ICI institute for chemical immunology

Interview

"ICI SHOULD NOT BECOME A CLOSED CIRCUIT"

SJAAK NEEFJES
Scientific Director ICI
Professor of Chemical Immunology at Leiden University

Following a positive review, ICI has now entered its second five-year phase. The first set of new projects has been selected and preparations for the second round of applications are ongoing. But Sjaak Neefjes, ICI's scientific director, is already looking further ahead. He is mobilizing the younger generation within ICI to think about the future of chemical immunology as an independent field of research.

The review committee was obviously convinced of ICI's past achievements and future plans. But they must have had some comments as well.

"Of course, they did have a few suggestions and critical remarks. One of those concerned the gender balance, or really the lack thereof, in our Scientific Advisory Board. We immediately tackled that by inviting Professor Brenda Schulman, director of the Max Planck Institute of Biochemistry and a very dynamic personality, to the board. Her expertise is in biochemistry and structural biology and she is currently also a Boerhaave visiting professor here in Leiden."

"Another comment pointed to our lack of programs that focus on overarching themes. This is a valid point. We have our twin-projects that foster cross-discipline collaborations, but there are possibilities for connecting a number of projects within a bigger program. I think that this will create added value from a scientific perspective. Sander van Kasteren and Martijn Verdoes suggested that our various projects on vaccine development would be a good start to creating a thematically connected program and they are now elaborating their ideas ▶

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into a proposal. I am really looking forward to seeing what they come up with."

Does this mean that ICI will give priority to larger programs during the second phase? And are there specific topics or technologies that have been selected as focus areas?

"We, being the executive board, decided right away that we do not want to be too directive when it comes to the scientific content of the proposals. It is very important to be open minded and we do not want to block new ideas just because we didn't think of them. We also don't want big themes to dominate everything. There is definitely room for smaller, more explorative projects. Or projects that focus on the development of technology or methods that are relevant to the broader community. And we also have projects ongoing that are almost 'stand-alone', for example, a project run by Jannie Borst and Celia Berkers on the metabolome in immune cells. There are no direct links to other ICI projects, but that should not be prerequisite. Scientific quality is the most important."

What about new researchers who would like to join ICI? Is that possible now with the second phase being granted?

"Yes, certainly, it is essential that ICI does not become a closed circuit. Communities evolve; young group leaders enter the field and establish new research groups, while at the same time other researchers retire or move on to new positions. For example, Ton Schumacher decided to focus more on his entrepreneurial activities. He will stay involved with ICI, but no longer as an active project leader and principal investigator."

"Vaccine development could become an overarching theme"

Being open to new ideas and new researchers makes sense, but what about successful projects from the first phase? Shouldn't they get priority to further develop their findings and perhaps even move towards clinical applications?

"That is always a difficult issue. Explorative and application-focused research are both important. It is like comparing apples to oranges. However, you need to realize that translational research in our field quickly requires budgets that are way beyond what we can provide. And good results during the first phase are also no guarantee for a solid follow-up. There were also proposals building on the first phase that basically just repeated the same trick. Those were not honored. Just for the record, we were not involved in the assessment of the proposals. That was the responsibility of the Scientific Advisory Board. We based our choice on their judgment."

Looking even further ahead than the coming five years, is there a future for ICI outside the context of the Gravitation program?

"If money is the only reason that people participate, then you know that everything will quickly fall apart once the funding runs out. So, we need a solid plan to ensure that chemical immunology is strongly embedded in the scientific landscape. But I don't think it is wise if people like myself or other senior staff come up with a plan for the future. That should be in the hands of the younger generation, they should think about the best way forward. Of course, we can contribute insights and suggestions from our own experience with large-scale research initiatives and funding schemes, but we should not be in the lead. I have asked a few younger members of the community, including those on an ICI tenure track, to start thinking about these issues. It is essential that younger generations also recognise the importance of chemical immunology as a discipline and I am confident that this group is committed and will play a leading role in the future."

"Explorative and application-focused research are both important"

Will there be new tenure track appointments?

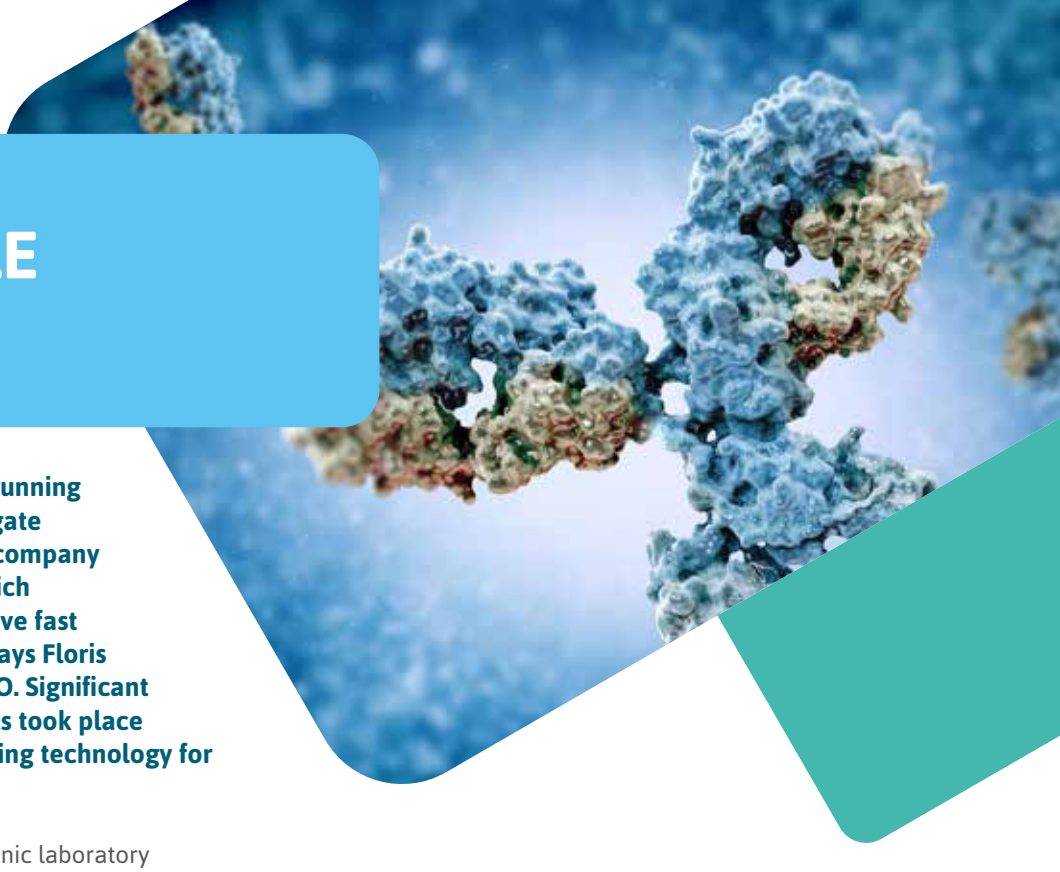
"No, that part of the ICI program has been completed."

Convincing policy makers and funding agencies that a new research field like chemical immunology deserves public funding will require more than a plan. Show, don't tell. Will there be something to show in the end?

"Oh yes, no doubt. We already have several projects that are moving towards an application and are being tested. Translation has been initiated in a number of cases and I am not at all afraid that we will not be able to demonstrate the impact and value of chemical immunology. We will deliver practically useful results and moreover, we will deliver them at a bargain. When you compare the budgets of our activities to the burn rate of the pharmaceutical industry for similar projects, it will be clear that ICI has turned out to be a highly profitable investment." ■

"We need a solid plan to ensure that chemical immunology is strongly embedded in the scientific landscape"

TOP MOLECULE AT THE BASIS



Synaffix possesses unique and front-running 'one-stop shop' antibody-drug conjugate (ADC) technology. "The seed for our company was laid by 'bicyclononyne'(BCN) which proved to be a top molecule to achieve fast and unconditional bioconjugation," says Floris van Delft, co-founder and current CSO. Significant further development and adjustments took place later at Synaffix resulting in a promising technology for targeted cancer therapy.

The origin of Synaffix lies in years of organic laboratory research at the Radboud University, where the founders, Floris van Delft and Sander van Berkel, shared their interest in click chemistry-based bioconjugation. They discovered bicyclo[6.1.0]nonyne (BCN), which proved to be a powerful probe for copper-free click chemistry by enabling highly efficient and completely orthogonal bioconjugation to complex (bio)macromolecules. Van Delft: "We realized the special feature of 'our' molecule and its potential for commercialization."
Shortly after the patent application for their magic molecule, the organic chemists decided to set up a company and in 2010, their initiative resulted in Synaffix.

ADC technology

Technologies centered around BCN are suitable for application in a broad area of fields, ranging from life sciences and health products to material sciences. "Therefore, it was of crucial importance for our business development to find out what application and product requirements could lead to high-value creation for Synaffix," Van Delft explains. "In the end, we chose to focus on antibody-drug conjugates (ADCs), a class of promising anticancer therapeutics." ADCs utilize a highly potent cytotoxic anticancer drug connected to a monoclonal antibody through linker technologies.
"The biggest challenge is maximizing the clinical therapeutic index of these ADCs," Van Delft emphasizes. "Our research focuses on enhancing the effectiveness of these targeted cancer therapeutics while also improving their safety and tolerability." These efforts resulted in ADC technology platforms that have proven to enable highly competitive targeted cancer therapeutics.

Synaffix
connect to cure

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Out-licensing

Synaffix'current successful platforms comprise GlycoConnect™ designed for site-specific antibody-drug conjugation, and HydraSpace™ involving a polar spacer technology. Most recently, Synaffix ADC technology has been expanded with toxSYN™, an ADC payload platform that includes various payloads with different mode-of-action. "We do not develop ADC drugs ourselves," Van Delft explains. "Our business model is based on out-licensing. Pharmaceutical companies can license our patents to perfect and further develop ADCs based on their antibody. They use our platforms to build proprietary ADCs for their pipelines."
In 2013 Synaffix moved to Pivot Park in Oss (see page 8,9). Now, nearly ten years after its foundation, the company has become a main player in the field of ADC anticancer therapeutics, collaborating with numerous large pharmaceutical companies all over the world. For example, ADC Therapeutics (Switzerland), Mersana Therapeutics (U.S.) and Shanghai Miracogen (China) have licensed Synaffix technology.

Milestone

Benchmarking studies demonstrate that Synaffix' ADC technology has proven to generate exceptional ADC product candidates in terms of therapeutic index. Success has been demonstrated in laboratory and test models. The next step is the patient. Van Delft: "Last January, the first ADC drug candidate generated by using our technology reached the clinic. A milestone! We are eagerly following the results of these first patient studies." Anyway, 2019 was a tremendous year thanks to the new and promising commercial license agreements. "Recent progress strengthens our real ambition, namely to realize our company's tagline: connect to cure." ■

Turning TLRs on and off

Unraveling the outcome of Toll-like receptor signaling from specific (sub)cellular sites

Toll-like receptors (TLRs) are found at the surface of cells and in intracellular compartments. According to some first experiments the outcome of TLR signaling depends on their location. PhD students Michel van de Graaff and Timo Oosenbrug develop the biochemical tools to unravel this signaling dichotomy beyond any doubt.

"It's a running joke in our lab: you are on the right track when your TLR ligand gets impossible to handle," says organic chemist Michel van de Graaff. "I often have problems getting the compounds I've synthesized out of the purification columns." TLRs play an important role in the innate immune system: they recognize viral and bacterial structures and initiate immune defense. These structures have a characteristic that gives scientists who want to study TLRs a headache: the ligands are highly lipophilic and therefore almost insoluble. Van de Graaff: "It took us quite some time to tackle that problem, but we found some linkers that add solubility without disturbing the ligands activity."

Switch on TLR signaling

Signaling via TLRs starts when two receptors 'sandwich' a ligand at the membrane's surface. Van de Graaff creates 'caged ligands': modified ligands that bind to the receptor but do not initiate signaling because they carry an additional group too bulky to sandwich. The blocking group can be removed by UV light or by adding an 'uncaging' chemical. Life scientist Timo Oosenbrug: "We've proven that we can switch on TLR signaling fast and reproducibly in this way, both for receptors on the cell surface and intracellularly, and both in mouse and human cells."
To specifically trigger intracellular TLR signaling, nanoparticles have been functionalized with the uncaging reagent tetrazine, and macrophages are prepared that 'swallowed' these nanoparticles. "I need to wash away the non-internalized particles thoroughly and then add our caged ligand. Then we should only see intracellular signaling," predicts Oosenbrug. He hopes to succeed in doing so in the coming weeks. "It would be super cool if I could include that in my PhD thesis too."

"My compounds are immediately useful in immunology; that makes our duo-work extra special"

While Oosenbrug is running final experiments, Van de Graaff is writing up all his syntheses of the ligands. "Not the most fun part," he comments. "Fun is when I see that I succeeded in making the target molecule we drew on paper. I still think it is kind of magic that you can do that as a chemist. And my compounds are immediately useful in immunology; that makes it extra special."

Complementary PhD partners

Van de Graaff and Oosenbrug are ICI partners avant la lettre. Oosenbrug: "My PhD is funded by the NWO graduate program 'Immunity, Infection & Tolerance.' I wrote my own research plan, which included a one-on-one cooperation with an organic synthetic chemist. I started a few months before the ICI PhD program that couples chemists and biologists was launched." Van de Graaff: "I really wanted to do a PhD in organic chemistry. To be honest I took it sort of for granted that an immunologist was involved in the position I was offered. However, it turned out to be very interesting. I don't think there are many chemists who can interpret immunological data. I learned that from Timo."
Both are busy with their options after completing their PhDs. Oosenbrug would like to continue research in immunology. "After four years I still get up every day looking forward to working in the lab on my own project. It is super fun." Van de Graaff feels it's time for a change. "I've been at the same university for ten years now. It's been great, but it's time to try something new. As from January I will start as Formulation Scientist at the start-up company SeraNovo." ■

Timo Oosenbrug
Cell and Chemical Biology, Leiden University Medical Center
Maaike Ressing group

Michel van de Graaff (image)
Bio-organic synthesis, Leiden University
Sander van Kasteren group

How to organize a membrane

Organizing molecular complexes of CD37 and CD9 in immune cells

Tetraspanins organize cell membranes by arranging functional micro domains. Viviana Neviani and Sjoerd van Deventer pinpointed lipidation as a key to tetraspanins' organizational skills.

"All membrane proteins are difficult to study because they don't easily crystallize," relates structural biologist Viviana Neviani. "Tetraspanins are even more problematic because they are scaffolding proteins. They are not directly involved in any cellular activity which could also give clues about their functioning in biochemical experiments. So, yes, it is quite a challenge to study them."
Yet studying tetraspanins in detail was exactly the topic of the ICI research project Neviani and her research partner, postdoc Sjoerd van Deventer, a molecular scientist specialized in cell biology, just finished.

Greatest moment

Tetraspanins are transmembrane proteins present in every human cell and are relevant for all kind of processes in immunology: cell signaling, cell adhesion and cell-cell interactions. They come in at least 33 'flavors' and are essential to membrane organization by interacting among themselves and with other membrane proteins in larger networks. Van Deventer: "During our studies we focused more and more on the role of lipidation. We could prove that these modifications steer tetraspanins' ability to interact with other transmembrane proteins."
In Utrecht Neviani focused on the isolation, purification, structural and biophysical studies of tetraspanin CD9, which is expressed in all cell types. "My greatest moment was behind a computer in Grenoble at ESRF, finally looking at its structure resulting from X-ray crystallography using synchrotron radiation. I immediately realized that we were seeing first evidence of CD9 forming dimers. However, we still need to prove the dimerization with other experiments."
Van Deventer focused on the cell biology of tetraspanins in Nijmegen. He studied immune cells with and without particular tetraspanins or tetraspanin mutants, also using super resolution microscopy. "We noticed that replacing a particular cysteine with a tryptophan has the same effect as lipidation. That may be a useful tool for future studies into tetraspanins and other membrane proteins."

> *"It takes time to discover what exactly the other person is doing"*

Support each other

At the start of their project Van Deventer and Neviani worked quite separately. Van Deventer: "It takes time to discover what exactly the other person is doing, before you know where and how you can support each other. In the past two years we have been working together more closely and certainly became each other's go-to person for all kind of questions." For example, Van Deventer introduced Neviani to immunoprecipitation techniques and Neviani taught Van Deventer to read structural data to establish the location of mutations. "And she also helped me out with a very special gift: a 3D-printed tetraspanin, 15 centimeters high," adds Van Deventer.
Neviani is looking for a job in Dutch industry. "I made a lot of friends in the Netherlands. I'd like to stay. I also speak Dutch pretty well. I got Dutch conversations lessons in return for teaching Italian." Van Deventer is about to leave for Bochum, Germany for half a year. "I'm going to learn some new skills in membrane biochemistry that are highly useful for my current project." And thereafter? "I'm not sure yet. I love research, but I don't necessarily want to become a group leader myself. In the coming years I am going to keep my eyes open for opportunities both inside and outside academia." ■

Viviana Neviani, PhD (image)
Crystal and structural chemistry, Utrecht University
Piet Gros group

Sjoerd van Deventer, PhD
Center for Molecular Life Sciences, Radboudumc
Annemiek van Spriel group

“I want to make immunology more visible”

Yvette van Kooyk is one of this year’s recipients of the Spinoza Prize for her groundbreaking work in glycoimmunology. “Immune-suppressing sugars in the tumor microenvironment also act as a checkpoint. If we can release this ‘brake’, we can strongly enhance the effectiveness of other anti-cancer drugs.”

The Spinoza Prize, named after the famous seventeenth century philosopher Baruch de Spinoza, is the most prestigious scientific prize in the Netherlands. Accompanied by €2.5 million, the prize is not only a tribute to past achievements, but also stimulates further research. Among the 2019 laureates is Yvette van Kooyk, professor and head of the department of Molecular Cell Biology and Immunology at Amsterdam UMC, location VU and participating researcher within ICI. According to the jury, Van Kooyk’s groundbreaking research in glycoimmunology has made her an absolute world leader in this extremely complex area.

Release the brake

In glycoimmunology, it is all about - no surprise - the interplay between sugars (or glycans) and the immune system. These interactions are not trivial; they form an essential part of a tumor’s ability to evade and inhibit the body’s immune response. “A variety of sugars in the tumor microenvironment can bind so-called siglec receptors, which are very strong immune inhibitory regulators that are present on a wide range of immune cells including tumor associated macrophages, natural killer cell, dendritic cells, neutrophils, T cells and B-cells,” Van Kooyk explains. “Sialic acids, glycans that bind to siglecs, therefore act as an immune checkpoint. If we can release this brake, we can boost the immune response and strongly enhance the effectiveness of other anti-cancer drugs.” The key is to interfere with the tumor’s ‘sugar profile’, as Van Kooyk puts it. Think of immunotherapy focused on sugars, but always in combination with other forms of anti-cancer therapy. “My idea is to combine our work with, for example, targeted therapies. Envision a kind of sugar removing compound, such as a sialidase [enzyme that hydrolyses glycosidic bonds, ed.] that goes to work in the tumor microenvironment to remove the suppressive sugars. By doing that, you create a window for another drug to act.” .

“If we can release this brake, we can boost the immune response”

▼ *Yvette van Kooyk, Professor of Molecular Cell Biology and Immunology, received the Spinoza Prize 2019 for her groundbreaking work in immunology.*

Science meets art

Key issue is of course to get the sialidases to the tumor microenvironment and make sure that they are only active there and retain their activity long enough to really sort a strong clearing effect. A nice challenge for chemists and Van Kooyk has another one at hand. “We also need more probes to specifically bind sugars so we can extend our work on mapping the sugar profiles of pancreas, breast and lung tumors and matching those immune suppression in the tumor microenvironment. This way, we want to come up with new tools to predict the risk of metastasis or the response to certain checkpoint inhibitors.”

“We need extending our work on mapping the sugar profiles of pancreas, breast and lung cancers”

When it comes to her plan for the 2,5 million prize money, Van Kooyk looks beyond the realm of science. “I want to make immunology more visible. One of the things I would like to do is to bring immunologists and artists together to stimulate a dialogue between the two, which hopefully leads to new ways of visualizing and expressing the scientific questions we work on. This will result in a collection of new works of art that, in turn, can stimulate a discussion between scientists, artists and the public.” ■

Engineering antibodies using CRISPR: fast, easy and cheap

Looking for faster and cheaper ways to tune antibodies to your specific application? Engineering the constant domain using CRISPR in hybridoma's offers the prospect of obtaining antibodies that tick all the right boxes. A combined Nijmegen/Leiden effort describes the approach in a recent Science Advances paper.

Hybridoma technology is the method of choice to generate immortal cell lines capable of secreting a monoclonal antibody (mAb) with the desired antigen specificity in large quantities. However essential antigen specificity is, mAb format and isotype are also important determinants for performance in a (pre)clinical context. "Numerous clinical trials with new candidate antibody-based therapeutics are ongoing, but in many cases mechanistic insights on therapeutic efficacy are lacking," says Martijn Verdoes, group leader at the Tumour Immunology department of Radboudumc and co-senior author of the Science Advances paper. "Studies have revealed that in some cases, the working mechanism is not the blocking of ligand-receptor interaction as expected, but rather the killing of mAb-bound cells."

Fixed

Different mechanisms can explain why clinical trials using apparently similar antibodies generate very different effects. Verdoes: "One example is the use of mAbs that target CTLA-4, which were evaluated in multiple clinical trials. It turned out

> *"Altering the genome of hybridoma in a very targeted manner"*

that the isotype of the mAb greatly affected the results and explained why in some trials patients showed no response, whereas in others the clinical outcomes were very good." With this in mind, the logical solution would to be to also tune the mAb's isotype to fit the clinical requirements. But that is problematic, due to the fixed nature of the mAb heavy chain's sequence in the hybridoma. Altering that sequence is not impossible, but for an average academic laboratory this is technically challenging, labour intensive and time consuming. "Outsourcing to specialized companies is the preferred approach of the pharmaceutical industry, but is way too costly for academic labs," according to Verdoes. Out of frustration over the limited possibilities for genetically engineering the mAb's isotype, Verdoes teamed up with the group of Ferenc Scheeren at the Leiden University Medical Centre to explore the possibilities of using CRISPR for this purpose. "Bas van der Schoot, PhD student in my group, went to work and together with the Leiden team managed to apply CRISPR/homology-directed repair (HDR) to genetically engineer hybridoma's to generate the desired isotype panels."

Chemical tags

A real breakthrough, says Verdoes. "The beauty of our approach is that it is fast, easy to perform and low-cost. This allows research groups to simply generate different antibodies with different isotypes for preclinical evaluation and mechanistic studies. In my view, this is very important to better determine the clinical potential of an antibody at a much earlier stage." But there is more. Being able to alter the genome of hybridoma in a very targeted manner also opens the way for introducing tags that allow chemo-enzymatic modifications. That is particularly interesting to a chemist like Verdoes. "We see all kinds of possibilities emerging for new therapeutic, diagnostic or imaging applications. Think about

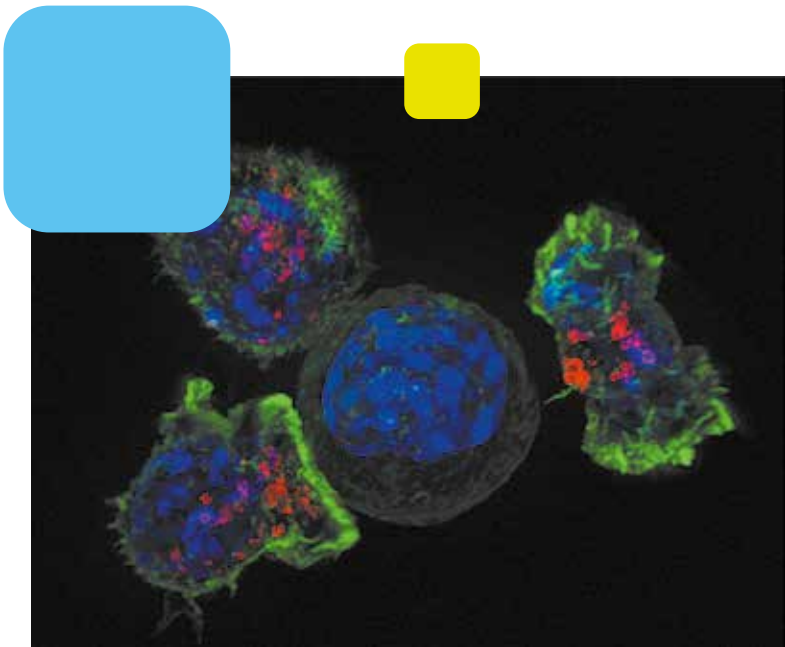
> *"Allowing to determine the clinical potential of an antibody at a much earlier stage"*

modifying mAbs to introduce chemical cargo or imaging labels that specifically target a certain type of cancer or biomarker. Or combinations thereof." With such a versatile platform, there must be plenty of interest from other groups. "Yes, we already have quite a number of collaborations ongoing. Our technology is open source and available to anyone who is interested." ■

Reference

Johan M. S. van der Schoot et al. (2019) Functional diversification of hybridoma-produced antibodies by CRISPR/HDR genomic engineering, **Science Advances** , Vol. 5, no. 8, eaaw1822
DOI: 10.1126/sciadv.aaw1822

▼ *In the middle a cancer cell that is attacked by three killer T cells. (NIH via Wikimedia Commons, public domain)*



Pivot Park

Hotspot for biopharmaceutical innovation

Pivot Park aims to create a world class environment and community to foster biopharmaceutical innovation. "Based on decades of international know-how and R&D experience, we believe that through continual discovery we will develop products and therapies that improve global health," explains CEO Brigitte Drees.

Pivot Park, located in Oss at the former Organon R&D site, houses promising research and product development companies and valuable pharmaceutical service organizations. Together these form an attractive ecosystem for research and development of medicines. Drees: "Our campus is becoming increasingly interesting due to the constant growth in the number of companies, people, knowledge and interactions that reinforce one another."

"Europe's most exciting biopharmaceutical campus"

Eight years after its creation, Pivot Park accommodates 60 companies with more than 550 employees working at the park.

Breeding ground

Entrepreneurs at Pivot Park are part of a high-quality network of companies and knowledge institutes all focused on pharmaceutical research and drug development. "Thanks to this strong focus, both start-ups and existing companies are increasingly aware of how to find the campus," Drees says. Pivot Park includes laboratory and office spaces of all sizes with high-quality pharmaceutical R&D facilities, GMP-qualified test-production facilities, on-site analytical support, an ultra-high Throughput Screening Center and a well-equipped open-access laboratory.
The broad representation of biopharmaceutical business activities provides entrepreneurs with opportunities to accelerate their business and contribute to a healthier society. The campus offers the required ingredients. "Our approach has proven to lead to a stimulating and unique,

"Tailor-made facilities and infrastructure"

pharmaceutical knowledge community and to provide start-ups and scale-ups with the support, equipment and talent pool they need to excel and grow," Drees affirms. The biopharmaceutical ecosystem is gaining appreciation. "Due to its open innovation culture and its close-knit community, entrepreneurs experience Pivot Park as a breeding ground for new and promising pharmaceuticals."

Partnerships and collaboration

Participating companies have every opportunity to be inspired by one another through networking sessions, project-based partnerships or scientific conferences. There is a central area on the campus with coffee corners, lunch buffets and sports facilities. Drees: "This center, the heart of campus, plays a crucial role in promoting mutual meeting and knowledge exchange."

Apart from internal cooperation, there are also many partnerships outside the campus. For example, there is close contact in the region with the universities of Nijmegen and Eindhoven leading to a wonderful synergy: Cure (Pivot Park), Care (Health Valley Nijmegen) and Technology (Med Tech Eindhoven). In addition to this regional cooperation, there are collaborations with universities, knowledge institutes and pharmaceutical companies in the Netherlands and abroad. Drees considers partnerships and collaboration as significant elements in the success of the campus.
"Growing and flourishing business activity will strengthen Pivot Park's ecosystem and further increase our appeal," Drees says. The CEO foresees plenty of potential for the future and welcomes new partnerships. In this context she also invites the ICI community, which is focused on chemical immunology, to cooperate. "I am convinced that we can reinforce one another."
Synaffix, a campus-based company and leading innovator in the field of ADC technology, is associated with ICI through its CSO Floris van Delft, who holds a special chair at Wageningen University & Research. As a professor in Bioconjugate Chemistry he supervises an ICI research project focused on next generation antibody-drug conjugates. Van Delft explains the synergy: "Our company offers plenty of room for wonderful commercial challenges, whereas the university provides the opportunity for curiosity-driven new research, which also fascinates me. In Wageningen I can work on the frontline of fundamental new methodology in the field of biomolecular conjugation with potential for innovative ADC technology."

Expansion required

Despite their growth and development, companies tend to stay at Pivot Park and new companies sign up, for instance due to the arrival of the EMA in Amsterdam. To accommodate new activities, expansion must take place. The current campus is getting full and some buildings are reaching the end of their life cycle phase. So, something needs to happen. Preparations for rebuilding and renovation are currently in full swing. "We are aiming for a multi-tenant building based on the open innovation concept. Therefore, the current central place for meeting, free thinking and relaxation surely will remain. And to stimulate further creativity, there are plans for an incubator that includes accessibility to flexible workplaces and room for discussing innovative and stimulating ideas."
The coming years are going to be at least as challenging as the preceding ones. "In the beginning there were empty buildings to be filled. Now we have to be creative with the space that we have. That is why it is so important that we build and continue to grow," the CEO concludes. ■

pivotpark

Innovation hub

Companies experience Pivot Park as a wide-ranging campus with many useful facilities and a lot of opportunities for cooperation. The campus provides one of Europe's foremost biopharmaceutical innovation hubs. Two companies explain why they chose - and keep choosing - Pivot Park.

"Campus breathes pharma"

Synaffix is a spin-off of Radboud University. Floris van Delft has been involved from its start in 2010. As CSO he is responsible for the scientific ins and outs of the company. In 2013, three years after its foundation, the company felt the need to be in a pharmaceutical environment and moved to Pivot Park. Van Delft explains: "The campus 'breathes pharma' in the broadest sense of the word. All business activity is focused on pharma and everything is in close proximity." The environment stimulates cooperation. "By working together, we can join forces. And that has an effect." Furthermore, the campus offers lab and office space of any size with access to high-quality pharmaceutical R&D facilities and infrastructure and expertise. "This gives companies the opportunity to accelerate, grow and excel in the area of drug discovery and development. And not only that, other important scientific centers in the Netherlands that we frequently collaborate with, such as Radboud UMC and Leiden University, are just a stone's throw away. It makes Pivot Park a very attractive location for our company." (Company Profile see page 3)

"Right location of great importance"

In six years Acerta Pharma has grown from a start-up to a world player in the pharmaceutical industry. "The location is very important for a start-up," says Nico Stam, Vice President Research Europe. "At Pivot Park we were able to use shared services and we had access to equipment that we were unable to purchase at the time. The campus has proven to be an ideal spot to put down our roots." The founders could also rely on its extensive knowledge network, which allowed them to succeed in attracting investors and bringing together the right people. Today Acerta Pharma has become a world player in the field of new medicines and therapies against various cancers. The company is now part of Astra Zeneca, with two locations in the United States. "However, that does not mean that we are leaving here. On the contrary, we are expanding considerably at the campus. In addition to current international collaborations, we also work closely with companies at Pivot Park and several Dutch University Medical Centers. Therefore, the Pivot Park in Oss remains a top location for us." ■

Immunology in lab and class room

After finishing their PhDs, Jorieke Weiden is pursuing an academic career, while her ICI partner Dion Voerman began teaching chemistry at a secondary school. "He's an expert at explaining" and "She never gives up."

When Dion Voerman introduced himself to a third-year class at the start of the school year, one of the pupils told the class that her mother was about to start immunotherapy. "I took the time to explain a bit more about immunotherapy and about my own research project. The class was very quiet; some pupils asked questions and everyone listened respectfully - an impressive experience. This class is known to be noisy and easily distracted, but in my chemistry lessons they work very well. I think that has to do with that very first lesson about immunology."

"I took the time to tell my pupils a bit more about immunotherapy"

Preference for a scientific career

Chemist Dion Voerman and biologist Jorieke Weiden worked together on an ICI project at Radboud University Medical Center during their PhD studies. They developed synthetic polymers and gels that can activate and release T cells near tumors. Voerman synthesized the materials; Weiden focused on their biological effects. Having defended her thesis, Weiden is currently continuing the project as a postdoc: "I'm currently testing our materials for the first time in animals - really exciting."

She is firmly resolved to stay in the academic world. "I would love to become a group leader one day and a professor later on." Being creative and being your own boss is what attracts Weiden to an academic career, but the colleagues also draw her: "Nobody works in academia for the money or the office hours; scientists are intrinsically motivated." "Jorieke always remains optimistic and comes up with new solutions," says Voerman. "She never gives up, which is a pretty essential quality in research, I think."

Weiden's next step is a postdoc in Switzerland. She is applying for a scholarship at L'Ecole Polytechnique Fédérale in Lausanne where she will be working in immunology, but with an even greater focus on material sciences. "Already knowing a thing or two about chemistry because of my project with Dion definitely turned out to be an advantage."

Wonderful to be a teacher

Voerman on the other hand never thought of himself as a professor and didn't enjoy writing scientific papers. "Don't get me wrong, I really enjoyed the research. I learned a lot and wouldn't have missed it." Voerman started thinking about a career in teaching when he saw an appeal from Trainees in Education. "During my master studies I tutored a lot to earn some money. I tutored in chemistry, but also in climbing." He applied for a traineeship, got selected and started teaching and studying just a few weeks later.

His choice met with some mixed reactions. "Some people consider it a step backwards, because you don't need a PhD to become a first-grade teacher. I don't agree. The years in research provide me with a lot of examples and stories to share in the class room. And the traineeship is in innovative teaching. I'm also looking forward to introducing research projects at my school." Weiden: "Dion always took the time to explain the chemistry behind the compounds he prepared for our project. He explains things very well and very enthusiastically. It inspired me to follow a course in organic chemistry. I'm convinced he will be a great teacher." ■

Reference

Duo PhD project Jorieke Weiden and Dion Voerman: Polymer based synthetic dendritic cells (see ICI Bul 2017, issue 4, p. 4)

Jorieke Weiden, PhD
Postdoc Biomedical Sciences, Radboudumc, Nijmegen

Dion Voerman, PhD
Trainee in Education/Chemistry teacher, Arnhem

Post PhD

Duo ICI projects from the first phase of the Chemical Immunology Gravitation are gradually being finished. Some PhD students have already defended their thesis and earned their PhD degree. In this section, Career, we follow the young scientists' first steps on their career ladder.

News

News from the ICI office

As of August 2019, Pauline Hoftijzer is the ICI's new contact for administrative matters. She will combine this new role with her existing position as management assistant of the Chemical Immunology section, department of Cell and Chemical Biology at the Leiden University Medical Center. For all your questions relating to general administrative issues, Pauline is available during office hours either by phone, 071 526 87 27 or e-mail p.hoftyzer@lumc.nl.

"I still matter scientifically"

Carl Figdor, professor of Tumor Immunology, officially retired last October. But he will not say farewell to the university and Radboudumc yet. Figdor will continue to work for at least five years, thanks to a recent ERC Advanced Grant of € 2,5 million. His second ERC grant. With the money of his recent grant, he can support himself and appoint several new PhD students. The European subsidy was one of the reasons why the faculty gave Figdor permission to continue his career.

ICI conference 13 March 2020

Following the successful previous conferences, ICI will host a conference in 2020 as well, that offers all participants the chance to learn something new. The conference will take place on 13 March 2020 at the Rode Hoed, Amsterdam. More information will follow soon. So mark your calendar and make sure you will be there.

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Column

TEAMWORK MAKES THE DREAM WORK

Paving the way to novel immunotherapeutics

In recent years remarkable progress has been made in our understanding of the immune system and how to manipulate it. One of the biggest breakthroughs that comes to mind is, of course, the development of immune checkpoint inhibitors that release the brake on T cells to boost our adaptive immune system to get rid of cancer cells. While T cells are inarguably star players in anti-tumor immunity, they are certainly no soloists. Optimal and long-lasting T cell responses require activation of innate immunity, the other arm of our immune system.

Innate immune pathways are normally activated by microbial ligands, such as virally-derived molecules, by a dedicated group of receptors. It now turns out that the same pathways can also be activated by non-microbial molecules. In some cases, such spontaneous innate immune activation leads to severe autoinflammatory diseases. But in the case of cancer, activation of the innate immune system by our own molecules can steer anti-tumor immune responses and promote tumor rejection, sometimes even independently of T cells. This leads to a better prognosis in cancer patients. What exactly drives innate immune responses in a sterile tumor microenvironment is still unclear, but certainly deserves attention, as the innate immune system holds great potential to be exploited in future (complementary) immunotherapies.

This creates a fantastic opportunity for chemical immunologists! Molecules that can steer the innate immune balance in a certain direction would prove extremely useful, but only a few such molecules are currently under investigation. As an example, cyclic dinucleotides activate STING and type I interferon production and are currently being evaluated in clinical trials in combination with immune checkpoint blockade. The synergistic effort between immunologists, who can identify suitable immune targets, and chemists, who have the expertise to design or screen for agonistic or antagonistic compounds, should lead to the discovery of the next generation of immunomodulatory drugs.

ANNEMARTHE VAN DER VEEN AND CELIA BERKERS
ICI PROJECT LEADERS

Van der Veen is assistant professor of Molecular Immunology at LUMC
Berkers is professor of Metabolomics at Utrecht University

We are now in the second phase of the Chemical Immunology Gravitation program. Great successes have been achieved through collaborations and joint efforts within the ICI community. Let's remain united and find a path forward to continue our collaborative approaches in the upcoming years and beyond 2023. After all, it is teamwork that makes the dream work! ■

About ICI

The Institute for Chemical Immunology (ICI) is a Gravitation project, made possible by the Ministry of Education, Culture and Science, in collaboration with the Netherlands Organisation for Scientific Research (NWO). ICI will define and exploit a new field termed chemical immunology and train a novel generation of interdisciplinary scientists. It aims to promote academic excellence. The ICI publishes twice-yearly the 'ICI Bulletin' featuring ICI research, education and other relevant developments. To (un)subscribe please send an mail to info@chemicalimmunology.nl.

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