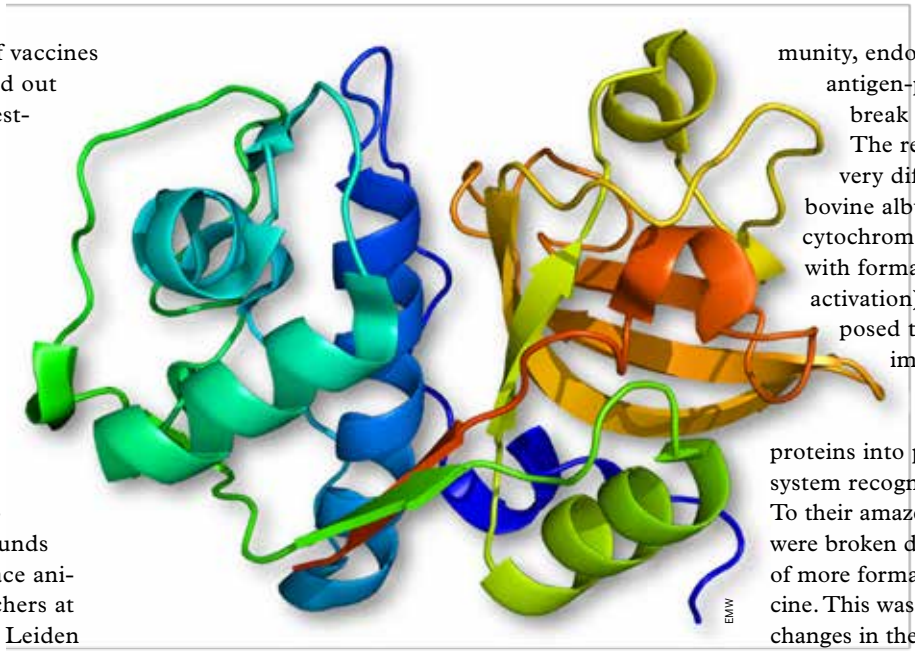
▶ Rother, N. *et al.* (2020). *MedRxiv*

Towards non-animal-tested vaccines

In theory you can carry out quality checks on vaccine production without the need for animal testing.

Quality control of vaccines is generally carried out through animal testing, but scientists are searching for alternatives to replace, reduce or refine (the 3Rs) animal testing. One example is the consistency approach: if in vitro tests show that a vaccine has been produced in a consistent manner, there are grounds to reduce or replace animal tests. Researchers at Intravacc and the Leiden Academic Center for Drug Research developed such an in vitro test for vaccines on the basis of bacterial toxins from diphtheria and tetanus infections.

These vaccines are often based on toxins that have been inactivated with formaldehyde. The researchers suspected that this slows down the breakdown of the proteins in the vaccine. To stimulate immunity, endolysosomal proteases in antigen-presented cells have to break down the protein antigens. The researchers selected three very different model proteins: bovine albumin, β-lactoglobulin and cytochrome c. They first treated them with formaldehyde and glycine (inactivation), and subsequently exposed them to cathepsin S – an important endoprotease (see illustration) – that breaks down the model proteins into pieces that the immune system recognises.



Cathepsin S breaks down proteins.

To their amazement the model proteins were broken down faster in the presence of more formaldehyde, even without glycine. This was not so much caused by changes in the primary structure of the proteins but rather in their conformation. The Dutch researchers see this as a major step towards less animal testing. (DL) ●

▶ Michiels, T.J.M. *et al.* (2020) *Scientific Reports* 10(11535)

Wanted: shepherds of the herd

The rich, the famous, the beautiful, do not understand what happened to them during the COVID19 pandemic and do not accept their inability to change it. They start searching for the truth and find a new religion: the religion of self. In this religion, the government, large corporations, medical establishment and mainstream media are the devil, denying the self to be free and to determine its own daily life.

These rich, famous, beautiful people are the missionaries of this religion of 'believe in yourself'. They distrust authority and institutions. For years, the degree of vaccination in Beverly Hills has been as low as in South Sudan. Where anti-vaxxers used to be limited to orthodox groups and anthroposophists, their bubble has now merged with the Deep State bubble. Anti-vaxxers now range from the political left to the right. These missionaries are influencers with millions of followers. Research by Johnson *et al.* (*Nature*, 13 May 2020) has shown that anti-vaxxers outcompete pro-vaxxers on social media.

However, as a community we may need as much as 70 % herd immunity against SARS-CoV2 to protect the weak. If we want this growing bubble to listen to reason and evidence, and to not be selfish, we could try to enter their bubble, with our small number of followers on social media. But it is far more effective to focus on the influencers with their millions of followers. They should spread the word that not the self, but the community, is at risk. And that not the self but the community is the solution, in the form of herd immunity. Not scientists, politicians, doctors, or CEOs, but the influencers might be able to turn this information around. We ask them to not be selfish but to be the shepherds of the herd. ●

Ed Moret, managing director of the Utrecht Institute of Pharmaceutical Sciences (UIPS) and FIGON Secretary

Clémence Ross-van Dorp: 'Our first task is to identify all the players in the field'

Ambassador for bottom-up actions

This January, Clémence Ross-van Dorp was appointed ambassador for a new Dutch life sciences and health action programme. By strengthening the sector and promoting the Netherlands as top player in the international arena, she hopes to foster innovation and help patients. 'It's very inspiring to be a part of that process.'

Every dark cloud has a silver lining. That has been the general sentiment in the Dutch life sciences and health (LSH) sector in the past few years in the context of Brexit and, more recently, the COVID-19 pandemic. Brexit may cause upheaval in European markets and science, yet the move of the European Medicines Agency (EMA) from London to Amsterdam presents new opportunities for the Netherlands. COVID-19 has devastating impacts on people's lives and economies worldwide, yet it brings scientists together in a joint search for a vaccine and optimal treatment.

It is in this landscape that Clémence Ross-van Dorp (63), a veteran in public health policy, is now working as ambassador for the Dutch LSH sector, appointed by the Dutch government. Starting in January of this year, the former State Secretary for Health, Welfare and Sport is overseeing the making of a national action programme to support the Dutch LSH sector. The programme has two objectives: to strengthen ties between Dutch LSH clusters and create new networks, and to present the Netherlands as a strong and valuable partner in the global LSH arena. This fall, the programme will result in a report.

Was the EMA move to the Netherlands the trigger for your ambassadorship?

'Partly, yes. But around the same time, in 2018, the Dutch Top Sector LSH was on a mission to strengthen the sector and take a more international perspective. Several top professionals and representatives of Dutch LSH clusters made a trip to Boston to learn about the American approach to LSH development, and to present the Netherlands as a valuable partner in this regard. People then realised that even though our country is very small, the LSH landscape is rather fragmented. If we want to force more scientific breakthroughs and strengthen our position in the global arena, we have to work more closely together within the country. That is why the government appointed an ambassador: to put a finger on what defines Dutch LSH as a whole, how to strengthen these points, which networks can be improved, and how to unite and boost initiatives that are already underway. That is what this new action programme is about.'

'You can't tackle challenges in a fragmented landscape'

It sounds like a paradox: bringing the field together. After all, there is always fierce competition for funding, breakthroughs and markets.

'It's not a paradox at all. Better cooperation fits perfectly in the current developments in the field. Scientists and businesses are forming consortia anyway, to pool their resources and expertise and to secure funding – also internationally, for instance through European grants. It becomes increasingly hard to do anything on your own, and rightly so. After all, none of us work in this field for ourselves. We work for the patients. And that is better done in larger consortia. For the reasons I mentioned earlier – pooling expertise and funding – but also to access more data. Many studies in the field of personalised medicine, for instance, involve small patient cohorts. If you work together within Europe, you get a much larger


PAUL TOLENAAR

Clémence Ross-van Dorp
▶ **2020-present**
ambassador for the Dutch Life Sciences & Health Sector
▶ **2013-present**
director-owner Clémence Ross Consultancy; director Agora (palliative care)
▶ **2007-2012**
director Netherlands Institute for Sport and Exercise (NISB)
▶ **2002-2007**
Dutch State Secretary for Health, Welfare and Sport
▶ **1998-2002**
member of Dutch Parliament for Christian Democratic Party (CDA)
▶ **1990-1998**
policy officer at European Parliament CDA/European People's Party
▶ **1979-1989**
teacher training Dutch and English; Chinese studies, University of Leiden
▶ **1977-1979**
doctor's assistant training

cohort and thus more accurate – and quicker – results.'

But then I see another paradox in your ambassadorship... if international cooperation is so important, why do we need to promote the Netherlands as an important LSH country? It sounds a bit nationalistic, in a world that is internationalising...
'You need both: intensive international networks and high-level national science and business. You need both if you want to keep attracting top-level scientists, to maintain our quality education for young professionals, and to have flourishing businesses. In other words, we need a well-functioning ecosystem in order to be a valuable partner internationally. Especially in these turbulent times, not just with COVID-19 but also with ongoing challenges such as microbial resistance. You can't tackle those issues in a fragmented landscape. So that is why my ambassadorship focuses on both aspects. They strengthen each other.'

What needs to be done nationally?
'It may sound surprising, but in the Netherlands we don't even have a clear picture of exactly which LSH businesses there are. So that is our first task: to identify all the players in the field. Then there is the challenge of regulation. In our country, legislation tends to lag behind the superfast innovative developments in the field. Take CAR-T-cell technology for instance: there is still much debate about the legislative aspects, while our neighbour Belgium has been able to move forward much more rapidly. That is an undesirable situation: in Europe, you need to be able to measure up to your neighbours. We need to step up our national efforts in order to take on our international responsibility, if you ask me. And then, of course, there are areas in which all countries have work to do nationally. For instance when it comes to the affordability of medications. We have a separate national project focusing on that.'

Can you elaborate? Which project is that?
'It's called FAST: Future Affordable and Sustainable Therapies, a project initiated by the Netherlands Organisation for Health Research and Development, ZonMw. That started in March this year. As an ambassador, I have adopted the principles of FAST, as it has large areas of overlap with the LSH action programme. This projects aims to find connections nationally, for instance in terms of financing, legis- ▶

FIGONDMD

DUTCH MEDICINES DAYS

VIRTUAL SERIES

Due to the Coronavirus (COVID-19), a physical meeting on September 14 and 15 was not possible. The health and safety of our members, speakers and attendees is our number one priority. Even in the midst of COVID-19, the work cannot stop - we must continue to meet, engage, learn and advance. Therefore, this year's DMD edition will be organized virtually throughout the remainder of 2020 and possibly early 2021. Thanks to the support of our sponsors we can offer you free participation in all online sessions.

Please vitsit our website for all scheduled webinars in 2020:

FIGONDMD.NL

Platinum Sponsors

Pfizer

janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Gold Sponsors

LEIDEN BIO SCIENCE PARK

ZonMw

Vereniging Innovatieve Geneesmiddelen

lation, regulations and quality control. In the Netherlands, these issues are often spread across various ministries, which makes matters very complex. My task is to mainstream all efforts aimed at making therapies more affordable and sustainable.'

Are you talking about environmental sustainability?

'That too, but in this context sustainability also includes adherence to the principles of Good Manufacturing Practice, GMP, for instance, and cost-effectiveness. And it includes transparency: as developers and manufacturers, you have to be able to account for what you're doing. It sounds self-evident, but in practice it still often proves to be a hurdle. As part of the LSH action programme, we aim to make an inventory of all of these aspects, in order to identify what we excel at, and what organisations still need in order to develop the best innovations.'

Can you give us a glimpse of what will be written in the report? What do we excel at?

'First of all, we have top-quality institutes and researchers, who already operate in top-quality networks. Take our University Medical Centres, for instance. It is quite unique to have so many of them so close together, geographically. This makes collaboration relatively easy. Overall, our LSH institutes and businesses exert a strong attraction all over the world. They know how to present themselves and are direct in their communication. That is also a potential weakness, by the way. Our openness is sometimes interpreted as bluntness. We need to keep working on that – also on how we receive our high-level visitors, for instance. We tend to serve them a cheese sandwich, while our neighbours would be offering a full dinner. So all in all, we have a lot of unique selling points, but we need to keep working on that enabling ecosystem, with all the right conditions in place.'

'None of us work in this field for ourselves'

PAUL TOLENAAR

How is COVID-19 impacting the action programme?

'It accelerates things tremendously. It makes clear why all these actions are necessary. Like soccer player Johan Cruijff used to say: 'Every disadvantage has its advantage.' Now more than ever, everyone realises the added value of sharing data and working together towards a common goal. There are a lot of initiatives coming from the field – rather than being forced top-down. This is in fact an opportunity for Europe to be a hub in the world – and for the EMA to be hub in Europe.'

What will happen with your report?

'I will present the action programme report at the end of this year to the Dutch ministers of Health, Welfare and Sport and Economic Affairs. From there the content will surely trickle down to the respective departments. I have been asked to stay on as ambassador for a number of years to oversee the implementation of the recommendations in the report. That is really nice – that I can take responsibility for the entire process, at least for the first few years. After that, we'll see what happens. And what the world looks like at that time.'

You are confident that the report won't collect dust somewhere in a drawer?

'Oh yes! These ambitions will become actions, for sure. The report is full of concrete recommendations that originated in the field. They are bottom-up: this is what everybody wants.'

But sometimes the government doesn't carry out what the field wants. Like in the case of CAR-T-cell technology.

'Yes. Of course there are cases like that. There will always be ambitions that aren't followed through, at least not immediately. But overall, these are urgent, realistic, feasible actions. Clear actions that will directly benefit patients. They offer our country concrete opportunities to stimulate innovation and economic growth and patient well-being. That energy and enthusiasm is truly noticeable in the field right now. Very nice to witness. Very inspiring to be a part of.' ●


ADOBE/PHONLAMAIPHOTO

Linking sugars for influenza characterisation

From glycans to viral evolution to a new assay for influenza surveillance. Rosanne van Beek's research shows that science can move in mysterious ways.

For those who have a sweet tooth, don't worry: cells cannot live without sugars either. 'All living cells have a sugar coating on their surface, which is crucial to cellular communication', says Rosanne van Beek, PhD student in the Chemical Biology group of Geert-Jan Boons at Utrecht University. 'My research focuses on the role of these sugars in host-pathogen interactions. We study which sugars are recognised by influenza viruses and how that specificity is evolving.'

Hands-on application

Van Beek concentrates on A/H3N2, one of the influenza virus subtypes that cause flu in humans. 'We are interested in the evolution of viral binding specificity. Which sugars are recognised and how is that changing over time?' This requires intricate knowledge of the composition and structure of the highly complex glycan layer on the cellular surface. Van Beek not only analyses which sugars are present, but also modifies the structure to study the functional role of specific residues in interacting with the virus.

Even though her work is about understanding basic mechanisms in the evolution of host-pathogen interactions, it has also generated a hands-on application. Influenza viruses are continuously monitored through a worldwide surveillance system that involves more than 140 National Influenza Centres around the globe. To detect and characterise which subtypes of influenza are circulating, so-called hemagglutinin inhibition assays are applied. In these assays, red blood cells are used to bind the virus.

But for A/H3N2, problems are emerging. Van Beek: 'A/H3N2 is increasingly difficult to characterise, because the virus' binding specificity has changed. As a result, the standard assay can no longer be used for most viruses. But in our work to understand the evolution of A/H3N2, we developed a new way to study and modify the cell's sugar coating. That gave us the idea to use this method to adapt the assay for A/H3N2 characterisation.'

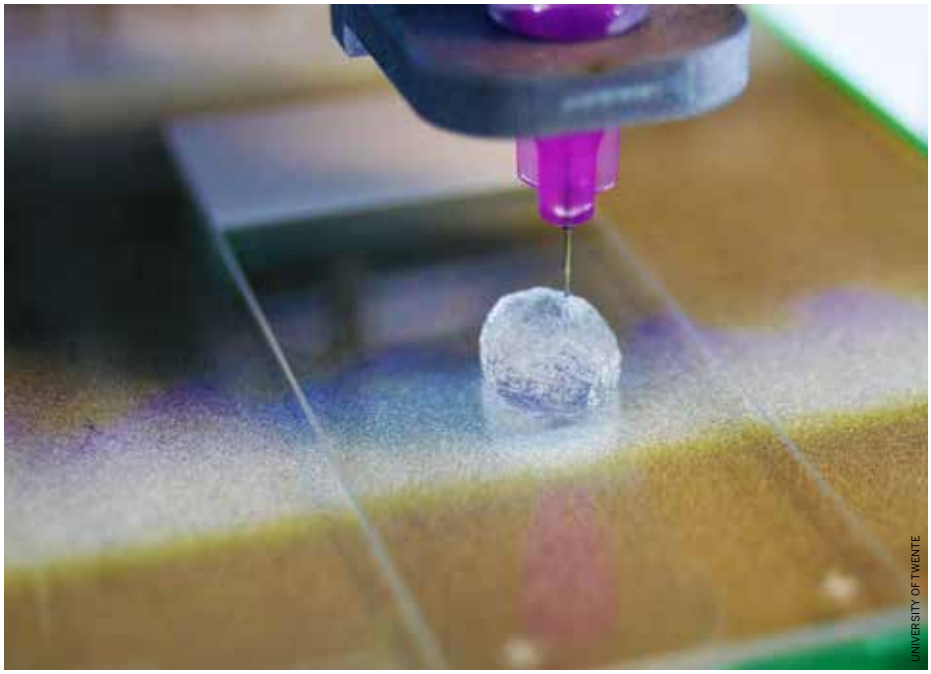
'Now we are ready to move fast'

Branching

Van Beek's in-depth knowledge of the virus' binding specificity paid off. 'We discovered the missing link that disables the virus' capacity to bind red blood cells. And because we know the biosynthesis routes of all the sugars on the surface, we could modify the coating in exactly the right spot to enable recognition again.' Van Beek explains the process. 'In the coating, monosaccharides connect to each other to form a branched structure and each branch is built by enzymes. We apply those enzymes to construct the right 'tree' on the surface of the red blood cells.'

Together with the Virology Department at Erasmus MC in Rotterdam, which is also the Dutch National Influenza Centre, Van Beek performed a validation study. 'We tested our assay against a large set of viruses and the results are very promising. But there is still work to be done in terms of optimisation and scaling up.' And if this new assay will become part of the surveillance programme, how long will it remain useful? The virus will probably continue to evolve. 'That is hard to predict, but now that we understand viral binding specificity and we have the techniques in place to modify the red blood cell's sugar coating, we can move fast if new adaptations are needed.' ●

Rosanne van Beek is participating in the PhD Student Competition at the FIGON Dutch Medicines Days



3D-bioprinted mini-brains

Glioblastoma is an aggressive brain tumour that currently has no effective treatment. Marcel Heinrich developed 3D-bioprinted mini-brains that can be used to evaluate novel therapeutics.

'When testing new drugs, the transition from 2D cultures to animal studies is challenging', says Marcel Heinrich, PhD student at the University of Twente. 'There is a big gap in between. These mini-brains can serve as a bridge.' 3D mini-organs in themselves are not new, but when bioprinted, they yield better results, according to Heinrich. In 3D bioprinting, living cells are used to print living structures layer by layer. 'Regular 3D culture techniques, such as using a hydrogel as a scaffold, does not give sufficient control of the architecture of the fabricated organ', says Heinrich. 'Control, however, is very important in situations in which the required biological structure is complex, like in a brain tumor surrounded by glial and stromal cells. When 3D bioprinting, you can print the cells exactly where you want them to be.'

Heinrich printed a brain tumour called glioblastoma multiforme. Patients with this type of cancer usually live no longer than two years after diagnosis. 'The only treatment is cutting out the malignant cells', explains Heinrich. 'But you cannot remove the whole tumor, as you will be cutting into healthy brain tissue. There is a need for drugs to specifically target the diseased brain part. I think my model can be used to test those drugs.'

'Evaluating new drugs in our mini-brains can be an interesting tool'

For his PhD research, Heinrich focused on two 3D-bioprinted brain tumour models. 'In the first, we studied the interactions of glioblastoma cells with macrophages. These macrophages are known to be sort of brain-washed by the tumor cells to become tumour-promoting cells. In our model we saw exactly this. We also checked patient data regarding biomarkers that were upregulated in the tumor. We saw very similar expression levels in our model.'

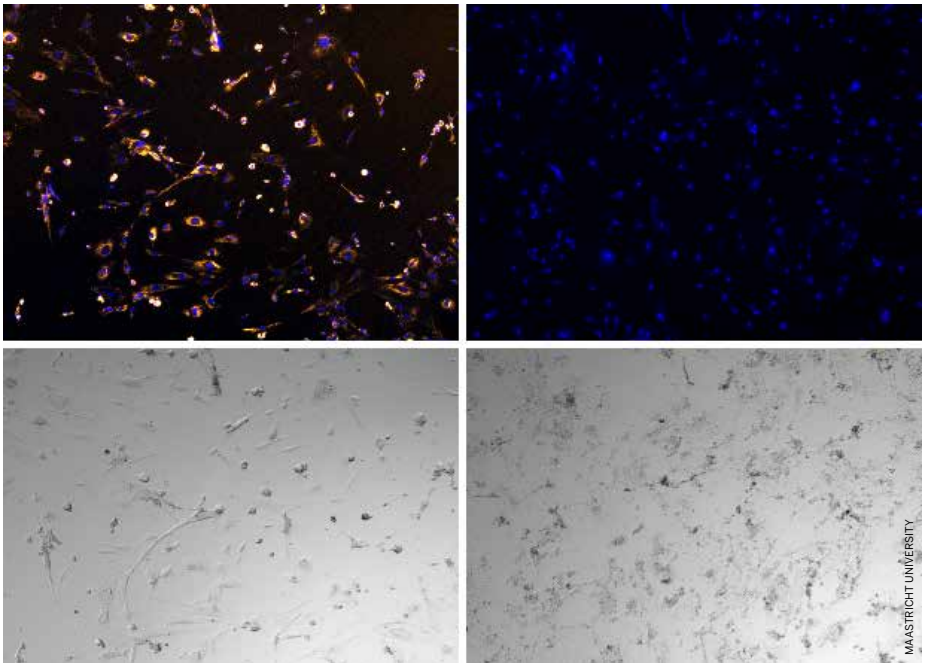
Heinrich also used the mini-brains to test drugs that are already used in clinics or in preclinical and clinical trials. These drugs work by inhibiting macrophage activity and eventually tumor growth. 'That was indeed what we saw happening in our models. So hereby we demonstrated that evaluating new drugs in our mini-brains can indeed be an interesting tool.'

Sustainable models

Heinrichs next goal is to use the same principle for pancreatic and breast cancers. He also aims to use a more complex second version of the glioblastoma mini-brains to study more intricate interactions. 'For example, the role of supporting brain cells such as microglia and astrocytes. It is not yet fully understood how these cells interact with tumour cells and how they eventually promote tumor growth and invasion.'

Can these mini-brains eventually replace animal studies altogether? 'No, at least not yet. I do envision the use of this technique to cut back the use of animal models. Say you have ten new drugs. Instead of taking all of them to animal studies right away, you can first test and screen them in a 2D culture and then in a 3D mini-organ. After that you may only have one or two really good candidates left for animal studies. That saves a lot of time and many animal lives.' ●

Marcel Heinrich is participating in the PhD Student Competition at the FIGON Dutch Medicines Days



Left: calcifying cells treated with protein S Gla peptide; right: control.

A peptide against atherosclerosis

One of the leading causes of death worldwide is atherosclerosis. PhD student Anouk Gentier developed a peptide that can both trace and block calcifications in atherosclerotic plaques.

'Atherosclerosis is like a dam being built inside your arteries', says Anouk Gentier, PhD student at Maastricht University. 'This dam mostly consists of cholesterol, dying cells, scar tissue and microcalcifications. The latter is my study focus.'

Protein S

A microcalcification is like a ticking time bomb. Gentier: 'It increases the pressure the atherosclerotic plaque experiences. If rupture occurs, there could be nasty consequences, including stroke, myocardial infarction or necrosis of limbs. So, timely identification of these microcalcifications is essential.'
Gentier has found a way to do just that, and more. 'I am developing imaging agents that target microcalcifications even earlier than those currently used, like in PET imaging. We have the impression that these molecules actually inhibit the growth the microcalcifications.'
The molecule in question is a modified version of protein S Gla domain. Protein S is an endogenous anticoagulant and the Gla domain consists of multiple amino acids called glutamic acid. 'These glutamic acids are adjusted so that they carry two carboxyl (COOH) groups. These groups seem very important in the functioning of the peptide.'
Patient material was being used to test the peptide. Gentier: 'We get both healthy and diseased smooth muscle cells taken from patients that underwent surgery for their lesions in the University Hospital of Maastricht. These cells are then cultured, put upon a plate, and incubated with a medium enriched by either calcium, phosphate or both. We then treat them with either protein S Gla, bound to an imaging agent, in various concentrations or a negative control. Then we use a colorimetric assay to measure the number of microcalcifications formed.'

A microcalcification is like a ticking time bomb

Promising vesicles

Not only is the protein S Gla domain capable of detecting microcalcifications in the body. The peptide can also block the formation of these ticking time bombs. 'We see fewer microcalcifications in the treated cell cultures than in the negative control cultures', says Gentier. 'The exact mechanism of action is still unknown, but we think the peptide binds to the phosphatidylserine residues of the cell membrane of smooth muscle cells that are exposed to a calcifying environment. Through this binding the cells seem less prone to calcification.'
These findings may lead to a promising new treatment against atherosclerosis, hopes Gentier. She and her colleagues have ideas on how this could take shape. 'We have yet to finalise this, but we are planning on making extracellular vesicles in which we introduce both protein S Gla and annexin A2. The latter protein is known to have anti-inflammatory effects. So, we would have two ways to make atherosclerotic plaques less dangerous or even disappear.'
For a long time, doctors and researchers have assumed that microcalcifications inside an atherosclerotic plaque were stabilising the plaque. 'We now know it is quite the opposite, thanks to better tracers to monitor the process', says Gentier. 'And with this new endogenous tracer we can learn even more, and – as a big bonus – we can even treat the condition at the same time.' ●

Anouck Gentier is participating in the PhD Student Competition at the FIGON Dutch Medicines Days

Using drugs in concert to combat side effects

Bart Kramers at the UMC Groningen works towards a better treatment for ADPKD, a common but serious kidney disease. He aims to reduce the adverse side effects of the current standard medication.

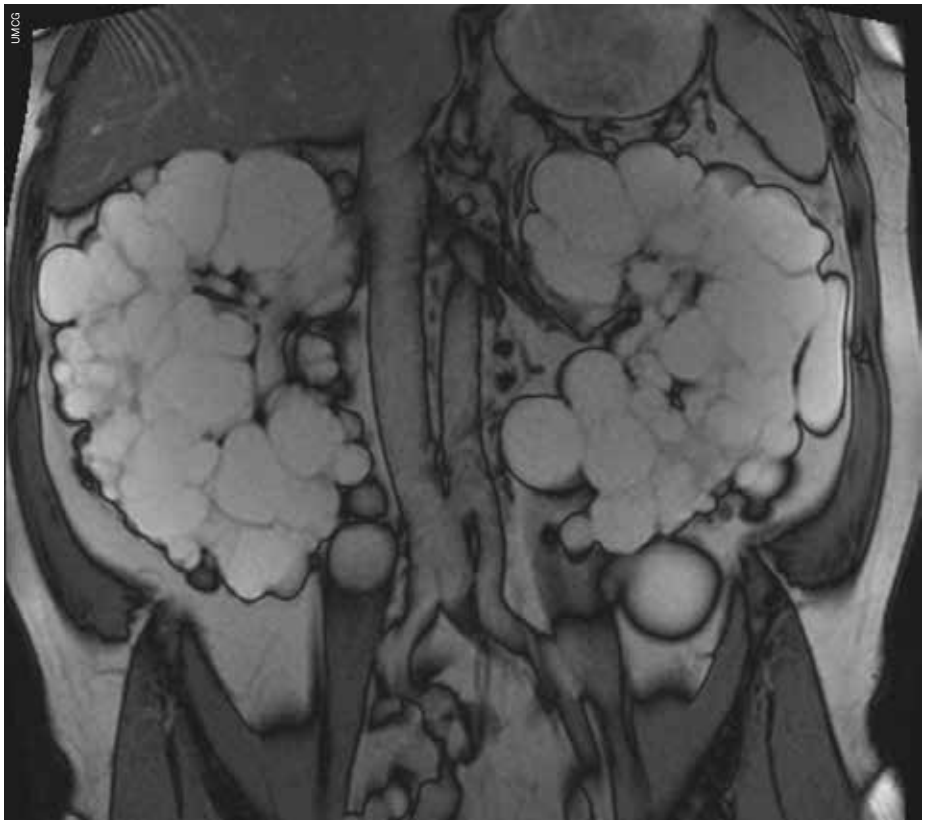
ADPKD (autosomal dominant polycystic kidney disease) is the most common hereditary kidney disease worldwide, affecting one in approximately 1.000 to 2.500 people. It manifests itself in the growth of cysts, or fluid-filled vesicles, throughout the kidneys. These cysts displace healthy tissue and gradually impairs its function. Although there is wide variation in the severity of symptoms, many patients need renal dialysis or transplantation before they are sixty years old.

Quality of life

'The working mechanisms of ADPKD are only partly understood', says Bart Kramers, PhD student at the University Medical Center of Groningen. 'Therefore, medication options are limited. There is only one drug that has been shown to suppress the progression of the disease: tolvaptan. Unfortunately, this drug has side effects that limit its clinical use.'

Kramers' research focuses on reducing the adverse effects of tolvaptan. 'Tolvaptan was introduced around three years ago', says Kramers, 'and it is a real improvement: is slows the disease significantly. But it also makes patients extremely thirsty. They drink all day long and produce 6 to 8 liters of urine per day. They often have to get up during the night and lose a lot of sleep. This has a major impact on their quallity of life.'

Tolvaptan is a vasopressin receptor antagonist. Vasopressin, also known as antidiuretic hormone, stimulates the reabsorption of water from the kidney tubules. In other words, it ensures effective water reuse in the body and decreases the amount of urine produced. Tolvaptan inhibits vasopressin, which in turn increases urine production. Via a different pathway, however, it also slows the growth of the cysts in ADPKD patients. 'The overall balance is positive', states Kramers, 'but it would be a tremendous improvement for patients if we could reduce the adverse side effects.'



Longer term

First, Kramers focused on identifying factors that affect the severity of the side-effects. It appeared that salt and protein intake both play important roles. 'This is something that patients have direct influence on, through their diets', explains Kramers. 'Interestingly, dietary salt intake also seems to affect cyst growth. The exact effects of both protein and salt are still being investigated.'

'It greatly improves how people feel'

In the meantime, Kramers also studied whether additional medications may reduce the side effects of tolvaptan. One candidate is the diuretic hydrochlorothiazide, a drug commonly used in hypertensive patients to control blood pressure. 'Paradoxically, if vasopressin is inhibited, this drug has an anti-diuretic effect', says Kramers. 'In a study with thirteen ADPKD patients, we found that hydrochlorothiazide reduces urine production by around twentyfive percent and greatly improves how people feel.'

Kramers is now finalising his PhD thesis. In the near future, he would like to continue his line of research. 'I'm interested in a longer-term follow-up', he says. 'I'm curious as to how the use of hydrochlorothiazide impacts on APKD progression. There are some indications that it slows the disease. And perhaps there are other medications that have an even better combined effect. This would be interesting to study in larger patient groups, and over longer periods of time.' ●

Bart Kramers is participating in the PhD Student Competition at the FIGON Dutch Medicines Days

A fiber matrix for scalable chromatography

Cytiva has developed Fibro: a new technology for chromatography. Its fiber matrix allows for high binding capacities at very short residence times, resulting in increased throughput and productivity in mAb purification.

Biomanufacturing is trending towards higher numbers of monoclonal antibody (mAb) projects and smaller batch sizes. These trends are fueling demands to screen more clones faster, and improve the efficiency of process development and flexible multiproduct facilities in mAb manufacturing.
"To help meet these needs, Cytiva developed ready-to-use Fibro PrismA units for capturing mAbs", says David Westman, Bio Process Marketing Manager at Cytiva. "Our first-launched products are HiTrap Fibro PrismA and HiScreen Fibro PrismA. Both are designed to support researchers and process developers by enabling them to purify monoclonal antibodies with significantly improved throughput."

Fibro PrismA, as Westman explains, is a scalable rapid cycling chromatography technology that complements chromatography resins, especially in circumstances where speed and flexibility are important. It offers significantly improved mAb purification throughput in research and process development. Westman: "For large-scale manufacturing it increases flexibility and productivity through its single-use operations. This creates substantial cost savings, especially for multiproduct facilities, and helps bring therapies to market faster."

MINUTES INSTEAD OF HOURS

Fibro PrismA units have a protein A cellulose fiber matrix with an open pore structure. In this matrix, mass transfer is governed by convective flow. This structure allows high mAb binding capacities at very short residence times, which results in cycle times of minutes instead of the hours needed for resin-based chromatography.
"Fibro PrismA uses the same chromatography systems, infrastructure, and ligands as resin chromatography", stresses Westman, "allowing for simple transition into existing biomanufacturing facilities."
In research and process development, the fast purification time results in up to 20 times increased throughput compared to resins. In clinical and commercial settings, the rapid cycling enables manufacturers to utilize the full lifetime of the unit (around 200 cycles) in a single batch-increasing productivity up to 400 g/L/h. "For clinical manufacturing, where you normally only utilize a fraction of the full lifetime of resins, this means significantly reduced cost", says Westman. "In commercial manufacturing, the Fibro technology enables cost-efficient single-use operations with added flexibility for multiproduct facilities."

"For large-scale manufacturing it increases flexibility and productivity"

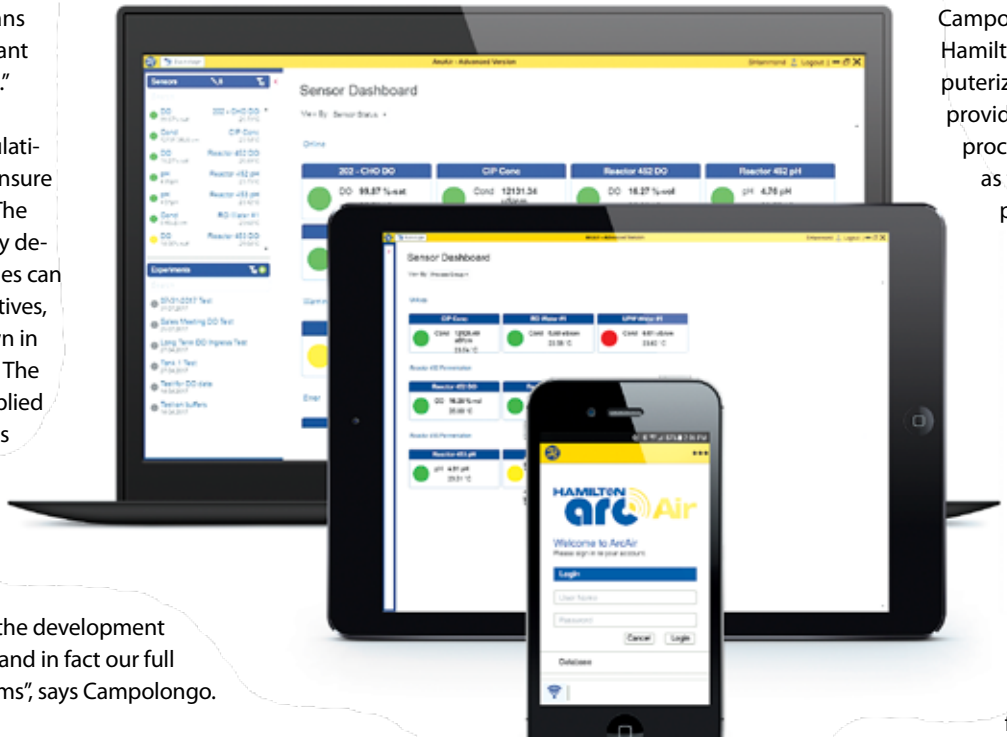
APPLICATION AREAS

The beauty of the Fibro platform lies in its versatility, concludes Westman. "All ligands available for resins may also be attached to the Fibro units. Its macro porosity gives it a strong potential for usage in vaccine and viral vector purification. In the coming years, we plan to develop products for these areas." ◆

Full support with GMP-ready systems

Good Manufacturing Practice, or GMP, is rapidly becoming commonplace in biopharmaceutical manufacturing. It may seem daunting, but individual companies don't have to reinvent the wheel. Suppliers such as Hamilton provide full GMP solutions.

"GMP is a risk managememt system to ensure the quality of pharmaceutical systems", explains Giovanni Campolongo, process analytics manager at Hamilton. "This doesn't just mean that a medicinal product is 'not harmful'. It also means that it has a significant therapeutical effect."
In Europe as well as North America, regulations are in place to ensure adherence to GMP. The objectives are strictly defined. How companies can achieve these objectives, however, is laid down in voluntary guidance. The most commonly applied voluntary standard is GAMP5: Good Automated Manufacturing Practice v.5. "This is also the standard that we use in the development of our own sensors, and in fact our full computerized systems", says Campolongo.



ENTIRE PACKAGE

According to GMP guidelines, a computerized system consists of all hardware, software and network components involved in product manufacturing, including the training of the people who operate the system, and all associated traceability documentation. Campolongo: "The entire package has to be ready to be GMP compliant. We often get the question: is your sensor GMP compliant? This is a logical error. A sensor can be ready for compliance."

Suppliers such as Hamilton can assist their clients in the entire system lifecycle, from design qualification (what do you want the instrument to do?) via installation qualification (is it correctly connected?) and operation qualification (does it work for your specific application?) through to performance qualification (does it continue to be fit for purpose and controlled?). GMP, as he continues, is a shared responsibility between the supplier and the end-user. "The end-user specifies and selects the instrument, reviews and approves the installation qualification, and confirms the intended use and the continued performance."

"The entire package has to be ready to be GMP compliant"

SUPPLIER INVOLVEMENT

As an example, Campolongo names Hamiltan's ArcAir computerized system. "We provide you with the process sensor, as well as the full deliverables package to validate it." Hence, the computerized system does not only comprise the intelligent Arc Sensor with embedded microtransmitter and ArcAir software. In also includes storage of the sensor's data into an encrypted database and many other features, such as user and rights management, logging of user actions, and digital reports. "GMP users don't have to manage everything themselves", emphasises Campolongo. "They can leverage on an experienced GMP supplier like Hamilton to identify the most suitable GMP package for the sensor's intended use. You'll also find this in the guidelines: '*although the responsibility for compliance with GMP regulations lies with the regulated company, the supplier may have considerable involvement in the process*'." ◆

The wide scope and potential of regenerative pharmacology

Towards humans-on-a-chip

Regenerative pharmacology allows an entirely new perspective on human physiology, health and disease. 'These new methods are more closely related to the intact human body.'

Combine 'classical' pharmacology with the latest insights into tissue repair, microfluidics techniques, innovative cell culture methods and advanced stem cell technologies, and you are entering the world of regenerative pharmacology. 'It really is a highly interdisciplinary field', says Amalia Dolga, adjunct professor of Regenerative Neuropharmacology at the University of Groningen and organiser of a four-session webinar on the topic during this year's virtual Dutch Medicine Days. 'I think it is a highly relevant field to the Dutch drug development community. It brings together pharmacology with tissue engineering and regenerative medicine.'

What really distinguishes this field from more classical pharmacology is the stronger focus on human models, according to Dolga. 'Thanks to the huge breakthrough in stem cell technologies, especially with the advent of induced pluripotent stem cells, these new platforms, like organ-on-a-chip and organoid technology, allow us to develop completely new methods for testing and research in a setting that is a more closely connected to the intact human body. Regenerative pharmacology touches on so many different applications, disease areas and therapeutic opportunities that it offers interesting insights for a very broad audience.'

'We need to focus on multiple pathways'

With presentations ranging from restoring kidney function to modelling lung damage caused by smoking and from the effects of hypoxia in premature infants to modelling vessels in patients with head and neck tuberculosis, the DMD webinar certainly demonstrates the scope of regenerative pharmacology.

Microglia and mitochondria

In her own research, Dolga concentrates on neurodegeneration, particularly on Parkinson's and Alzheimer's diseases. Incorporating microfluidics and iPS (induced pluripotent stem cells) into her work enlarged the scope of processes and mechanisms to study. 'When I was appointed as a Rosalind Franklin Fellow in Groningen in 2015, I got the opportunity to start my own lab', she says. 'That allowed me to think broader about my work and implement new trends in the field. I studied the role of potassium channels in neurodegeneration. When iPS platforms became more broadly available, I decided to move towards using human cells and try out new types of models to better mimic the human condition.'

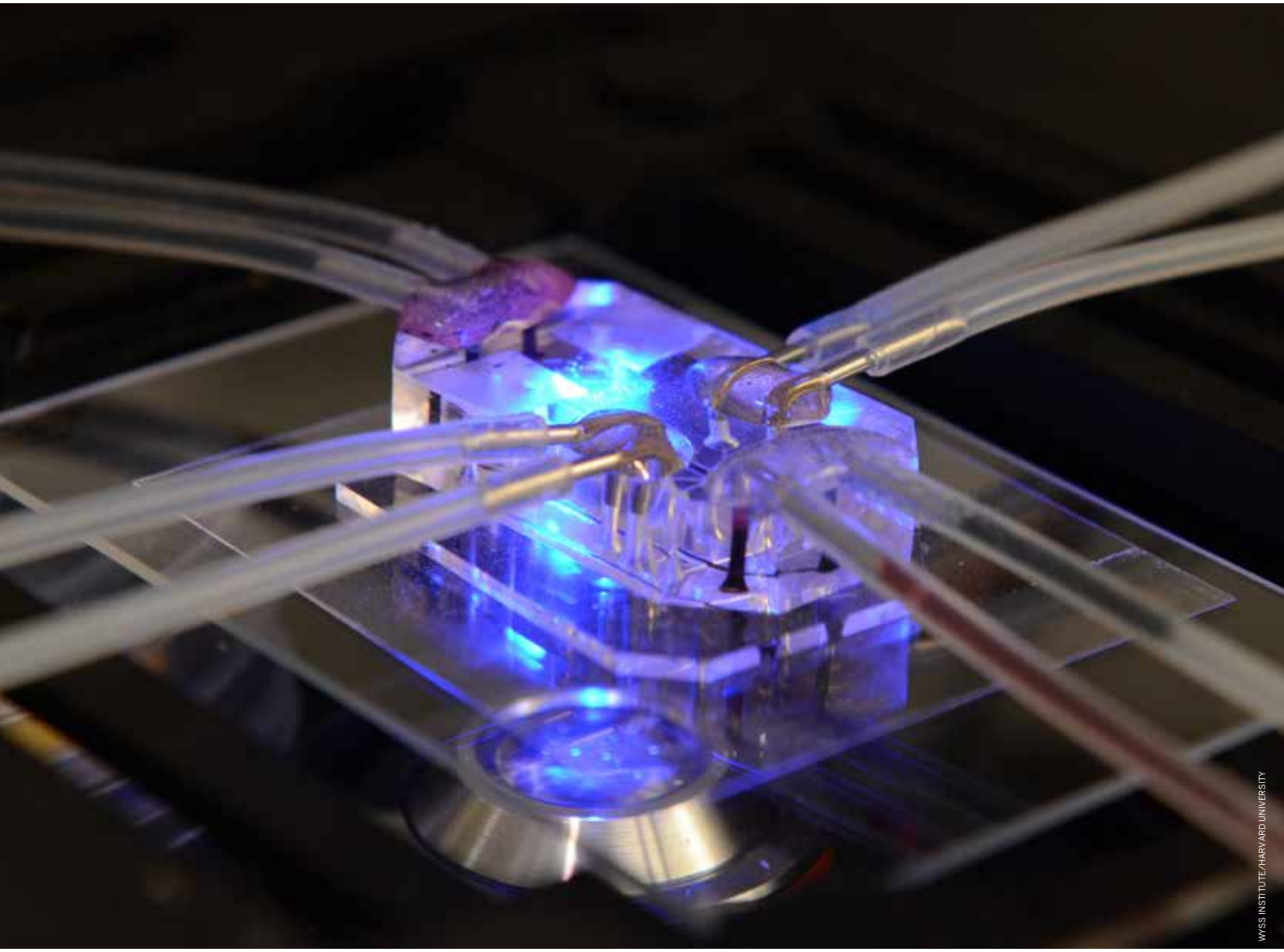
At first, Dolga worked with human differentiated neurons and astrocytes, two types of brain cell. 'It was hard work to get things running, but surely worth the effort.' Next, she expanded her experimental models by including immune cells, because of the role of inflammation in disease pathology – a new direction in the neurodegeneration field. 'For a long time, it was all about neurons in Parkinson and Alzheimer research. Lately, scientists have been moving away from that neuron-centred dogma and more attention is paid to immune cells, which in the brain comes mostly down to microglia. So, we are now studying the function of differentiated microglia, but there are still many questions to address.'

The connection between microglia and inflammation also directly links to the role of potassium channels and the bigger context of cell metabolism. 'We know that potassium channel modulation reduces inflammatory processes and prevents oxidative stress. We also look at mitochondria, since during disease pathology, mitochondria become highly dysfunctional and we want to know how modulation of mitochondria by these potassium channels contributes to neuroprotective pathways.'

And then there is the connection between inflammation and metabolism. Inflammation leads to metabolic reprogramming. All these processes are also observed in Parkinson's and Alzheimer's. 'To me, this interconnection shows that we need to focus on multiple pathways and it also explains why therapy development has been so difficult.'

Cellular communication

Recently, Dolga's group started to work on mimicking cellular communication within the brain using a microfluidics set-up. 'We



A lung on a chip.

are culturing brain cells in different parts of the set-up and then we see if and how they communicate. Initial cellular dysfunction affecting one part of the brain can produce damage in other areas through cell-cell communication.'

But how can all these new approaches of culturing and manipulating human brain cells contribute to drug development? Dolga: 'It can hopefully offer us new pathways to target, for example in the mitochondria. But I also see opportunities to study the connection between the blood-brain barrier and the infiltrated immune cell that could affect the microglia and disease progression. The broader view of all these processes may provide clues to reduce side-effects of new therapeutics.'

'It was hard work, but surely worth the effort'

The regenerative part is difficult when it comes to neuronal damage. Even when disease progression is halted, the damage remains. 'Regeneration is not feasible for all tissues, neurons don't regenerate, but to me this field is also about tissue repair and replacement. A combination of pharmacological compounds and other methods, like for example gene or cell therapy, is probably the most sensible approach. Just focusing on finding one compound that tackles one target or one pathway did not deliver on the promise of any new breakthrough that was announced in the past.'

Bioartificial kidney

Regeneration may be a bridge too far for neuronal pathologies, but for other tissues the possibility should get more attention, says Roos Masereeuw, professor of Experimental Pharmacology at Utrecht University. 'Most drugs diminish or treat symptoms, but in most cases the damage to tissues and organs is not addressed. The ▶

CY12438-26Mar20-AD

repair and regeneration of organs is often overlooked.'

The lack of proper techniques was the main reason, but with the strong rise in stem cell technologies over the past ten years, it is time to change that view. 'There has been so much progress in our understanding of how to use stem cells in culturing human tissues cultures and which biological factors are important to stimulate tissue and organ regeneration. That paved the way for this new field of regenerative pharmacology', says Masereeuw. She has a background in pharmacology and became specialized in kidney research. 'Studying how drugs are transported and processed by the kidneys led us to the development of cell lines that were predictive of kidney function, but they were also promising as a cell replacement therapy to treat kidney failure.'

Around that time, ten years ago, Masereeuw was approached by the Dutch Kidney Foundation to join a collaborative project aimed at the development of an bioartificial kidney to replace the function of the kidney tubules. This is not a replacement of the classical dialysis, Masereeuw explains. 'Dialysis replaces the filter function of the kidneys and our project focuses on replacing the tubular function, which plays a key role in active waste product excretion from the blood into the urine. For proper kidney function, you need both the filter and the tubules.'

As part of this project, the scientists built kidney tubules in an organ-on-a-chip set-up and lined the tubules with kidney epithelial cells. The tubules-on-a-chip not only demonstrate uptake and secretion, they also turned out to be predictive of how drugs and toxic compounds pass through the body and are eliminated. 'As a result, additional applications besides the bioartificial kidney have emerged along the way.'

'Additional applications have emerged along the way'

Integrated organs

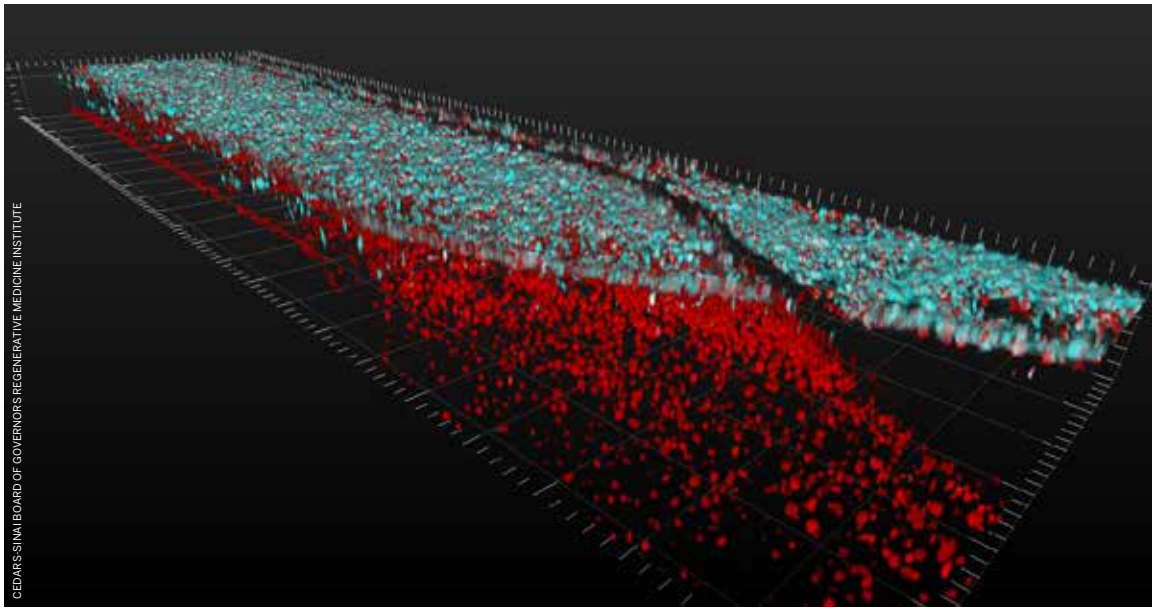
Using the tubules-on-a-chip, Masereeuw could shed new light on the influence of protein binding on excretion of drugs and toxins. In the blood, these compounds are largely bound to proteins, such as albumin, and the assumption was that molecules with a high protein-binding affinity would be more difficult to excrete. 'Our experiments showed the opposite', says Masereeuw. 'Because of a higher affinity for the transporter proteins, compared to albumin, the bound fraction of compounds is shifted to the free fraction, which can be taken up from the blood by the kidney cells and excreted at the other side into the urine. But to observe these processes on the molecular detail, you need the highly-controlled conditions of such a setting. In an animal model, this would not be possible.'

Next to a more fundamental understanding of kidney function, Masereeuw sees translational opportunities. 'The cells in the kidney tubules have a kind of sensor on their surface that monitors the concentration of 'waste' in plasma and, if necessary, activates the production of transporter proteins to accelerate the uptake and secretion process. This way, our body is protected from harmful accumulation of endogenous toxins.'

Now that this mechanism is known in detail, it could offer ways to treat early stages of kidney failure. For example, by activating the cellular waste-sensor. 'We are now exploring ways to stimulate the expression of transporter proteins in genetic kidney disorders. This is very important because we know that the longer we can maintain proper kidney function, the higher the chances for survival.'

Following the promising results of mimicking kidney tubules, Masereeuw has used the same approach to build models of the human intestine and bile ducts and is currently working on an integrated intestine-liver-bile duct-kidney model. 'That way, we can study and even predict pharmacokinetic behaviour of compounds. Looking further, I would also like to include an immune component in this system.' Are you working towards a human-on-a-chip? 'We are nowhere near that, but I'm convinced that if we can couple multiple systems in an effective manner, we will be able to provide new answers to long-standing questions.'

By showing the wide scope and potential of regenerative pharmacology, Amalia Dolga hopes that the DMD sessions will stimulate new ideas. 'We want to awaken the appetite of the Dutch drug development community for this exciting topic.' ●



Spinal cord nerve cells (top, in blue) and blood vessel cells (bottom, in red) interacting on a tissue chip.

Studying the universe of pharmacokinetics

This year's Ariëns Award winner is Malcolm Rowland. He was recognised for his groundbreaking contributions to physiologically-based pharmacokinetics. 'Both the general model and the quantitative principles of clearance and tissue distribution apply to every single drug.'

Since 1985, the Dutch Society for Pharmacology (NVF) has been recognising the work of outstanding international pharmacologists with the annual Ariëns Award. It was named in honor of the Dutch professor Everhardus Jacobus Ariëns, one of the founders of the field of pharmacology. This year's winner is Malcolm Rowland, professor emeritus of the School of Pharmacy, and former director of the Centre for Applied Pharmacokinetic Research, at the University of Manchester, UK. 'I am delighted. I have had a long association with scientists of academia and industry in the Netherlands.'

Predictive mode

Many pharmaceutical students around the world own at least one textbook on pharmacokinetic concepts written by Rowland and his co-author Thomas Tozer. The nestor and leading force in the field of physiologically-based pharmacokinetics has also authored over three hundred scientific publications. Rowland received his pharmacy degree and PhD at the University of London and was on faculty at the University of California San Francisco before taking up a professorship at Manchester.

In his early career, the subject of pharmacokinetics was in its infancy. 'It was all just descriptive back then', says Rowland. 'You gave a patient a drug and then looked what happened. With physiologically-based pharmacokinetics we ask ourselves the fundamental question: which are the underlying principles that cause the observations that we see? If you don't get the 'whys' right, you can't progress any further. You need to get the basic understanding of biology, biochemistry, pathology, and analytics, and integrate all those areas within a modelling frame. As such, we moved from the descriptive mode to the mechanistic, predictive one.'

In addition to the general frame of physiologically-based pharmacokinetics, Rowland was most involved in clearance – quantifying the efficiency of drug elimination – and tissue distribution. One of his keynote publications appeared in 1973: *Clearance concepts in pharmacokinetics*. He laughs: 'The paper is almost indecipherable for most people, but it described nicely the early principles of clearance of drugs in the body. This was a useful parameter for relating the rate at which you had to administer drugs to maintain an effective concentration. Many drugs are being used chronically, and you need to be careful in choosing the right dosage. Understanding clearance is essential for this.'

'If you don't get the 'whys' right, you can't progress any further'

Software platforms

Several papers followed in the late 1970s and 1980s, focusing on models that describe the different ways in which the organs of elimination, notably the liver, deal with drugs. Rowland: 'Companies were also developing animal and in vitro models and they wanted to extrapolate their findings to the human situation. Modelling clearance became an important connection between these studies and human clinical trials.'

The critical importance of tissue distribution is that the interaction of a drug with tissues, coupled with recirculation, defines its systemic pharmacokinetic profile. Historically, this information was obtained experimentally, in animals. This is a demanding situation, which severely limited progress in mechanistic pharmacokinetics, explains Rowland. 'My first keynote paper on this topic, published in 2005, provided a way forward of predicting distribution in all tissues of the body, by relating a tis-

sue's affinity for drug to its physicochemical properties and tissue composition, thereby opening the door to modelling this process.'

For both clearance and tissue distribution many different factors are relevant, including blood flow, blood concentration of the drug, binding of the drug within blood and tissues, impact of enzymes and transporters, and many lifestyle differences between individuals. 'Of course, integrating all these factors cannot be done by hand', Rowland clarifies. 'Enter the age of commercially available software platforms, currently an essential tool for any pharmaceutical enterprise engaged in drug discovery and development.'

Rowland is no longer directly involved in experimental research, but he continues to engage in fostering the development and application of physiologically-based pharmacokinetics through his participation on the scientific advisory board of the most widely used software platform, SimCyp.

Learning every day

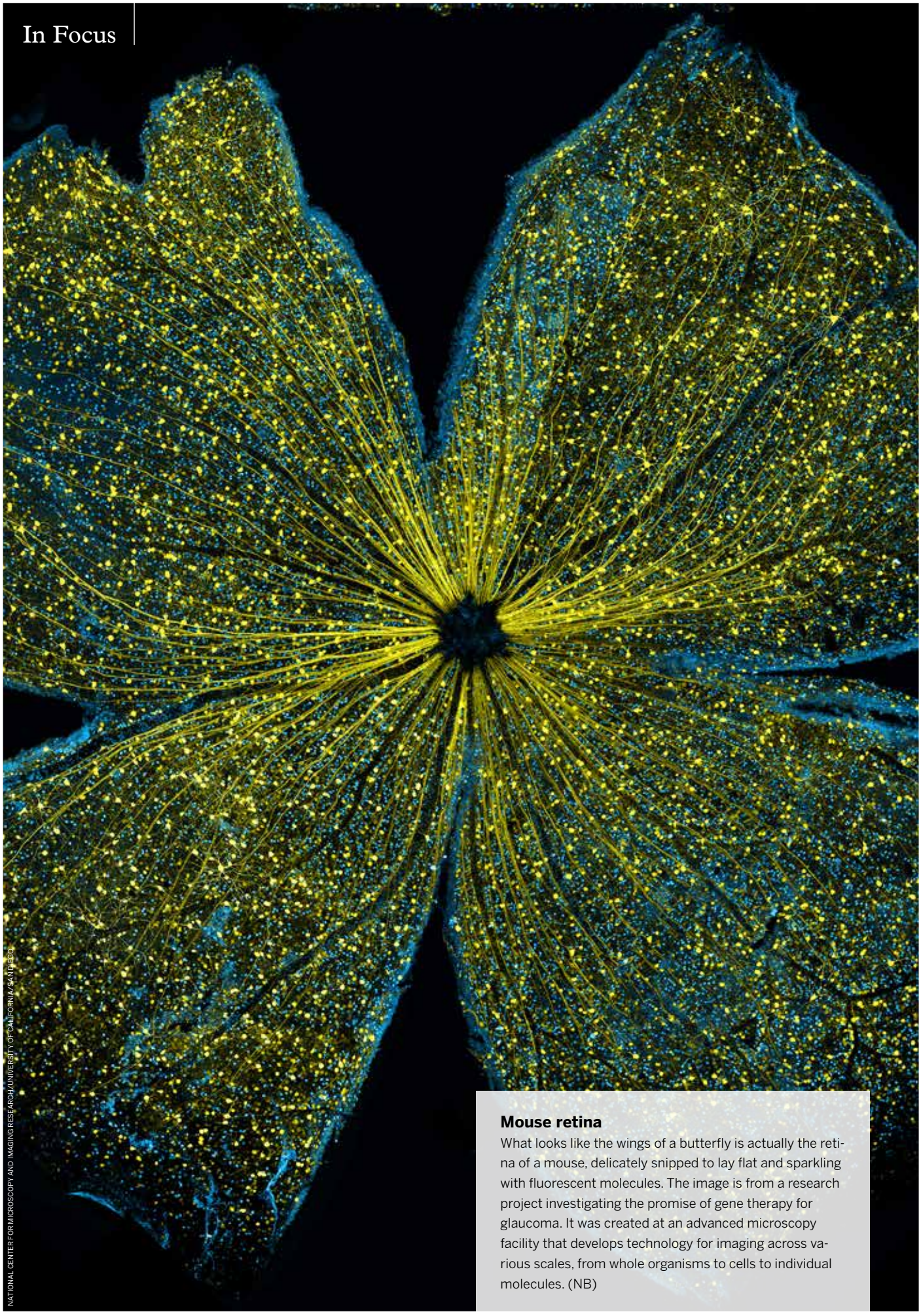
In the coming years Rowland foresees exciting new developments. 'There will be a marriage between physiologically-based pharmacokinetics and systems-driven pharmacology, the response side of the story', he predicts. 'Connecting these two areas means adding other aspects, such as how the disease is changing the body and therefore the kinetics and dynamics of the drug. Another aspect is pregnancy and infant maturation. Futhermore, adverse and immunological effects can be studied better. I think this is going to be a very powerful technique for the future of drug development and clinical use.'

'The biologics call for extra care in modelling'

Of course, there are still bottlenecks. 'For example, the engineering of human tissue and cells that are being used to finetune in vitro modelling still needs improvement', explains Rowland. 'Also, we need to further evolve the techniques to accommodate the upcoming novel class of drugs: the biologics. These large, complex, engineered molecules call for extra care in modelling, so that we are still able to correctly predict the behaviour of these drugs inside the body.'

The FIGON Dutch Medicine Days are held virtually this year due to the COVID-19 pandemic. This is a strange phenomenon for Rowland. 'I am actually a bit disappointed that I will not be there in person. There are always interesting people to meet. I enjoy the challenge of researchers coming up to me and asking about the pharmacokinetics of their drug and how to model their system. Personally, I am still learning every day.'

Looking back at his scientific career, Rowland cannot help but feel proud of what he has accomplished. 'They say I am one of the founders of mechanistic pharmacokinetics and only now am I starting to realise this', he says. 'One of the really nice things about the field is that the principles are very general, irrespective of the therapeutic class of compound. So, if someone asks me what I do for a living, I say: I am studying the universe. This gives me a great sense of satisfaction.' ●



NATIONAL CENTER FOR MICROSCOPY AND IMAGING RESEARCH/UNIVERSITY OF CALIFORNIA/SAN DIEGO

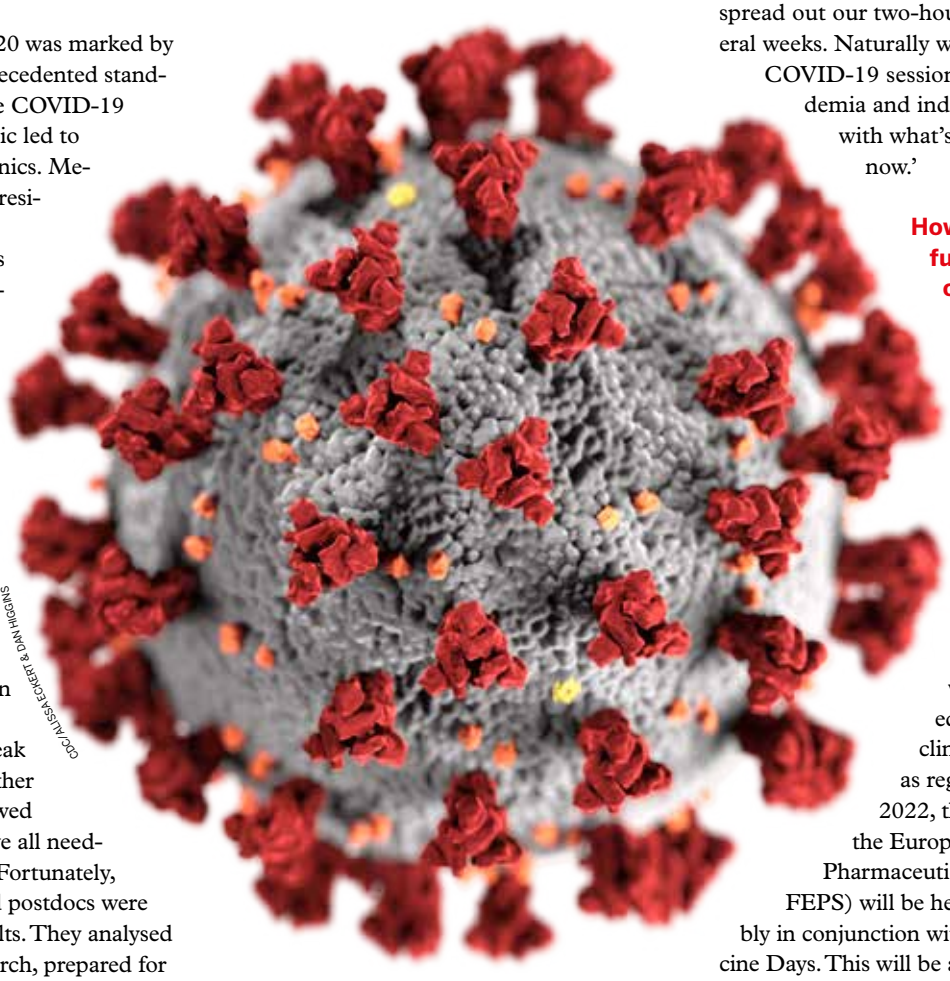
Mouse retina

What looks like the wings of a butterfly is actually the retina of a mouse, delicately snipped to lay flat and sparkling with fluorescent molecules. The image is from a research project investigating the promise of gene therapy for glaucoma. It was created at an advanced microscopy facility that develops technology for imaging across various scales, from whole organisms to cells to individual molecules. (NB)

COVID-19 as a catalyst in drug research

This year, the FIGON Dutch Medicine Days were held online due to the COVID-19 pandemic. Although this saddens FIGON president Anke-Hilse Maitland-van der Zee, she also sees opportunities for the field.

March 2020 was marked by an unprecedented standstill. The COVID-19 pandemic led to quiet labs and empty clinics. Medicines asked FIGON president Anke- Hilse Maitland-van der Zee, who is also a professor of Precision Medicine in Respiratory Diseases at the University of Amsterdam, to reflect on this exceptional year for FIGON and the Dutch pharmaceutical sciences.



CDC/ALISSA ECKERT & DAN HIGGINS

How did the pandemic affect your own work so far?

'My team works partly in the laboratory, partly in the clinic. During the peak of the crisis this work either ceased altogether or slowed down considerably, as we all needed to work from home. Fortunately, many PhD students and postdocs were still producing nice results. They analysed data, did literature research, prepared for new studies, wrote publications and even applied for grants. So we did adapt well to working from home. But I think most people are very happy now that projects are starting up again – of course with the appropriate restrictions.'

The pandemic has also brought benefits to your field. Can you explain this paradox?

'The entire world is suddenly very interested in the search for a vaccine, or a treatment. Dutch scientists are involved relatively much in clinical trials and production facilities. And Dutch pharmaceutical company Janssen Vaccines is still in the race to develop a COVID-19 vaccine. I think FIGON can play a role in all of these developments. We are the umbrella organisation that brings together researchers in industry and academia and facilitates their knowledge exchange. If we want to combat the virus, we need this network more than ever.'

The FIGON Dutch Medicine Days were held online this year. Was this a tough decision to make?

'To be honest, I prefer live DMD, where you can meet everyone and have a chat. But since this was not an option, I think it was important that we at least organised something. We had to take this opportunity to advance the pharmaceutical sciences even further by connecting people. If not in person, then online. We have chosen to spread out our two-hour sessions over several weeks. Naturally we also held a specific COVID-19 session to bring both academia and industry up to speed with what's happening right now.'

How do you see the future of pharmaceutical sciences in the Netherlands, and FIGON's role in this?

'COVID-19 has been a catalyst in bringing attention to this type of research in the Netherlands. FIGON can help channeling this, as we are active in education, lab and clinical research as well as regulatory affairs. In 2022, the annual meeting of the European Federation of Pharmaceutical Sciences (EUFEPS) will be held in Leiden, probably in conjunction with the Dutch Medicine Days. This will be another opportunity to bring Dutch research into the spotlight and engage other European researchers. Hopefully this will stimulate collaboration and the exchange of information. We have some exciting years ahead of us!' ●

DIRK GILLISSEN

Anke-Hilse Maitland-van der Zee

Ab Osterhaus: 'We shouldn't let it slip through our fingers'

Criticaster of The Dutch Approach

After a lengthy career and extensive experience with viral outbreaks in animals and humans, Ab Osterhaus has become the Netherlands' best-known virologist. He is often critical of the Dutch response to the COVID-19 pandemic and calls for a more thorough preparation in peacetime. 'I can assure you: this is a relatively mild pandemic.'

Ab Osterhaus (72) has worked in Germany for many years now, but since the coronavirus outbreak he is often seen on Dutch television. He tends to strongly criticise the approach taken in the Netherlands regarding the pandemic and warns of imprudence and the possibility of new outbreaks. Being labelled a purveyor of doom and gloom does not worry him, says Osterhaus. He doesn't read Dutch newspapers and social media. Moreover, he has become accustomed to such criticisms.

'My communications have always carried a cautionary message. Beware, it may get completely out of hand. For instance, during the BSE crisis in the nineties I chaired the Scientific Committee on Veterinary Measures in Brussels. From the very outset I warned that it could be dangerous for humans too. In England, there were attempts to fire me, given that I was harming British meat exports. And the funny thing was that some years later the same journalists who had originally criticised me asked: why didn't you tell us earlier that it could be so harmful for people? You just can't seem to do anything right.'

Is issuing warnings one of the tasks you have imposed upon yourself?

'If as a scientist you foresee danger in your own field you have to warn people of that threat. It's better to be too cautious than to be not careful enough. It's like fortifying a dyke to resist a potential flood that might never happen. Preparing yourself for a pandemic is similar. I have been saying this for years, also when the Mexican swine flu came about. At the start I said: it would not be unwise to stock up on vaccines for a third of the population in the Netherlands. Many people were vaccinated. Ultimately, the Mexican swine flu passed relatively easily, partly thanks to the vaccinations, even though hundreds of thousands of people died around the world. Subsequently, there was an absolute boom of criticism, plus a false accusation that I had made money on the production of the vaccine. That is annoying and and that image sticks with you.'

If it turns out to be not all that bad, do you, as an expert, get chided for it?

'Oh, I can live with that. Moreover, I've usually been right. Take the mad cow disease for instance, and the bird flu as well. I pointed out the danger of bird migration in connection with the spread of bird flu. At a given moment I was nicknamed the 'poultry confinement professor' because I strongly urged keeping free-range chickens indoors. Nowadays that is almost the standard policy during periods of bird migration. But if you're the first person to make such claims, you will not be thanked for it, certainly not by the people who are directly affected. The same thing holds for Covid-19.'

'I've usually been right'

You warned of a second wave of Covid-19 on Dutch national television. People complained, saying you were too negative.

'All I'm saying is that it is not wise to relax measures too soon. More than ninety percent of the population has not yet been infected with this new coronavirus. I think the first thing you should do is strongly implement effective screening, testing, contact tracing and isolation. Just like they did in South Korea. Wide-scale testing and ensuring that infected people are quarantined. Luckily, that policy is now gradually being introduced. If I look deeper into it, I think a couple of opportunities have been missed to limit the effects of the virus. All those people returning from their winter sports activities in Italy and Austria being immediately allowed to go to the carnival...


ANTON DOMMERHOLT

Ab Osterhaus

▶ **2013-today**
professor and director, Research Institute for Emerging Infections and Zoonoses, Veterinary University of Hannover, Germany

▶ **1993-2013**
head of virology, Erasmus MC, Rotterdam

▶ **1993-2013**
professor of virology, Erasmus MC, Rotterdam

▶ **1990-2011**
professor of environmental virology, University of Utrecht

▶ **1978-1994**
Netherlands National Institute for Public Health and the Environment (RIVM)

▶ **1974-1978**
PhD on a corona virus in cats, University of Utrecht

▶ **1967-1974**
MSc in veterinary sciences, University of Utrecht

At that time, reports had already come in from China that the virus could be spread before symptoms appeared. That really made me scratch my head.'

Does your commentary annoy any of your colleague virologists, since you are on the sidelines while they are setting out the guidelines?

'There is a difference between the role I had in the past, when I was a member of the Health Council and outbreak management teams, and the position I am in now. Now, I can speak freely. Maybe that does cause irritation. If you are on the Outbreak Management Team, OMT, you are required to observe discretion when speaking to the media. I don't think that's always the right thing to do. For instance, a couple of times I said: show the computer model that illustrates the actual spread of the virus. That is available online in the UK. In the Netherlands, it is the National Institute for Public Health and the Environment, RIVM, that manages the model. But a discussion on that subject is virtually impossible. I don't think that is the right policy.'

'The solution lies at the beginning, not at the end'

You are too knowledgeable and experienced to just sit back?

'Well, I do sometimes tend to let things take their own course. In fact, I retired, but took up my career again in Germany where I'm now working with a large group of researchers. On the other hand: my family and friends all live in the Netherlands. And if everyone, including the Prime Minister, says: I follow the science completely, then I think: there is no 'the' science. Scientists have to publish and discuss their work and lay bare the results of their work for review by colleagues. I can imagine that certain matters are not really suitable for public debate. However, I feel that it is somewhat inept for an OMT to categorically not enter into discussion with the scientific community.

There is also a lack of practical experience in the Netherlands.

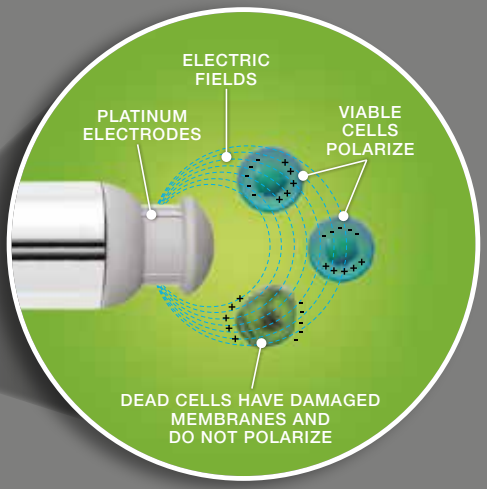
'Yes. I remember being asked on a national TV show whether a lockdown should be imposed like in some Asian countries. Of course it should, I said, with strict enforcement. That also resulted in a surge of outrage. A lockdown wouldn't be commensurate with the Netherlands, certainly not if enforcement is involved. I also said – and this too went against the grain – that the Netherlands is pursuing a 'wimps' policy. Ultimately, everyone had to stay at home and police were taking action in public parks.' ▶

Automate Process Adjustment

IncyteArc Measures Viable Cell Density in Real Time

Incyte**ARC** is insensitive to media changes, microcarriers, dead cells and floating debris. It can be used to monitor changes in cell physiology, cellular respiration, **viral infection** timing, automated harvesting and much more.

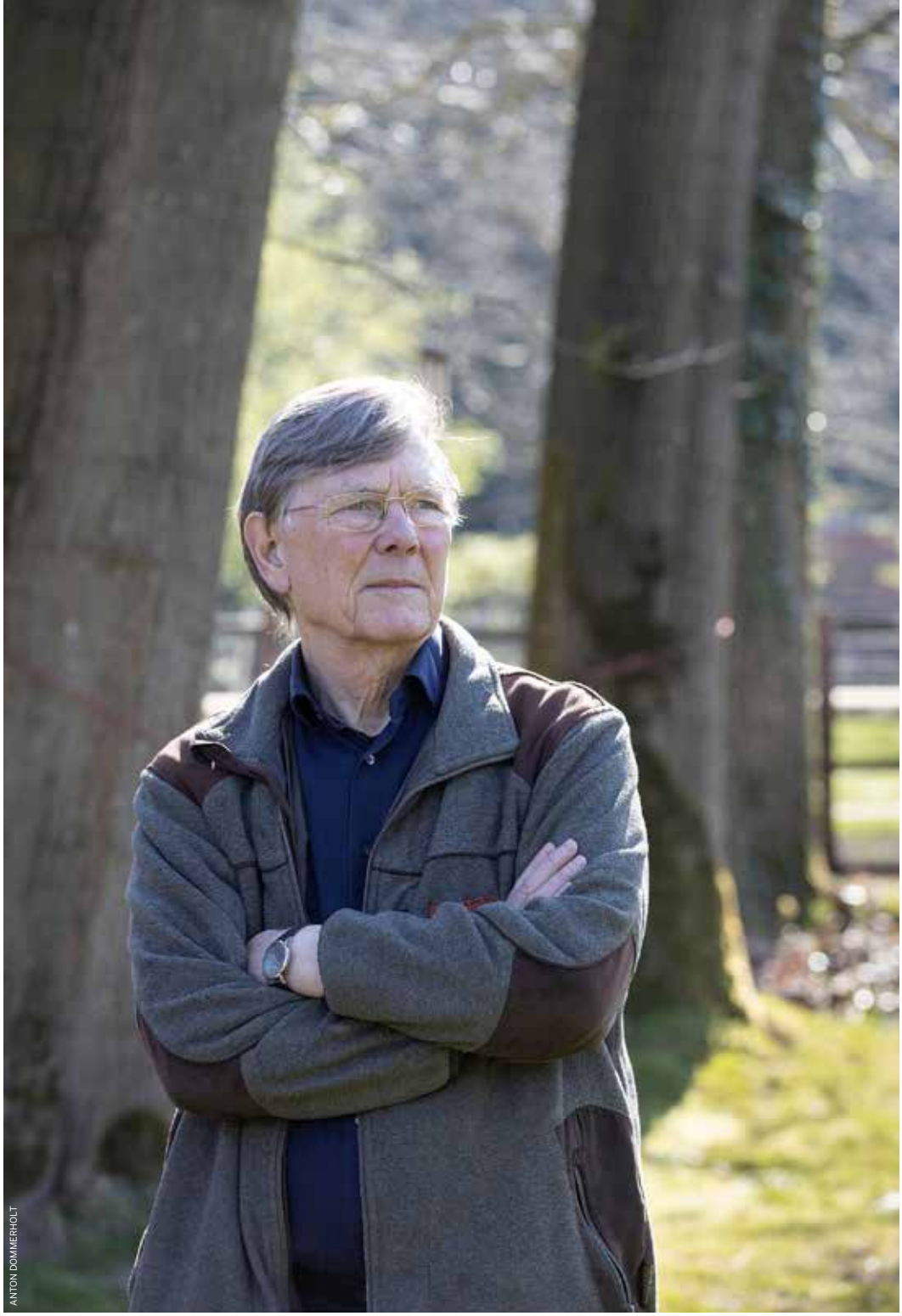
- **Precise control of process actions**
- **Early detection of process events**
- **Detection of changes in cell physiology**



Learn more at www.ham-info.com/0962

www.hamiltoncompany.com

HAMILTON®



ANTON DOMMERHOLT

You also said that the world was simply insufficiently prepared.

'I frequently use the metaphor of the Delta Works. Every year we spend tens of millions on monitoring and reinforcing our dykes. How many people have lost their lives since 1953 in the Netherlands through flooding? Suppose we had developed generic antiviral drugs against corona and influenza viruses. We would not have needed to muddle through with drugs such as chloroquine. In peacetime you have to prepare yourself with diagnostics, a good stock of face masks and generic drug and vaccine development. Because I can assure you that we are still in a relatively mild pandemic. I could mention some four or five other pandemic scenarios that could emerge after COVID-19.'

'Certain matters aren't really suitable for public debate'

Will we look at this crisis like we did at the flood in 1953 and then prepare properly for the next pandemic?

'People have short memories. We are well aware of outbreaks of infectious diseases with a huge death toll from our history books, but we don't really think about them seriously. Even if you've warned of the Mexican swine flu you are subsequently faced with moans about the cost of a vaccine, at least half of which has not been used. That demonstrates a sort of small-minded mentality and the Netherlands is by no means an exception. If you look at how hard the economy is being hit, wouldn't it have been much better if we had been able to invest € 10 billion world-wide in preparing for a pandemic? I hope people will start to see that as an insurance policy.

That the press and politics act so blasé, I find somewhat disturbing. They say: things are now reasonably under control. But it's so important that now of all times we don't let it slip through our fingers. You have to be cautious, keep testing, and ensure that infected people and their contacts are quarantined. That is ultimately also better for the economy.'

It is remarkable to see the different approaches of nations and heads of state.

'Exactly. Look at Boris Johnson, Donald Trump and Jair Bolsonaro. Total denial at the beginning, and that's the start of all the misery. Many countries are now getting things reasonably under control. A Dutch hospital physician said recently: our intensive care units can now handle it, so we can reconsider the measures. From his point of view, after all the heroic work they have performed, that's understandable. But obviously not from the national point of view. As if the number of beds in intensive care units is the criterion. We should be happy that – partly thanks to the efforts of care workers – we have actually passed through the eye of the needle, but it must not happen again. The solution is not to be found at the end of the journey to the hospital, but at the beginning, in curbing the virus.' ●

Immunology text book deserves an update

It has long been believed that the congenital immune system did not have a memory. But there is an increasing number of indications that it does, as well as that vaccines can have both a positive and a negative effect.

It is 2010 when a researcher is carrying out a study into the effect of the BCG vaccine against tuberculosis – an attenuated version of the tubercle bacillus that infects cattle – in the laboratory of Mihai Netea, Professor of Experimental Internal Medicine at Radboud UMC in Nijmegen. In half the lab dishes she exposes blood samples from vaccinated volunteers to the tubercle *Mycobacterium bacillus tuberculosis*, and to the control dishes she adds Candida yeast in its stead.
One day the researcher reports to Netea that something has probably gone wrong: after the BCG vaccine the immune cells in the blood were resistant not only to the tubercle bacteria but also to the yeast. Is that really possible? After all, that's not the intention of the vaccine, is it? She repeats the experiment, but arrives at exactly the same conclusion.

Preparedness

Netea decides to delve into the literature and comes across a considerable number of studies in which the effect of BCG on several pathogens was described, ranging from malaria to listeria and influenza. Together with two of his colleagues he publishes the first article on this phenomenon in 2011 in *Cell Host Microbe*, calling it 'trained immunity'. Over the past ten years, Netea and other researchers have discovered that BCG triggers specific white blood cells of the congenital immune system, called monocytes, to become more active. These monocytes can transform into macrophages that devour unwelcome intruders. These changes occur partly due to epigenetic changes: the genes involved in the metabolism of these cells are activated or switched to a higher gear.
This higher level of preparedness occurs not only in the blood monocytes but also in the bone marrow that produces these cells and gets them ready to take action. This means that the effect can continue for months. 'We also demonstrated that this higher level of activity leads to a higher level of protection', says Netea. 'After injecting the yellow fever vaccine, there are fewer virus particles found in the blood taken from the volunteers in the vaccinated group five days later.'
The discovery of this congenital immune system's 'memory' was considered quite spectacular at the time. Up until then, it was worded in the textbooks as follows: our defence system consists of the congenital immune system, which rapidly, and more or less non-specifically, attacks anything foreign to the body and thus deals with 99 % of infections, and the trained immune system, which generates memory cells during the initial infection to ensure that the intruder is cleared up more quickly in the event of a second infection. This is the mechanism used by vaccines.
'There are probably more mechanisms that play a role besides the epigenetic changes', says Tobias Kollmann, a physician specialised in childhood infectious diseases at the Telethon Kids Institute in Perth, Australia. At a conference in February he presented results that show that vaccines like BCG can trigger emergency granulopoiesis in newborn babies, a process in which in a short space of time more neutrophils – another type of cell of the congenital immune system – are released. These lower the number of bacterial infections and consequently the chance of sepsis. 'This process only lasts a week after vaccination', says Kollmann. 'But because the effect is so strong it makes an enormous difference.'

'We advocate giving a second, live vaccine after the first one'

Live vaccine

The findings of Netea and others are in line with observations in practice. For dozens of years now, two Danish researchers, Peter Aaby and Christine Stabell Benn, have been researching the non-specific effects of vaccinations in Guinea-Bissau, West Africa. They looked at the number of deaths in the period after vaccinations and arrived at the hypothesis: live vaccines, such as BCG and the rubeola vaccine, raise the resistance to other pathogens and consequently lower the total number of infections by up to 70 %; on the other hand, dead vaccines or vaccines with only pieces of the pathogen lower resistance and therefore the number of infections rise. The most important vaccine is the one against pertussis, generally given together with those against tetanus and diphtheria in developing countries. 'We therefore make a case for giving a different live vaccine subsequent to the pertussis vaccine, for instance the one against rubeola, in order to negate the immune attenuating effect', says Stabell Benn.

Tuberculin testing army recruits. Image from National BCG committee annual report 1960.

Negative effects

Netea is not yet completely convinced of the damaging effects of the pertussis vaccine and that strict division of 'living-favourable' and 'non-living-unfavourable'. 'That division is fabricated. It is important how a vaccine is made non-living. It is probably to do with the kind of stimulus, depending on the molecules that trigger the immune system.'

Boosting the congenital immune system sounds positive, but could also have negative effects. In theory it could contribute to chronic infections resulting from an overactive immune system, was the view of another researcher at Radboud UMC, professor of Vascular Medicine Niels Riksen, shortly after the first publication.

The immune system, as had become known in previous years, also plays a role in atherosclerosis. Out of this flowed a project on which PhD candidate Siroon Bekkering started working: 'If a bacterium is able to boost the congenital immune system, can a molecule like cholesterol do the same? And if so, under what circumstances? And could that also explain why some people do and others do not get atherosclerosis?'

'There are probably other mechanisms besides epigenetic changes'

In the laboratory, she exposed the white blood cells of healthy volunteers to cholesterol-containing particles and discovered that – a few days later – this gave rise to a stronger immune response to bacteria. 'Currently, we know there are numerous particles associated with cardiovascular disease that promote the congenital system, whereby the white blood cells respond more actively and can therefore cause more cardiovascular diseases', says Bekkering.

In response to this line of research, Netea feared that people whose chance of infections had been lowered in the short term, for instance by BCG, would have an increased risk of developing atherosclerosis in the long term. 'But fortunately that is not the case', he concludes. It even looks as if the reverse is possible: American researchers demonstrated in *Diabetes* that the BCG vaccine apparently is effective against diabetes mellitus type 1, an autoimmune disease. It appears that the vaccine activates certain regulatory immune cells that bring the defence system in balance again.

Over the next few years Netea hopes to gain understanding which specific molecules will be key in boosting or lulling into sleep the congenital immune system, both for combatting infectious diseases and inflammatory processes such as atherosclerosis. This would pave the way for the potential adjustment of existing vaccines and specific administration of adjuvants. ●

COVID 19 – an accordionist's approach to drug development

All our FIGON partners have no time to lose.

It seems hardly necessary to discuss the impact that 'the Virus' has on every part of our society, on every fiber of our system and on every aspect of our daily lives. Equally so, it has affected the life and work of all our FIGON partners. These partners have at least one thing in common: dedication to innovative drug research and development. To rapidly respond to the medical need in the face of the pandemic is a mammoth task. It will require combined efforts from medical specialists, researchers, governments, drug development companies, and many others in order to succeed. We have no time to lose.

ADOBE/LEIGH PRATHER

Progress has already been made. Within weeks, the full-length genome sequence of SARS-CoV-2 was elucidated, allowing the start of drug development. An adequate pharmaceutical response to SARS-CoV-2 infection may prevent disease and allow patients to recover.

This task is taken to heart by all of us. Our FIGON partners are all involved in the search, the research, the development, the evaluation of potential safe and effective treatments and vaccines, or the treatment of patients, whether experimentally or in the clinic. All involved are pushed to reach out and collaborate across boundaries in an unprecedented exercise to find multiple, effective solutions. With combined efforts we can compress the time it takes. Where most aspects of drug development were sequential in the past, now they are increasingly overlapping. COVID-19 requires us to address every aspect of the development in parallel, like an accordionist pressing the bellows of his instrument to squeeze out the last whiff of air.

The 2020 DMD Virtual Series presents insights in the efforts of our partners, who operate at the forefront of this development. Over the next couple of weeks, we will host several sessions that address the challenges that we face addressing this global health threat and show you how, through collaboration, we can face this global challenge. ●

Just Weemers,
Chair of the DMD Organizing Committee 2020

▶ Please visit **www.figondmd.nl** to participate.

COLOFON

WWW.FIGON.NL

FIGON is the integrative platform for innovative drug research in the Netherlands. The platform promotes interactions among all parties in the drug research in the broad sense, such as scientific and professional associations, universities, business and government. The platform reinforces existing initiatives in this area, identifies and explores new developments in the field and has an active policy in the context of the mission. FIGON is open to all relevant groups in this regard

FIGON Secretariat
Miranda Meulstee
Pelmolenlaan 2, 3447 GW Woerden, the Netherlands, +31 85 02 90 194, info@figon.nl

FIGON board

Chair: Anke-Hilse Maitland-van der Zee
Treasurer: Peter Bertens
Secretary: Ed Moret
Members: Martina Schmidt, Gerard Rongen, Ton Rijnders, Kees Kramers, Meindert Danhof, Saco de Visser

FIGON partners

- Nederlandse Vereniging voor Klinische Farmacologie & Biofarmacie (NVFK&B), kees.kramers@radboudumc.nl
- Nederlandse Vereniging voor Farmacologie (NVF), secretary@nvfarmaco.nl
- Nederlandse Vereniging voor Farmaceutische Wetenschappen, sectie Geneesmiddeltoxicologie (NVT/sectie GT), la.v.aerts@cbg-meb.nl
- Koninklijke Nederlandse Chemische Vereniging, sectie Farmacochemie (KNCV/sectie FC), peter.molenveld@mercachem.com
- Nederlandse Vereniging van Klinisch Farmaceutisch Analisten in Ziekenhuisapotheken, (NVKFAZ), liesbethindira@gmail.com
- Groningen University Institute for Drug Exploration (GUIDE), m.schmidt@rug.nl
- Leiden Academic Centre for Drug Research (LACDR), h.irth@lacdr.leidenuniv.nl
- Brain Center Rudolf Magnus (RMI), r.a.h.adan@umcutrecht.nl
- Utrecht Institute for Pharmaceutical Sciences (UIPS), e.e.moret@uu.nl
- ZonMW, info@zonmw.nl
- Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP), m.teichert@knmp.nl
- Nederlandse Verenging van Ziekenhuisapothekers (NVZA), secretariaat@nvza.nl
- Regulatory Science Netwerk Nederland (RSNN), p.v.meer@cbg-meb.nl
- Vereniging Innovatieve Geneesmiddelen, p.bertens@innovatievegeneesmiddelen.nl
- Lygature, info@lygature.org

Small molecules against SARS-CoV-2

A better model of the 3D structure of the coronavirus genome produces reference points for therapy.

'Elegant and innovative' research. That is how colleagues typify the recent work on SARS-CoV-2 carried out by Danny Incarnato, university lecturer of molecular genetics at the University of Groningen. Incarnato is looking at the 3D structure of the RNA of SARS-CoV-2 for reference points for the development of a drug; not at the proteins like most researchers do.

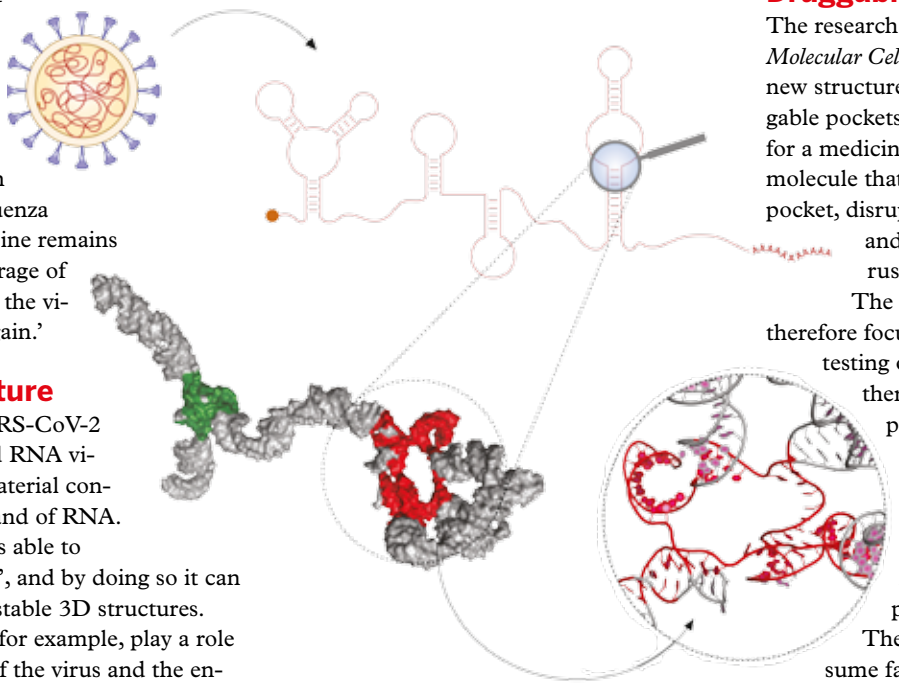
'The 3D structure of RNA can be conserved much better than the proteins and, consequently, there is less risk of a potential medicine becoming ineffective after some time if the virus mutates', says Incarnato. 'The fact that the virus will mutate seems apparent.' The type of virus to which SARS-CoV-2 belongs is well known for that. 'Take influenza for instance: a vaccine remains effective for an average of one year, after that the virus has mutated again.'

Crucial structure

Like influenza, SARS-CoV-2 is a single-stranded RNA virus. The genetic material consists of a single strand of RNA. Because of that it is able to 'fold back on itself', and by doing so it can form more or less stable 3D structures. 'Those structures, for example, play a role in the replication of the virus and the enveloping of the genome in the viral envelope', explains Incarnato.

Incarnato and his team used a combination of in-vitro-RNA-folding, multiplex PCR, mutation analysis and predictive software to obtain an idea of the virus genome 3D structure. 'Smaller sections had already been mapped out, but we were the first to do this for the complete genome of 30,000 bases', Incarnato explains. The validation of his method comes from the fact that the structure of the earlier mapped sections was correctly predicted by his method. 'Some sections of the SARS-CoV-2 and associated coronaviruses are highly conserved', says Incarnato. 'We also found that some eight percent of the SARS-CoV-2 genome shows covariation.' Covariation entails that a first mutation that causes structure disruption can be overridden by another mutation. This is a strong indication that certain structures are crucial for the virus. For example, it is known from other coronaviruses, including SARS from 2003, that a so-called pseudoknot is essential for the translation machinery to spring back during protein synthesis so that a second protein, which overlaps the first, is also synthesised.

'RNA can be conserved much better than proteins'



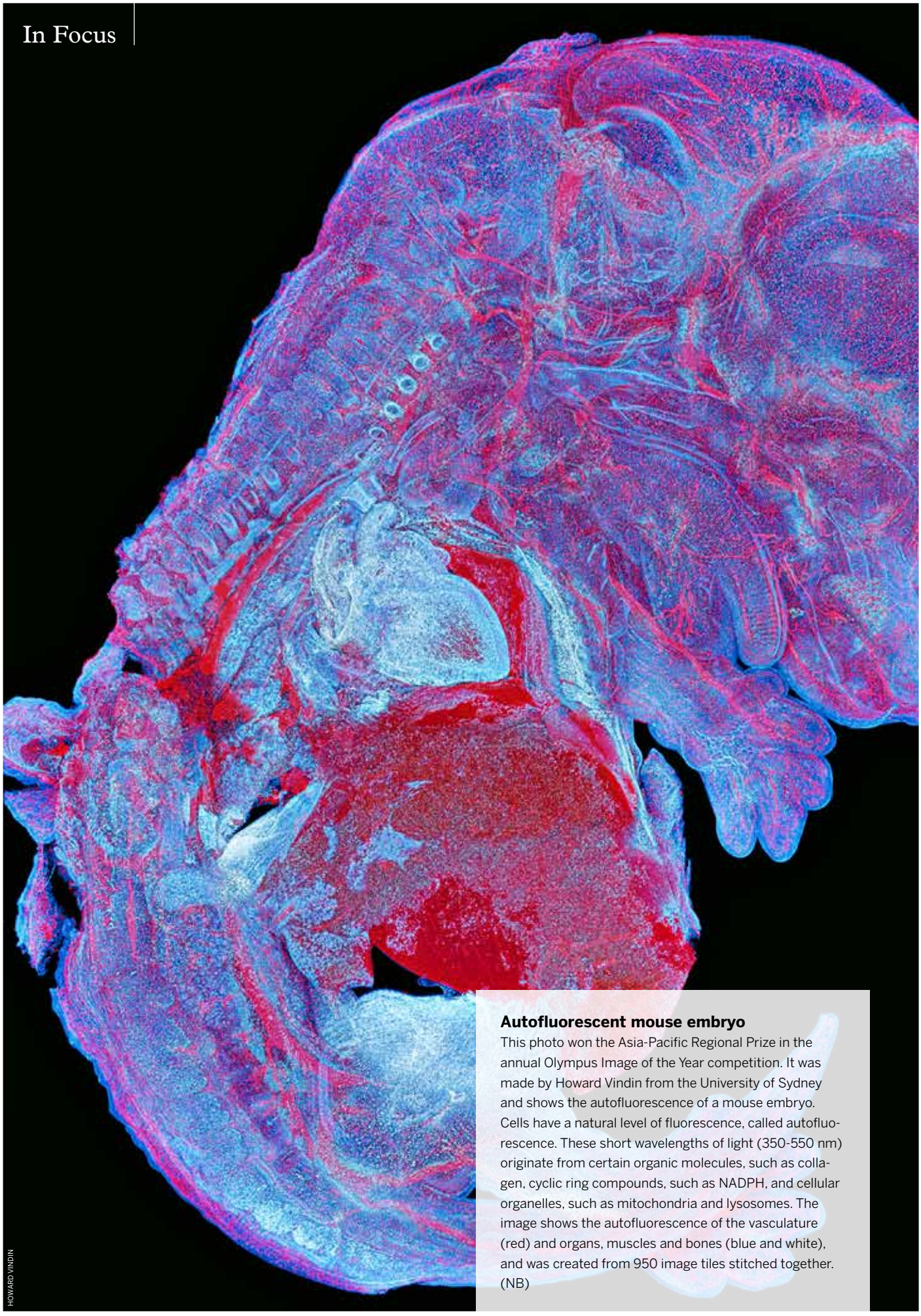
Top left: a SARS-CoV-2 virus particle. Top right: the complete RNA genome, partly folding back on itself. Bottom left: 3D segment of the genome, potentially interesting as a drug target. Bottom right: simplified representation of the fragment.

Druggable pockets

The research that Incarnato submitted to *Molecular Cell* in June identified different new structures. Incarnato calls them druggable pockets. Those are potential targets for a medicine. The idea is that a small molecule that fits exactly inside such a pocket, disrupts an important interaction and consequently renders the virus less effective.

The follow-up to his research therefore focuses on the development and testing of such small molecules for therapeutic application. 'That expertise is outside the realms of my own laboratory', says Incarnato. 'We have therefore started to collaborate with John Schneekloth of the American NIH who is an expert in that field.'

The follow-up phase will consume far more time than the one-and-a-half months Incarnato needed for this research. 'We already had many of the tools we needed, given that I had carried out similar research two years earlier on influenza', he says. 'And yes, I did ask a lot of my PhD candidates during that time.' ●



HOWARD VINDIN

Autofluorescent mouse embryo

This photo won the Asia-Pacific Regional Prize in the annual Olympus Image of the Year competition. It was made by Howard Vindin from the University of Sydney and shows the autofluorescence of a mouse embryo. Cells have a natural level of fluorescence, called autofluorescence. These short wavelengths of light (350-550 nm) originate from certain organic molecules, such as collagen, cyclic ring compounds, such as NADPH, and cellular organelles, such as mitochondria and lysosomes. The image shows the autofluorescence of the vasculature (red) and organs, muscles and bones (blue and white), and was created from 950 image tiles stitched together. (NB)

'Visual information stays in your memory longer'

Artistic science

Zuyd University of Applied Sciences in Maastricht offers a Science Illustration programme. Claudia Cárceles Román and Jon Jieh-hen Tsung followed this unique master's programme and share their experiences here.

After obtaining his bachelor's degree in life sciences and working for three years as a research assistant in Taiwan, Jon Jieh-hen Tsung (29) decided to change his career path completely. 'Although I really did enjoy doing neuropsychiatric research I realised that an academic career wasn't really my thing', he says. 'I needed more creativity and freedom, and I found just that in the international master's programme Scientific Illustration at Zuyd University of Applied Sciences.'
Claudia Cárceles Román (27) also had doubts about her next career step after completing her bachelor's in biology at the University of Gerona in Spain. 'In addition to science, I loved drawing and had always wanted to do something artistic', she says. 'When I found the programme offered in Maastricht, that combines both, I immediately fell for it.'

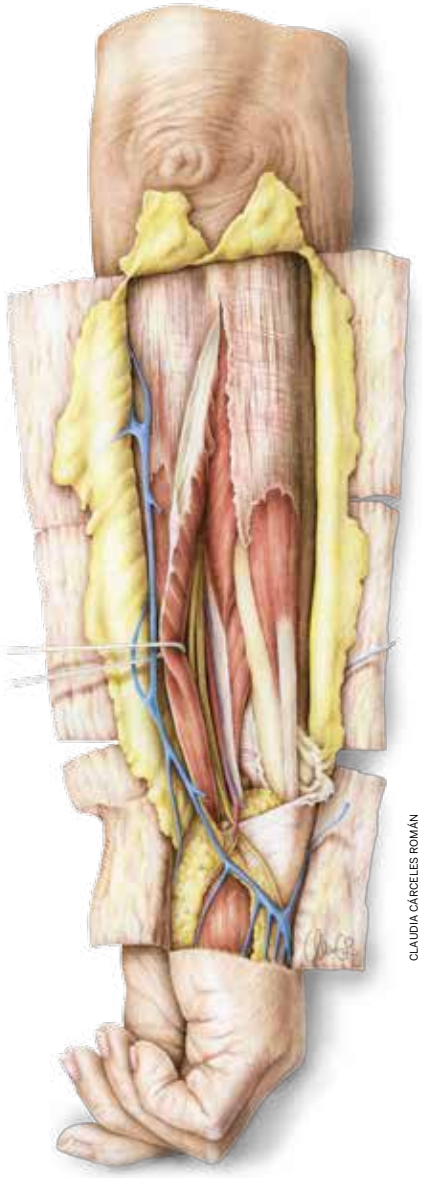
Communication

Students holding a bachelor's degree in the arts or sciences can enrol in the Scientific Illustration programme, which is unique in Europe. Over a period of two years the students learn to make accurate visualisations of clinical, medical and biological subjects in a splendid studio located in the centre of Maastricht. 'Among other things, we were given training in traditional and digital illustration techniques, such as life model drawing and Adobe Illustrator', tells Cárceles. 'We were also given practical lessons in anatomy in collaboration with Maastricht University's Medical Faculty.'
'In essence, you are taught to translate science into a fitting illustration that is of interest to a more general public', Tsung explains. The main thing is that you are able to communicate well with specialists from a variety of disciplines and also have a clear understanding of your target group, both Tsung and Cárceles stress. The programme curriculum therefore includes different communication subjects.

Attention

'Hopefully, a growing number of scientists and students will become aware of the importance of visualising complex medical and scientific subjects', says Cárceles. 'After all, visual information can be understood better and stays in your memory longer.' For the past eighteen months, she has been working in Grenada, West Indies, at The Center for Biomedical Visualization of the St. George University where, together with twelve other medical illustrators, she creates visual and learning materials for the medical faculty and the researchers of the university, including infographics, anatomical models and animations.
'My goal is to make research more visual so that it can be understood by a much wider public', says Tsung. Through his company, ScienceVisionary, which he founded after completing his master's degree, Tsung helps biomedical scientists to communicate about their research by means of graphical abstracts, videos and digital design. He also holds illustration workshops for students at various universities and hands out DIY tutorials for biomedical illustrations on his YouTube channel, DrawBioMed. Tsung: 'Hopefully, science will get more attention through my work and help researchers to find funding more easily.'
Cárceles advises students interested in science illustration to start drawing as much as possible. 'You might become as enthusiastic as I am and soon find your dream job', she says. 'You can be engaged in science in so many different ways', adds Tsung. 'The conventional route is not the most appropriate option for everyone. The most important thing is to do what you love.' ●

'My goal is to make research more visual'



CLAUDIA CÁRCELES ROMÁN

Watercolour illustration based on the disection of the forearm.

'Our ultimate goal is to eliminate waste-producing chemical processes'

Frustration results in start-up

Using computer models, you can make bacterial cell factories much faster, Linda Dijkshoorn discovered. She hopes to be able to storm the markets with her startup EV Biotech. 'We have the computational power to model all organisational layers of a micro-organism.'

Linda Dijkshoorn's start-up idea was born purely out of frustration during her PhD research at the University of Groningen. 'Bacterial cell factories are currently built by means of trial and error', says Dijkshoorn. 'You dump a complete signal transduction pathway into the organism and then hope for the best. It almost feels like working on an assembly line. Moreover, it's extremely time-consuming, costly and a waste of resources. With EV Biotech we hope to do it much more efficiently.'
EV Biotech uses systems biology to predict the correct combination of genetic modifications needed to allow a bacterium to make the required product. The models are subsequently improved with the aid of feedback from the lab. 'We cannot yet say: 'this combination works perfectly', but it does tell you for which ninety percent you need not even try', says Dijkshoorn. 'Imagine how many experimental rounds of optimisation and development that would save.'

'The idea was born on the basis of another idea'

Business case

While doing her doctoral research, geneticist Dijkshoorn studied a methylotroph bacterium to use it for the production of pharmaceutical substances. To get around the trial and error method, she asked computational modeller and PhD-colleague Agnieszka Wegrzyn if there were any models for the organism she was working with. This turned out to be the case. 'But I was enormously surprised that they were not used at all', says Dijkshoorn. 'Why not use those models to gain insight into the effect you would get from adding new metabolic pathways? I believe that is the future.'
Dijkshoorn tried to set up a business case for a methylotroph bacterium as reactor

vessel. Unfortunately the idea was slammed far too quickly by VentureLab North, an incubator that helps companies to start up. 'I then thought it was smarter not to focus on a single strain but more on the technology that can be used to make those strains according to the required product.' The methane project, by the way, is still on the back burner. 'As soon as our technology has evolved further, it will be easier for us to make such a complex bacterium', says Dijkshoorn. 'Ultimately the idea for EV Biotech was born on the basis of another idea.'

Vanilla and spider silk

Dijkshoorn, Wegrzyn and protein engineer Sergey Lunev got together one weekend in March, 2017, to scrutinise the plan for their start-up and simultaneously test whether the three founders could work together as a team. When this proved to be the case, Dijkshoorn and Lunev started to attend entrepreneur workshops at VentureLab North. Meanwhile they had found their first angel investor, as a steppingstone to more exposure. 'We then presented ourselves to three bigger investors in the north; that resulted in an investment of € 1.1 million in November, 2018', states Dijkshoorn. 'That meant we were able to double the size of our team straight away. At the start of 2020 we took on another two people, so we're expanding quite fast.'

It is exceptional to see that Dijkshoorn's team has not come across any obstacles during the company's first two years of development. 'I think that's mainly thanks to the fact that we put the team first. We always look for exactly the right person to join and strengthen our team and find the most appropriate tasks for him or her', states Dijkshoorn. 'It was sometimes difficult for the individual team members to understand one another. For instance, the language used by people working in the lab differs from that used by computer people. We all had to learn to make the data comprehensible for the others. I think we have been quite successful in that respect.'

One year ago, the company started to develop proof of concept strains. The outcome included bacteria that produce vanilla, the biodegradable plastic PHB and spider silk. 'We first want to show what we can achieve before we get customers.'

And they will get them, that's for sure. Currently, Dijkshoorn and her colleagues are engaged in discussions with three major European customers, one in the taste and flavours market, one in the pharmaceuticals industry and one in the biomaterials market. Dijkshoorn does not want to disclose who they are as yet. 'But before we were able to start up our sales activities, they were already knocking on our door. That's fantastic.'

Climate-neutral

The EV Biotech team is currently working on further improving the modelling technique. 'We already have the computational power to include all organisational layers of a microorganism in the modelling. But by integrating the -omics data and algorithms that can predict de novo metabolic pathways, we are becoming better at designing the correct bacterium.'

When asked what other products they would like to make, Dijkshoorn laughs. 'There is so much I would still like to make. I still find the pharmaceutical industry extremely interesting. For instance, complex molecules inspired by nature such as synthetic vitamins and paclitaxel, Taxol. But the main goal of EV Biotech is to replace as many chemical processes that currently generate a great deal of waste and CO_2 emissions by biological processes. I think that by doing that, we can be part of the solution to making the Netherlands climate-neutral by 2050.' ●

Ageing and the disposable body

Borrowed Time offers a surprisingly comprehensive list of the most recent molecular and cellular insights on ageing.

I must admit that it was a dormant professional curiosity that led me to read the chapter on cellular senescence of Sue Armstrong's book *Borrowed Time* first. When I was still doing lab work, there was a lot going on about this phenomenon of permanent cellular lethargy. We were aware that all cells isolated from a mouse or a human stopped dividing at a certain point. This constituted an appealing model to investigate which potential oncogenes could alleviate that lethargy and ensure unlimited division.

'Senescent cells actively promote the ageing of surrounding tissue'

Armstrong explains in detail what I did not yet know: senescent cells actively contribute to the ageing of surrounding tissue. They release substances that break down connective tissue and keep the place occupied to keep out new, healthy cells. However, they do help healing wounds and that supports the view that ageing is chiefly a consequence of processes which are favourable at a young age, but not as you become older.

The author delves deeper into this subject in the chapter on the disposable soma: the disposable body. In this theory on ageing, the body is simply a vehicle for our egg cells and sperm cells. For the survival of our species it is totally futile to invest in keeping our body fit as soon as we have raised our children. This theory, put forward in the 1970s by mathematician Tom Kirkwood, only received support decades later on the basis of experimental research. The most spectacular result dates back to 2004 when it appeared that embryonal stem cells – crucial in the phase during which a body must be fit and fertile – immediately scaled back their maintenance and repair machinery as soon as they differentiated into more specialised body cells. Kirkwood said at the time, while smiling at the author, 'I told you so!'

Prolonging suffering

Thanks to the short personal intermezzos, *Borrowed Time* goes significantly above and beyond the average popular scientific book. Other chapters are equally as interesting, obviously devoting attention to telomere shortening, Alzheimer's disease, epigenetics and finally some evaluations of potential longevity therapies.

At the same time, Armstrong distances herself from the heated discussion whether we really should want to become very old or even immortal. The American oncologist Ezekiel Emanuel is sceptical about the chances of success. He points out the limited results over the past few decades, which – according to strictly objective criteria – often prolong suffering: 'Over the past fifty years, health care hasn't slowed the ageing process so much as it has slowed the dying process.' ●

Borrowed Time – The science of how and why we age
Sue Armstrong
272 pages
€ 12,99 (paperback)

▶ CRISPR on Netflix

Netflix has added the documentary *Human Nature* (2019) about CRISPR-Cas9 to its catalogue. The documentary explains how this technique, originally a bacterial defense mechanism against viruses, can change DNA extremely accurately, and highlights the profound consequences this could have. Director Adam Bolt, who previously made the acclaimed documentary *Inside Job* about the financial crisis, has managed to interview all the protagonists of this burgeoning scientific revolution.

Infected by the research bug

Bieneke Janssen thought that research was not for her, yet she has already spent two years in the US working on her postdoc project.

As a master's student making choices is often difficult. This was certainly true for Bieneke Janssen (33), who followed the master's programme Drug Innovation at Utrecht University. 'I always thought doing doctoral research would not be for me, that I couldn't do it. But luckily, when doing my practicum, I found that it actually really appealed to me.'

Janssen did her research with Bert Windhorst's radio chemistry group at the VU Amsterdam, where she ultimately obtained her doctorate degree. 'We wanted to find out how the inflammatory reaction in the brain progresses in the event of disease', says Janssen. 'We developed radioactively labelled compounds that enabled us to visualise various receptors with Positron Emission Tomography, that is, a PET scan.' It was particularly the multidisciplinary aspect of the research that appealed to Janssen. 'You could really follow how others used your results.'

'The pressure and the working hours are more than acceptable'

Acceptable pressure

After her doctoral research, Janssen looked for a postdoc position. 'I just sent emails to professors in my discipline in English-language countries', she says. Ultimately I was offered a position in Robert Mach's radiology group at the University of Pennsylvania.' And she has now been in the US for more than two years. 'I was afraid that the pressure here would be enormously high and that you would have to work very long hours every day, but fortunately the pressure and the working hours are more than acceptable. It's more or less the same as in the Netherlands.'

Janssen is now trying to make the so-called α-Synuclein-aggregation visible with PET. The protein cluster plays a role in Parkinson's and other diseases. The location of the aggregation can help doctors diagnose correctly, because similar diseases often start at different locations in the brain. 'The problem is that patients with an accumulation of α-Synuclein often have other protein clusters in their brain as well. In other words, we are looking for a molecule that specifically binds to α-Synuclein. However, these aggregations look very much alike and that makes it very difficult.'

To find a solution, Janssen and her colleagues use different approaches. 'We do bioassays to find suitable points of reference and are increasing our use of computer models. I too am involved in that, and that means I am learning more about different technologies in addition to radio chemistry.' According to Janssen the broad approach will certainly reap rewards in the future.

Janssen and her colleagues already found the first tentative points of reference. She hopes that more progress will follow within ten years. 'And I would very much like to be a part of that success and carry on with my research. Also, I would love to return to the Netherlands, to my family and friends, but finding something in the academic world can be quite challenging.' ●

Christine Van Broeckhoven, professor of Molecular Biology and Genetics and Group Leader Neurodegenerative Brain Diseases at the VIB-UAntwerpen Centrum voor Moleculaire Neurologie in Belgium, received the Khalid Iqbal Lifetime Achievement Award in Alzheimer's Research from the Alzheimer Association USA. She was awarded this prize for her work on finding the amyloid precursor protein, among other things.

Biopharma sector welcomes 4th edition of Single-Use Event November 10 in Corpus Leiden

Challenges and opportunities in bioprocessing

"We are very much looking forward to the Single-Use Event, perhaps even more so than last year", says Zeger de Vente, area sales manager with Hamilton. "The corona crisis has left us with little opportunities to meet in person. This event will be the first of its kind this year."
The Single-Use Event will be organized for the fourth year in a row, succeeding last year's event in Antwerpen. Traditionally, it will mainly focus on technological and product developments in three areas: continuous bioprocessing, cell culture systems & microbial systems. Topics that are covered include USP, DSP, PAT, data management, validation, standardization, service, chromatography in continuous bioprocessing, transition processes, QbD, Flexible/Multi-product facilities and much more.
Next to ample networking opportunities, over twenty booths in the lounge of Corpus Museum host experts from key companies to provide live demonstrations of new equipment and innovations. For example, De Vente informed the organzing committee Hamilton is planning to launch two new products at the event.
In addition, scientists and experts from key companies as well as the academic world will share their views on the bioprocessing sector in a day-long lecture program with both plenary and parallel sessions. "Due to the current corona crisis, this sector is more relevant than ever", says Erwin Boutsma, member of the organizing committee. "We need cheap, flexible and scalable solutions for testing and vaccine and antibody production. Our partners will undoubtedly explain at the Single-Use Event how they aim to tackle these challenges."
The corona crisis has not been kind to events such as these. The Single-Use Event can therefore only be organized with strict safety measures regarding distance, routing, personal hygiene, et cetera. Boutsma: "Visitors can be sure the organizing committee as well as the location managers will take every precaution necessary to ensure everyone's safety." For example, the plenary lecture room has a capacity of 550, but will be limited to 120. "This is unfortunately also the maximum number of attendees this year. So it's important to register soon!"
The meeting will be concluded with a networking event, including drinks and snacks. ◆

Single-Use Event

Single-Use Event 2020
November 10, 10.00–17.45 h
Corpus, Leiden
www.single-use.nu

Colofon

Medicines is het onafhankelijke orgaan van FIGON, het integraal platform voor innovatief geneesmiddelonderzoek in Nederland.

Redactie
+31 88 6440640
hoofdredacteur: dr. Erwin Boutsma
redactiecoördinator/eindredacteur: drs. Nienke Beintema
eindredacteur: drs. Franny Scholte
vak-/eindredacteur: ir. Puck Moll
vak-/webredacteur: Daniël Linzel MSc

Advertentie-exploitatie
Bas van den Engel, +31 6 42306937, bas@archermedia.nl

Media-order/traffic
+31 88 2266690, traffic@archermedia.nl, trafficonline@archermedia.nl

Marketing
Lisa Plenge, +31 88 2266670, l.plenge@archermedia.nl

Over FIGON
FIGON bevordert interacties tussen alle partijen in het geneesmiddelonderzoek in de brede zin, zoals wetenschappelijke en beroepsverenigingen, universiteiten, bedrijfsleven en overheid. Het platform versterkt bestaande initiatieven op dit terrein, signaleert en verkent nieuwe ontwikkelingen in het vakgebied en voert een actief beleid in het kader van de missie. FIGON staat open voor alle in dit verband relevante groeperingen. De missie van FIGON is het bevorderen van het innovatief geneesmiddelonderzoek in Nederland.

Verschijningsfrequentie
Medicines verschijnt één keer per jaar, in aanloop naar de jaarlijkse Dutch Medcines Days.
Het hele jaar door is er nieuws rond FIGON en geneesmiddelonderzoek in het algemeen te lezen op www.medicinesonline.nl.

Vormgeving
Content Innovators, Yvonne Kramer

Druk
Veldhuis Media

Vakbladen.com crossmediaal uitgeven

Uitgever
Rik Stuivenberg, Vakbladen.com
Postbus 19949, 2500 CX Den Haag,
Enthovenplein 1 (5e verdieping),
2521 DA Den Haag

Credit cover
Adobe/Fotomek

Single-Use Event

Register via single-use.nu/event/register

Single-Use Event 2020

CORPUS | Leiden | November 10

On November 10th at location CORPUS in Leiden suppliers and users will meet at the ultimate networking event in the world of bioprocessing, biotechnology and (bio)pharmaceutical manufacturing. You are welcome to view and test new products, network with key suppliers in the single-use industry, and attend presentations about the latest developments in single-use.

[C2W] MENS MOLECULE MEDICINES

3M ELSCOLAB ondis HAMILTON Parker VAISALA cytiva CPC ANSERS

SARTORIUS PALL Biotech avantor FLOWMEISTER PHCbi M·FILTER

SOLARIS ESI Cell-tainer CerCell greiner I.LABEL WATSON MARLOW Endress+Hauser YPSO FACTO

CLS Services
CHEMISTRY OF CONNECTING PEOPLE

www.cls-services.nl
recruitment, selection and secondment in chemistry | pharma | biotech | food | feed

FIND THE NEWEST VACANCIES ON OUR WEBSITE

Recruitment is about people. Our drive is to make people happy. Not only by having excellent employment conditions but also by preparing you as good as possible for upcoming interviews and trying to make the whole recruitment process a more fun and positive experience. Increasing the chance of finding you a suitable position.

We have built expert knowledge in our field when it comes to recruitment, selection and secondment. We speak your language and understand your needs and the challenges you face.

Validation Engineer
Johnson & Johnson Surgical Vision - Groningen

Proces Engineer
Johnson & Johnson Surgical Vision - Groningen

Senior Scientist Homogeneous Catalysis
Innosyn B.V. - Geleen

Associate Regulatory Affairs Manager
Astellas Pharma Europe B.V. – Leiden

Regulatory Operations Associate
Astellas Pharma Europe B.V. - Leiden

Associate Scientist Release & Stability
Janssen Vaccines & Prevention - Leiden

Senior Fill/Finish Process Development Specialist
Janssen Vaccines & Prevention - Leiden

Technical Specialist quality and compliance
Janssen Vaccines & Prevention - Leiden

Process Engineer
Janssen Vaccines & Prevention - Leiden

Data Engineer Process Development
Janssen Vaccines & Prevention - Leiden

Scientist DSP development
Janssen Vaccines & Prevention – Leiden

Assistant Outsourced Coordinator - Analytical Project Manager
Janssen Vaccines & Prevention - Leiden

Scientist Molecular Bioassays
Janssen Vaccines & Prevention - Leiden

Associate Scientist USP
Janssen Vaccines & Prevention - Leiden

QA Specialist
Janssen Biologics B.V. - Leiden

Interested to know what we can do for you?
Visit our website for more information or send an open application.