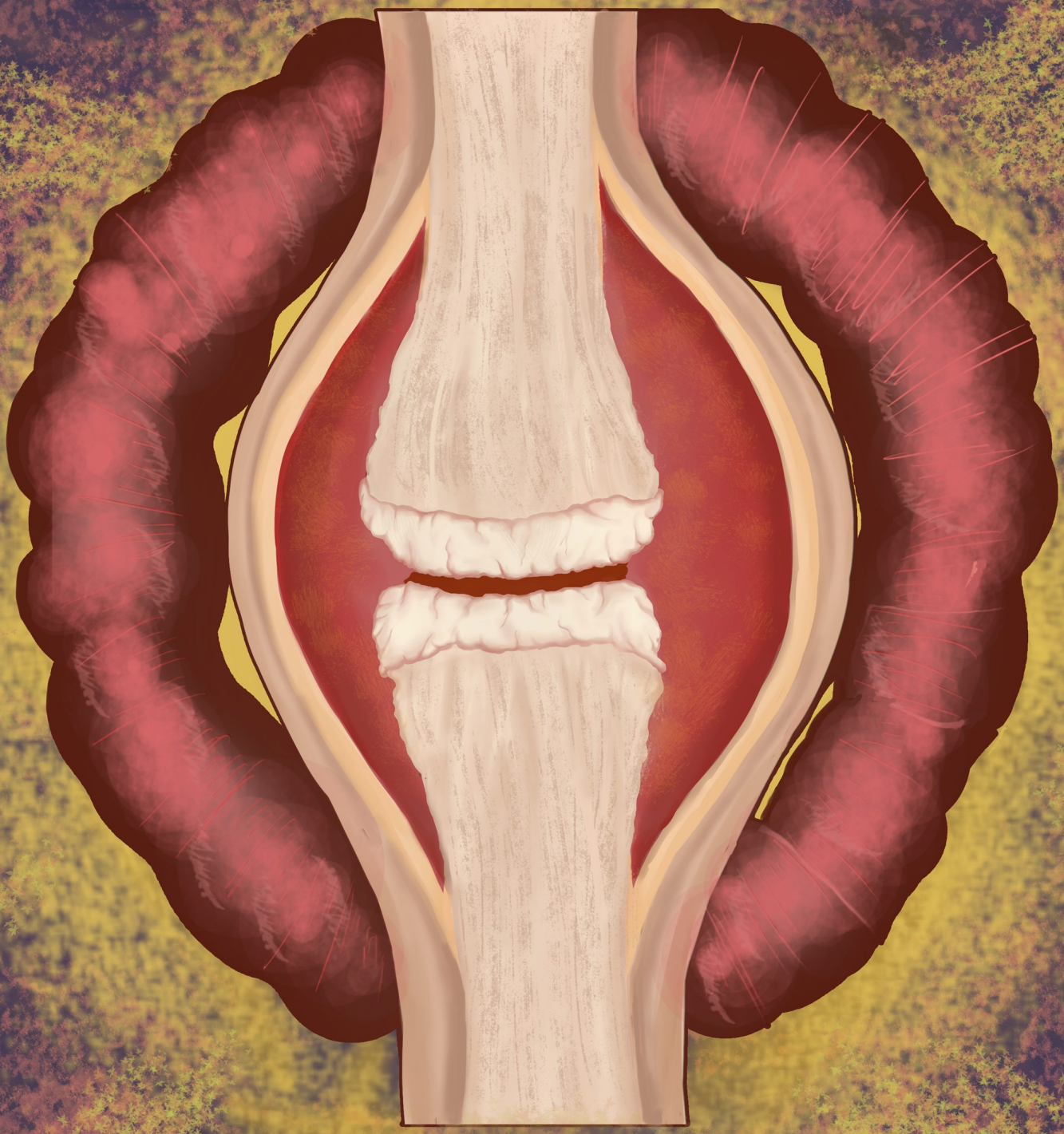
Drugs & Beyond

The HPPS Compass



An insight into rheumatoid arthritis

Interview with Mechiel Korte, an expert in neuroimmunopharmacology

PhD theses abstracts of Bo Lou and Ling Xiao

Dear HPPS community,

Welcome to the second issue of Drugs and Beyond! We have been working on this issue for the past semester to provide you with new updates about the HPPS community, such as running and recruiting projects and internship abstracts. Furthermore, this issue focuses on rheumatoid arthritis, a debilitating autoimmune disease. We provide information about the pathophysiology of this disease, and investigate which current and future treatment options exist. We interviewed Mechiel Korte, an expert in spondyloarthritis (a type of seronegative arthritis) who told us about his interesting research on fatigue associated with arthritis. Aside from this, you will also find summaries of two PhD theses by researchers in DDW, information on the Dutch Prix Galien, and the Nobel Prize winners of 2018.

We hope that you enjoy this issue, and that you will join us for the next issue before the summer holiday!

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What is rheumatoid arthritis?

Rheumatoid arthritis (RA) is an autoimmune disease, in which the body directs an immune response against the tissue in the joints, leading to inflammation and pain. (1) The main symptoms characterizing RA are joint swelling, inflammation, and stiffness. It usually affects the small joints of the body first in a symmetrical matter, such as the joints in the hands and feet. Symptoms in other parts of the body may also occur, including fatigue and cardiovascular symptoms. (2)

RA affects around 1% of the population worldwide. The exact cause of RA is unknown; however, it is believed to arise from a combination of genetic and environmental factors. One of the identified genetic risk factors are differences in the human leukocyte antigen (HLS)-DRB1 gene located on chromosome 6, which contains other genes coding for proteins important in RA as well, such as tumour necrosis factor (TNF). These differences are particularly common in patients that are positive for rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA). (3)

Moreover, it appears to be that the incidence of RA is increased in patients with HLA-DRB1 differences that smoke. Other environmental factors are the diet and the occurrence of infections. It has been also been proposed that environmental factors that might trigger the development of RA are hormonal influences, since women are more often affected by RA than men, and a variety of pathogens, such as cytomegalovirus and E.coli. (3)

The pathophysiological pattern of RA is the result of a complex interplay between the innate and the adaptive immune system, leading to autoimmune and inflammatory processes. In general, RA is induced by the generation of citrullinated proteins that are no longer recognized by the immune system as "self". This is then followed by the production of ACPAs by B-cells. (3) Smoking can induce the production of ACPAs, as has been shown by biopsies of RA patients, during which the same ACPAs were found in the lung and the synovium.

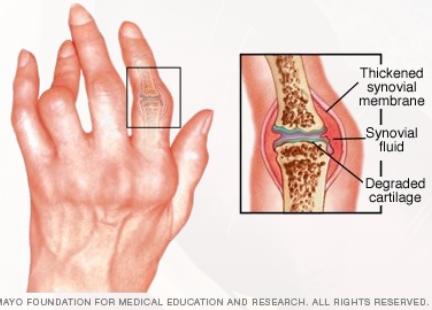


Figure 2: *synovitis in a finger joint*

These ACPAs are able to recognize a variety of citrullinated self-proteins. These can be vimentin, α-enolase, fibronectin, fibrinogen, histones, and type II collagen. Furthermore, ACPAs can be detected up to ten years before clinical manifestations of RA. Part of the pathophysiology of RA is directly linked to ACPAs, as they are able to activate macrophages and osteoclasts, the bone-destroying cells. (4) An overview of the pathophysiology of RA is given in **Figure 1**.

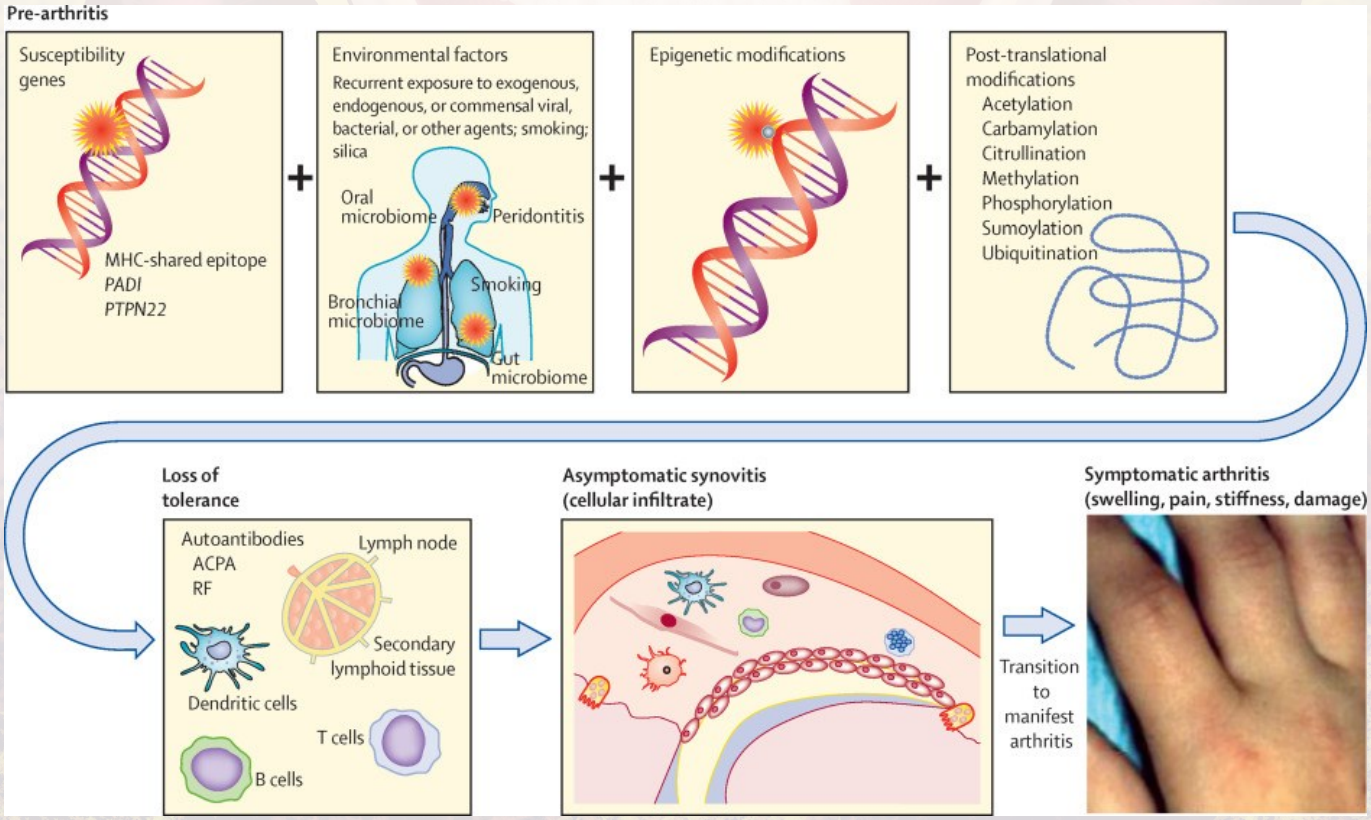


Figure 1: *pathophysiology of rheumatoid arthritis*

Synovitis is inflammation in the synovium caused by the accumulation of leukocytes locally. These leukocytes are attracted to the joint area by a variety of adhesion molecules and chemokines secreted by activated endothelial cells of the synovial vessels. (3) **Figure 2** shows synovitis in a hand of an RA patient. During joint inflammation, many types of immune cells can be found in the synovium, of both the innate and adaptive immune system. The concerted action of the immune cells eventually leads to bone and joint destruction by aggressive fibroblasts, osteoclasts, and chondrocyte catabolism. (4) Cytokines lead to the activation of endothelial cells in the synovium, which in turn release more cytokines and chemokines to attract more immune cells into the synovium, as well as activate fibroblasts. Ultimately, the expression of receptor activator of nuclear factor κ B ligand (RANKL) on T cells, B cells, and fibroblasts leads to the activation of osteoclasts by binding to RANK. Cartilage is destroyed by the catabolic effects of cytokines on chondrocytes and degradation by matrix metalloproteases (MMPs) and other enzymes. (4) **Figure 3** gives a detailed overview of the pathophysiology of RA.

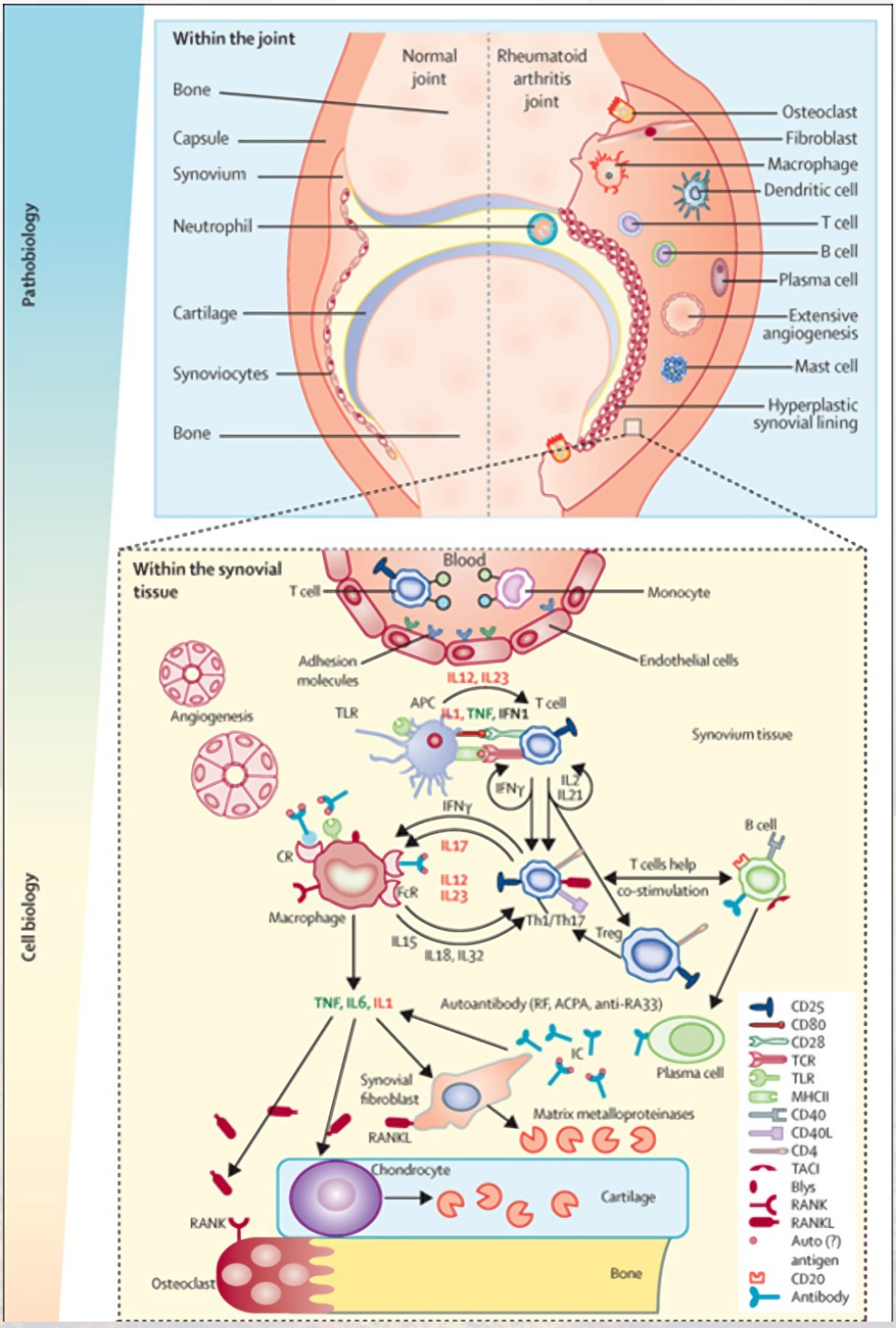


Figure 3: *immunological processes in a joint, leading to the inflammation and typical RA symptoms.*

Dendritic cells (DCs) play a crucial role in the immune pathway of RA. As antigen presenting cells, they stimulate T-cells present in the synovium. In order to effectively activate these cells, two signals are needed. The first one is binding of the antigen presented on an MHC class II molecule on the surface of the DC to the T-cell receptor on the T-cell. The second signal is a co-stimulatory signal, and is initiated by binding of the CD80/86 cell-surface molecule on the DC to CD28 on the T-cell surface. Blocking of the CD80/86-CD28 binding interferes with T-cell activation, and therefore also inhibits the downstream signalling cascade. This strategy has been proven a successful approach to relieving inflammation in RA, confirming the importance of DCs in RA pathophysiology. (3)

If the T-cell is activated, it can differentiate into either Th1, Th2, or Th17 cells. RA has long been considered to be mainly mediated by Th1 signalling, although it has recently been discovered that Th17 probably plays a much more important role. Th17 differentiation is stimulated by cytokines released by DCs and macrophages, and include transforming growth factor β, interleukin (IL)-1β, IL-6, IL-21, and IL-23.

Moreover, these cytokines also suppress Treg differentiation; therefore, allowing exacerbation of the inflammatory response. Th17 cells produce cytokines and chemokines responsible for the stimulation of fibroblasts, and the induction of IL-26 production by synoviocytes. IL-26 stimulates monocytes to produce the inflammatory cytokines IL-1b, IL-6 and TNFa, which causes more T-cells to differentiate into Th17 cells. (3)

RA is a highly complex disease. The exact causes of this autoimmune disorder have not yet been identified. RA can be a devastating disease that needs life-long treatment to prevent inflammation and the resulting bone and cartilage erosion. Nevertheless, RA remains to be a disease that involves a broad variety of inflammatory cells. These cells play a role in the progression of RA, and communicate with each other using a diversity of cytokines and chemokines. The most important cytokines, that are also targeted by various drugs, are TNFa and IL-6. (4)

Current standard treatment for rheumatoid arthritis

Optimal care for patients with RA consists of both pharmacologic and nonpharmacologic therapies. The treatment has three main goals: to reduce disease activity, decrease disability, and prevent structural damage. These goals can be achieved by bringing the disease to remission. Moreover, therapists can advise patients about dietary modifications or supplements, and tools or adjustments at home.

Starting with the treatment of RA as soon as possible will improve the prognosis of the disease significantly. The overall slogan in therapy is: 'Hit hard, hit early'.
Right after diagnosis, the patient receives different treatments categorized into nonsteroidal anti-inflammatory drugs (NSAIDs) and disease modifying antirheumatic drugs (DMARDs). NSAIDs are often prescribed in high doses to treat arthritis symptomatically until improvements occur. DMARDs, on the other hand, are the most important in the treatment of the disease. They can be divided into two groups:

- Conventional DMARDs (cDMARDs)
- Biological DMARDs (bDMARDs)

Conventional DMARDs are often the first choice, due to the costs. They include the drugs methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide. Methotrexate will be used first in treatment, when there are no contraindications present, and has the best benefit/risk-ratio. Methotrexate as monotherapy is considered to induce and keep remission in 50% of the patients with a recently emerged RA. When Methotrexate alone is not enough to induce and keep remission, another DMARD will be added, and a synergistic effect will be seen.

Biological DMARDs will be cost-effective in ACPA-positive patients. They will experience more damage to the joints, and it will bring more complications to the disease compared to ACPA-negative patients. Therefore, they will receive a more aggressive treatment and a biological sooner. An example of a biological DMARD is certolizumab pegol, a pegylated antibody to prevent TNF-α from binding to his receptor. Furthermore, corticosteroids are prescribed as a bridging method, which will reduce inflammation until the DMARD will start to work. (5)

Diet therapy for rheumatoid arthritis

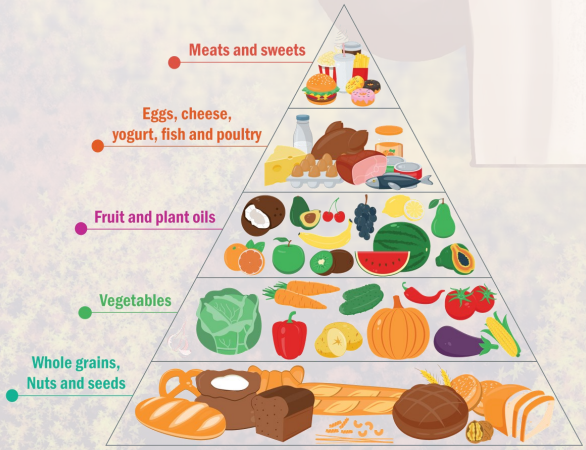
Multiple complications can arise with the use of pharmacotherapy for the treatment of rheumatoid arthritis (RA). For example, drugs used to prevent the progression of RA (DMARDs) and relieve its symptoms (NSAIDS) can cause severe side effects, such as cardiovascular events, gastrointestinal bleeding, peptic ulcers, and skin rashes. Additionally, not all patients respond to these drugs. Biologics are given as a second-line therapy, which include tumor necrosis factor alpha (TNF-α) inhibitors, anti-B cell therapy, specific anti-interleukins, and protein kinase inhibitors. However, these biologics can cause serious side effects, and are rather expensive compared to DMARDs and NSAIDs. (6) Therefore, research has been done to investigate possible alternatives for the treatment of the disease. Findings have shown that the gut microbiota is increasingly altered in patients, leading to further studies investigating the effects of diet therapy on RA.

Diets

Promising results were seen in patients who fasted for 7-10 days followed by a vegan diet or followed a Mediterranean diet alone.

Fasting patients have shown improvements in their symptoms, such as reduced swelling and tenderness of joints, less pain, and a reduction in other inflammatory measures. The diet of these patients included partial intake of vegetable broth, garlic, herbs and herbal tea, as well as juice extracts from other vegetables. The patients then had a vegan diet for a year, which was seen to be clinically beneficial for remission of the disease. This may have been the result of the elimination of certain food that can trigger the immune system.

Research has also reported that the Mediterranean diet was able to reduce inflammation, since some of the components seemed to have anti-inflammatory properties. This diet consisted of a high consumption of olive oil, cereals (such as whole oatmeal and whole wheat bread) fruits, vegetables, fish, and legumes. Inflammation was reduced in patients following this diet, and improvements were seen in their vitality and physical functions. Moreover, olive oil has particularly revealed to diminish cartilage destruction, joint edema, and the development of arthritis. It has even been suggested that olive oil may potentially prevent RA.



Dietary Components

Many dietary components used in the studies helped improve the signs and symptoms of the disease. These components have mainly been categorized into fruits, cereals, legumes, whole grains, spices, oils, herbs, among others. In this article, some of the categories will be briefly discussed.

Dietary Fibers and Whole Grains

Dietary fibers have been known to have beneficial effects for decades. Research has shown that intake of dietary fibers was associated with reduced inflammatory biomarkers, including cytokines.

However, the results were inconsistent and other studies showed otherwise. Whole grains, such as whole wheat and whole rice, contain high levels of antioxidants, phytic acid, vitamin E and selenium. These components have been found to have anti-inflammatory properties.

Fruits

Multiple studies emphasized that regular and high intake of fruits had antioxidative and anti-inflammatory effects, along with the ability to downregulate disease progression. The compound responsible for the antioxidative effects is anthocyanin, while kaempferol and p-coumaric acid are known for their anti-inflammatory properties and inhibition of cytokine synthesis. It has also been suggested that fruits may protect against RA.

Spices

A mixture of ginger and turmeric demonstrated protective properties against extra-articular complications, and independently reduced the signs and symptoms of RA. Curcumin also showed potent anti-inflammatory activity by blocking certain cytokines (interleukin (IL-)1 and IL-6) in vitro, and administration of the spice and folic acid were capable of diminishing methotrexate-induced vascular endothelial dysfunctions. Additionally, cinnamon bark was found to reduce TNF-α levels, and inhibit IL-2, IL -4, and interferon gamma (IFN-γ).

Essential Fatty Acids

Anti-inflammatory and immunosuppressive properties have been exhibited by omega-3 and omega-6 fatty acids. Omega-6 can be highly found in borage seed oil, and has shown to significantly diminish tender and swollen joints score in patients administered with the oil after 24 weeks. Black currant seed oil contains gamma-linolenic acid, omega-3 fatty acid alpha-linolenic, and stearidonic acid. It has demonstrated significant positive activity in pain relieving and joint tenderness after the same period of time. Omega-3 can also be found in fish oils, which was able to reduce morning stiffness and increase grip strength. Additionally, eicosapentaenoic and docosahexaenoic acids (ethyl ester derivates of omega-3) have shown decreased morning stiffness, pain, and tender joints.

Synbiotics

Probiotics (live microorganisms) and prebiotics (beneficial non-digestible food products) are what make up synbiotics, which have shown to lower oxidative stress in the body. For example, the probiotic *Lactobacillus (L.) casei has confirmed to lower pro-inflammatory cytokine levels, tender or swollen joints, disease activity score, and increase regulatory cytokine secretion, among others. L. rhamnosus GG (LGG) and L. bulgaricus decreased clinical scores of arthritis in vivo. Enhanced methotrexate activity was seen in combination with Escherichia coli 083 (Colinfant) in the models.*

Tea and Herbs

Green tea Camellia sinesis and Camellia assamica contain epigallocatechin-3-gallate (EGCG). This phytochemical has revealed to downregulate an anti-apoptotic protein, suppress matrix metalloproteases (tissue remodeling), and suppresses cytokines.

Boswella serrata, which is known for its anti-inflammatory properties, contains boswellic acid. This phytochemical inhibits lipoxygenase-5 enzyme involved in the synthesis of inflammatory leukotrienes, as well as the inhibition of inflammatory cytokines and components of the complementary pathway. Withania somnifera is another potent anti-inflammatory plant containing high levels of Witharin A, a steroidar phytochemical. It has demonstrated to decrease stiffness, inability of moving joints and knees, and pain score. Furthermore, it was established that the phytochemical inhibits the synthesis of inflammatory cytokines, and induced arthritis rat models demonstrated less damage to the bone collagen after treatment.

Taken together, diet therapy has revealed to be beneficial for patients with RA. Improvements in pain, inflammation, movement, disease progression, and quality of life of patients have been seen in many studies. Moreover, signs and symptoms at the early stage of disease can be detained with this intervention. Diet therapy is cheaper compared to the drugs currently used, and the dietary components can be easily added to the diet. Long term effects are very promising, making it possible for patients to decrease the dose of the drugs used and suffer from less side effects. Overall, diet therapy may not be used for the treatment of patients alone; however, it can be used to reduce the signs and symptoms of the disease. (7)

Latest Treatment News

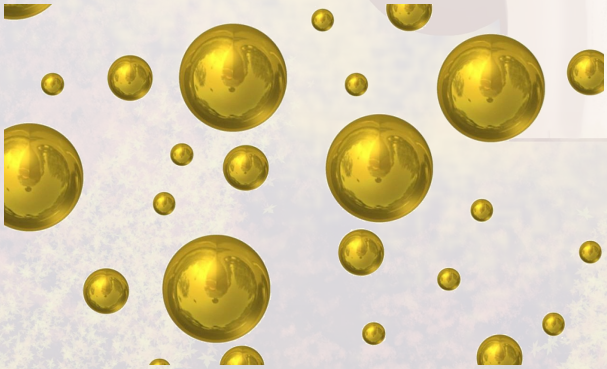
Although a lot is known about RA, there is still no cure for this disease. Therefore, there has been a lot of recent research investigating new treatment options for RA. This involves the development of new drugs, synthetic and biologic, research into comorbidities, and the immune pathways involved in order to identify potential targets for treatment.

New synthetic drug DEN-181

Research led by Ranjeny Thomas has led to the development of DEN-181, a vaccine-like treatment. DEN-181 consists of a liposomal delivery system, encapsulating two active ingredients: calcitriol and a collagen II peptide. The drug formulation is expected to more selectively regulate the immune system, and thereby, induce less adverse effects. It was recently administered to the first patient in a phase 1 clinical trial. (8)

Gold in anti-inflammatory treatment

Gold salts have previously been used in early RA treatments. However, gold salts are fairly toxic, and many adverse events were experienced by patients receiving these treatments. Although recently, interest in gold particle treatment has resurged. The gold particles that are currently used are less toxic, according to several studies (Xiao-Dong Zhang et al., 2010). In a study conducted by researchers at Harvard, gold nanoparticles were attached to natural anti-inflammatory molecules, which showed increased inhibition of immune responses. The nanoparticles were bound to IL-4 cytokines and delivered into mice with injured muscle tissue exhibiting inflammation. The gold particles act as a local delivery system, assuring that the IL-4 remains in the tissue where it is supposed to be, instead of distributing into the bloodstream and losing its potency. Therefore, although this technique was now specifically tested in regeneration of muscle tissue, it may also be possible to use this treatment strategy in other immune-related conditions. (9)



Upadacitinib found effective in clinical trials

The phase III clinical trials of a new RA treatment, upadacitinib (structure below, **Figure 4**), was recently completed in Berlin. The drug was found to efficiently reduce disease activity in patients that do not respond adequately to the conventional RA treatments. It decreased joint swelling and pain experienced by the patients, and increased joint function as well. Upadacitinib inhibits the enzyme Janus kinase 1 (JAK1), leading to the inhibition of a signaling pathway that induces inflammatory responses.

This treatment might be a new option for patients who do not respond to conventional treatments, or are unable to use biologicals due to other conditions. Additionally, the drug works quickly, allowing patients to respond to sudden symptom exacerbations. (10)

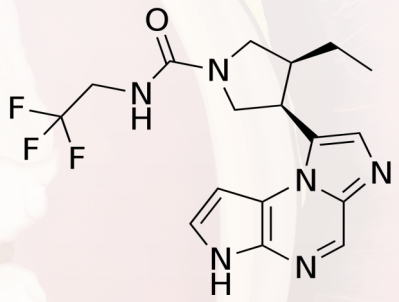


Figure 4: structure of upadacitinib

Link between diabetes and increased risk of arthritis

A team of researchers from the Nordsjaellands University Hospital in Hillerød (Denmark) recently presented the results from a study on the interaction between diabetes, osteoporosis, osteoarthritis, and rheumatoid arthritis. The study was performed using data from a Danish National Health Survey from 2013, that contained information of over 100,000 people. After randomization and selecting cases conform to inclusion criteria, they found that people with diabetes are more likely to also suffer from one of these disorders. In particular, the occurrence of osteoporosis is increased by 29%, for osteoarthritis by 33%, and for rheumatoid arthritis by 70%.

The team stated that a clear association between diabetes and RA might be explained through the presence of chronic inflammation in both diseases. Although, other explanations might be the use of steroids in RA treatment or the lack of exercise due to pain in RA. The first can increase the risk of diabetes development, while the later increases the risk of type 2 diabetes. Overall, no conclusions can be drawn concerning the cause-effect interaction as this was an observational study. (11)

Interview with Mechiel Korte: an expert in neuroimmunopharmacology

Mechiel Korte is an associate professor within the department of Pharmacology and is an expert in neuroimmunopharmacology, and guest professor at the department of Biopsychology at Ruhr-University, Bochum, Germany. After finishing his PhD research in the field of Neurobiology of Stress at the University of Groningen, he received a NWO-Talent stipendium which enabled him to obtain a post-doc position at the department of Neuropharmacology of the Scripps Research Institute in La Jolla (USA). In 1996, after returning to the Netherlands, he joined, as an Animal Welfare senior scientist, the Wageningen University and Research Centre, Lelystad. He was appointed as associate professor of the division Psychopharmacology at Utrecht University in 2008. Within his research, he focuses on the relationship between immunology, mainly arthritis, and quality of life (fatigue, depression, anxiety etc.).

Next to rheumatoid arthritis, there are many different classes of arthritis. In **Figure 5** an overview of different types of arthritis can be found. As can be seen, also Inflammatory Bowel Disease is a type of arthritis. '*Often people are not aware of it [arthritis]. They think it is a disease of bones, ligaments, and joints. But for example, also the heart, skin, eyes, intestine, and back can be involved.*' The type of arthritis Mechiel is mostly interested in is spondyloarthritis, which is a seronegative arthritis located in the vertebral column (see **Box 1**).

Figure 5. Types of arthritis

Box 1: Spondyloarthritis is an umbrella term for inflammatory diseases that involve both the joints and the entheses (the sites where the ligaments and tendons attach to the bones). Spondyloarthritis, in most cases, primarily affects the spine. Some forms can affect the peripheral joints - those in the hands, feet, arms and legs. (12)

Focus on the effect of inflammation on the brain

Instead of focusing merely on the inflammation, Mechiel focuses on the impact inflammation can have on the brain. '*What I am interested in is that a lot of people complain about fatigue, sickness, pain, and even depression. You can find much more depression in people with arthritis than in the normal population. Often scientists think the inflammation is the most important, but for the patients it is extreme fatigue. People don't stop working because of the inflammation, but because of fatigue and depression.*'

> *'I know how it affects the patients. I would have never written this grant if I wouldn't have known the problem myself.'*

Mechiel stresses that the effects on the brain are often neglected, and if a patient with arthritis complains about fatigue and depression they are often told that they simply cannot cope with having a chronic disease. However, when someone has an infection with for example Epstein-Barr virus and complains about fatigue, that is widely accepted.

'So what I did for many years already is trying to convince people with scientific data that there is an impact of inflammation on the brain, and that it really changes the chemistry and even structure of the brain.'

One of Mechiel's research goals is to improve the quality of life of patients with chronic inflammatory disorders; *'In my perspective, so from a patient's perspective, fatigue and pain are the most important aspects, because these directly affect the quality of life. A person in a wheelchair can have a perfect score on quality of life. But when your reward systems are affected then it really affects the quality of life. If you have a depression, you also feel more pain and fatigue. This goes both directions. The brain systems that are involved in pain and depression, I think there is an overlap of about 90% between these brain circuits. I always tell people that there is such a big overlap between the circuits because pain, whether it is emotional or physical pain, they have things in common. Funny is that a lot of the drugs used to treat pain, are antidepressants. And also, the other way around.'*

Measuring the effects of inflammation on the brain

Many patients with arthritis have central fatigue, which comprises both physical and mental fatigue. This includes difficulty doing things and concentrating respectively. *'Difficulty doing things also has to do with motivation and reward and dopamine, and with anhedonia. Because when you do not enjoy something, you are less likely to do it again.'* The first focus was to study the acute mechanisms, and when there are positive findings there, to move on to the second step; chronic mechanisms. Mechiel has used lipopolysaccharides (LPS) to induce inflammatory responses in mice. LPS are parts of gram-negative bacteria, and are well known to cause an increase in inflammatory cytokines such as TNF-alpha.

> *'In my perspective, so from a patient's perspective, fatigue and pain are the most important aspects, because these directly affect the quality of life. '*

He has been measuring sickness behavior, reward systems, anhedonia, serotonin, and dopamine. *'In 1994, I did an experiment, where we injected LPS, we had sensors implanted for 3 days, we observed an increase of heart rate directly after LPS, and fever, the area under the curve was higher in arthritis rats. Healthy animals were more active than sick animals, meaning the healthy animals showed less sickness behaviour.'* Thereafter, we wanted to know the feelings of this animals. However, this is not easy to do. *'It is quite difficult to measure absence of pleasure (anhedonia) in animals. You can't just ask them 'are you happy?'. So what we did is that we adapted a method from drug addiction.'*

In drug addiction, animals can turn a wheel and they get the drug (e.g. cocaine) when they turn the wheel (see **Figure 6**). By measuring how often the animals will turn the wheel in order to receive the drug, it can be determined how motivated they are to get the drug, and thus how addicted they are.

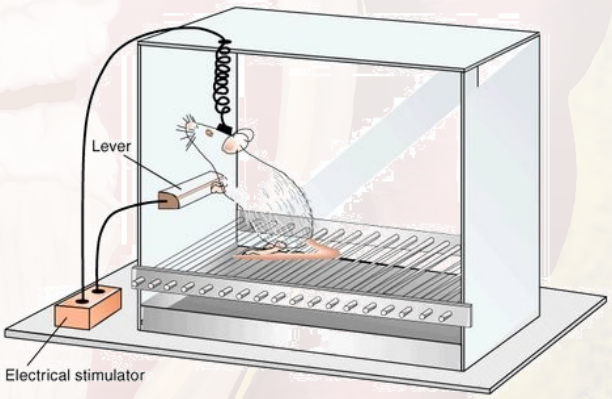


Figure 6. Test for addiction.

'We put an electrode in a part of the reward system in the brain where dopaminergic neurons project into the nucleus accumbens (NA), when you stimulate them. When an animal then turns a wheel, it stimulates the reward center and animals are more motivated to turn the wheel. If they don't like it, they don't turn the wheel. So, in a way you can find a threshold for every animal, which current they want to have before they start turning the wheel. We use this procedure and then inject TNF-alpha, and it showed nicely that it increased the current needed to motivate the animals to turn the wheel. We were one of the first to show that TNF-alpha really affects the brain, in a way they experience less pleasure.'

In another experiment, he worked together with Gerdien Korte-Bouws, who is an expert in measuring small quantities of neurotransmitters in the brain using HPLC. They measured different neurotransmitters in the nucleus accumbens (NA), which is a key player in the reward system in the brain. *'We gave a drug that works in the same way as cocaine. And what we discovered is that when you give LPS alone, the animals have more of the metabolite dopac [dopac is the main metabolite of dopamine]. When you block the reuptake transporter there will be more dopamine and less metabolite. We found that LPS increased the dopamine transporter activity. Thus, you will have more reuptake and more break-down. This might also explain why you have less pleasure when you have an inflammation. It also predicts why normal antidepressants [e.g. selective serotonin reuptake inhibitors (SSRIs)] are not completely effective in treating this type of fatigue and anhedonia in arthritis patients, because most antidepressants mainly act on the serotonin transporter. They are only partly effective'*. The effects on serotonin was even stronger. LPS strongly increased serotonin reuptake transporter activity in the NA. *'This might be a reason for arthritis patients with fatigue and depression to start using an SSRI, because that might help'*.

> *'We were one of the first to show that TNF-alpha really affects the brain'*

'Interesting is that there is a lot of evidence that people with depression, even without arthritis, have increased inflammation levels. But nobody knows where this inflammation comes from. And this is why we have to do research in this direction. Perhaps we should treat treatment-resistant patients not only with antidepressants, but also with anti-inflammatory drugs. Maybe that is the reason why only 30-40% of the patients really react to SSRIs and SNRI's'.

The mechanism underlying the effects of inflammation on the brain

'What we know is that pro-inflammatory cytokines bind to the p38 mitogen activated protein. This protein brings the inactive transporter to the surface to become active'. If you want to know more about the specific mechanisms, there is a very interesting article that Gerdien published earlier this year. *You can find the publication at the end of the page.*

Studies in humans

The results Mechiel and his group have found, have recently been replicated in humans. *'We collaborated with the children hospital to see if we could find the same things in humans. We had juvenile arthritis patients with both high and low disease activity. In this disease they always start with methotrexate (MTX), which is a terrible drug because the drug itself produces fatigue. Patients with high disease activity showed decreased well-being compared to patients with low disease activity. MTX reduced some of the inflammation but also decreased wellbeing. Which fits well with the data we found in animals'*.

Recently there has been a publication in The Lancet about the effects of etanercept on serotonin transporter levels in the brain. It shows that etanercept, which causes a decrease in TNF-alpha activity (so the opposite of what Mechiel has tested in his models), decreased serotonin transporter levels in the brain(2). Thus, this supports the findings in animals. To Mechiel the publication is ´a big milestone'. This recent human study was published in "The Lancet", discussing the link between inflammation and the comorbidity of rheumatoid arthritis and depression, showing that psychoneuroimmunology research is finally being taken seriously, and that it has arrived in the domain of the medical world.

Besides these studies there is more going on in this field. *'There are now the first publications on that when you treat people with arthritis and depression and block TNF-alpha, that you reduce both the inflammation and the depression. Blocking TNF-alpha can cause quite some side effects. But it is always a balance between the postitive drug treatment effects and the negative side effects.'*As long it is relatively safe and the postitive effects outnumber the negative ones.

Korte-Bouws GAH, van Heesch F, Westphal KGC, et al. Bacterial Lipopolysaccharide Increases Serotonin Metabolism in Both Medial Prefrontal Cortex and Nucleus Accumbens in Male Wild Type Rats, but Not in Serotonin Transporter Knockout Rats. *Pharmaceuticals (Basel). 2018;11(3):66. Published 2018 Jul 5. doi:10.3390/ph11030066*

Moving on to chronic effects

After having successful findings of acute effect of inflammation on the brain, his research is now moving on to the second step; chronic effects. For this, he received a grant from Reuma Nederland. He uses a rat model with a human gene called HLA-b27. This is a gene is very often seen in seronegative arthritis. '*The people who have seronegative arthritis, especially spondyloarthritis, 90-95% of these patients have one gene called HLA-b27. That is interesting, because then you can use this one gene. That is what we now do. We got transgenic rats from an expert in the USA, who put the human HLA-B27 gene in rats. And now these rats have the same symptoms as patients with spondyloarthritis. For the first time, I can investigate the brain in a way I could never do in patients, because I can do microdialysis to measure neurotransmitters in freely moving animals, and at the end of the experiments I make slides of the brain and I color them for all kinds of things. You can put humans in an imaging machine, which gives you a lot of information, but often it is not detailed and for a single moment in time.*'

Mechiel stresses that doing good research is important. When using animals, it is important to look at the validity of the animal model. How well does the model tell you what you want to know? '*There are a lot of animal models that don't have a high validity. This one has an extremely high validity. It is important to focus on what the model really tells you.*' Mechiel has recently sent an article in for publication wherein he has used this model and found a decrease in monoamines including serotonin and dopamine. We look forward to this article.

The importance of doing research

'*I still have to convince rheumatologists that what we do is important and that there is a link between arthritis, fatigue and depression. But I am also very motivated to find a solution, because I know how it feels having both arthritis and fatigue. I now go to meetings with patients, and I get many emails of patients who are happy that there is finally someone that investigates this problem, and who want to be involved in this research. Which motivates me even more. Psychoneuroimmunology started in the 80s, and the first papers they wanted to publish in nature and science, people thought this was placebo, they didn't believe it. When you look in the textbooks, you always see the sympathetic and parasympathetic system innervating all the organs. But they always leave out the immune system. Already since the 80s we know that all the immune systems in the body are innervated by neurons. And it's still not in the text books. When you have stress you immediately feel it in your joints, but when you tell people they think it is placebo. After 30-35 years, it is finally published in the Lancet and thus in the medical field. It is a real milestone.*' '*By doing fundamental research, I am convinced that it will finally end up in a real treatment. This is why we do it.*'

'First I thought I was a Viking. In Scandinavia, the [HLAb27] gene is much more common. You cannot find it in Africa. But then I discovered that in **Heida people** (first North Americans) even 50% of the population have the gene. So, I could also have said I am a native American. In 1862, there was a small pox outbreak. It killed almost everybody. This gene also protects people from diseases like small pox, HIV, hepatitis C, barr-virus, influenza. So I have a very strong immune system, a bit too strong.'

PhD theses abstracts

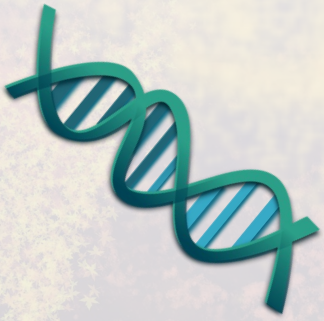
Multifunctional polymeric nanoparticles for RNA delivery: from carrier design to cancer immunotherapy?

Dr. Bo Lou

Dr. Bo Lou published his PhD thesis in September 2018, for which he did 5 years of research at Utrecht University. During these years, Bo worked on the development of a potent nanocarrier for RNA-based drug delivery. Because his research is so relevant and innovative, we will give a summary of what he did.

RNA-based drugs have widely shown to be very effective in the treatment of various diseases, including cancer. RNA-based therapies include interfering RNAs (siRNA), messenger RNA (mRNA), single chain RNA (ssRNA), and, nowadays, CRISPR-cas guide RNA (gRNA). However, delivery of this RNA remains a struggle, as RNA is degraded easily by nuclease enzymes. Also, RNA is recognised by our immune system, and the molecule can not enter the cell by itself, due to its size and charge properties. Polymeric nanosized delivery systems are among the favourite solutions, as these vesicles can easily be altered for specific delivery targets. Bo Lou worked in novel polymeric vectors for different RNA therapeutics for his PhD. He specifically looked at delivery of siRNA to target tumor cells, delivery of ssRNA as adjuvant together with a protein antigen for vaccines, and finally, delivery of mRNA antigen to dendritic cells for cancer immunotherapy. He used different stabilization strategies, such as addition of hydrophobic groups, crosslinks, and PEGylation. Additionally, he tried different target ligands for optimal targeting and improved endosomal escape. For all these different delivery systems, their characteristics and behaviour, including cellular uptake, clearance, and toxicity, were examined.

Since his publication consists of 217 pages and a ton of interesting findings, we can not tell you all the interesting details in such a short summary. If you would like to know more about what Bo Lou did, please find his book online. You can download it for free from his UU page!



Human milk oligosaccharides – Mama's sweet immunological secrets

Dr. Ling Xiao

Dr. Ling Xiao investigated the immunomodulatory effects of authentic human milk oligosaccharides (HMOS) and specific oligosaccharide mixtures for her PhD thesis. This involved the use of an autoimmune diabetes mouse model and a murine vaccination research model. She used in vitro mouse bone marrow derived- and human monocyte derived dendritic cell models to investigate the immune mechanism behind, while looking at certain specific topics.

First of all, she studied the effect of HMOS isolated from human milk on the non-obese diabetic mouse model and mouse bone marrow derived dendritic cells. She found that dietary intervention with authentic HMOS in early life protected non-obese diabetic mice from developing type 1 diabetes later on. Mechanisms through which this effect was accomplished were modulation of the gut microbiota composition and metabolites, and regulation of the immune response via dendritic cells.

Secondly, she investigated if the effects of authentic HMOS were translatable/comparable with data obtained using human in vitro cell models. From this, she concluded that HMOS induce direct immunomodulation and suppresses LPS-induced over activation of human dendritic cells.

Furthermore, she also looked at the effect of 2'fucosyllactose (2'FL) alone and/or in combination with scGOS/lcFOS on an influenza vaccination mouse model. 2'FL is one of the oligosaccharides which she found to enhance both the humoral and cellular immune response in an influenza vaccination mouse model. When giving a mixture of 2'FL and scGOS/lcFOS, a more pronounced vaccine-specific immune response was seen.

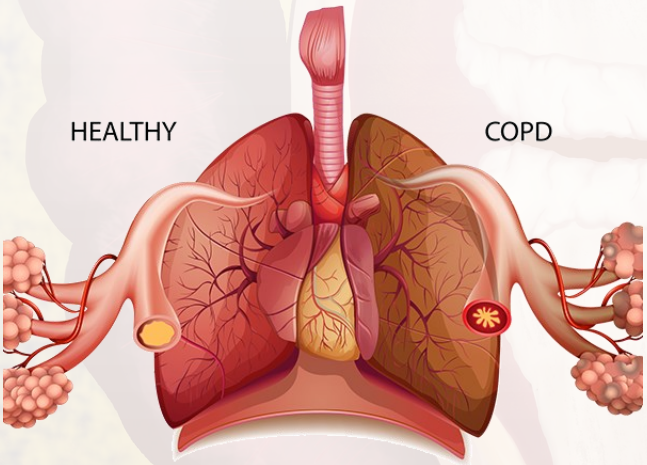
Promising results were revealed from the research. With her findings, it could be concluded that oligosaccharides in human milk support the development of the immune system and gut microbiota in breastfed infants.

Internship abstracts

Developing a mouse model for Chronic Obstructive Pulmonary Disease (COPD)

Sanne Hoepel

COPD is the third leading cause of death worldwide. In its pathophysiology, long term exposure to cigarette smoke or other pollutants cause, amongst others, systemic inflammation as a symptom. Furthermore, common comorbidities (found in +/- 55% of the patients) are central nervous system (CNS) disorders, such as depression. Exacerbations of the disease are mostly caused by bacteriological or viral triggers, and the patient often needs to be hospitalized.



In my bachelor internship, I'm assisting PhD-students Charlotte Pelgrim and Lei Wang (Pharmacology) in developing an improved mouse model for COPD, that also models exacerbations and possible comorbidities, such as depressive-like symptoms and muscle wasting. Within this research project, my primary focus is the role of microglial cells within COPD. Microglial cells are residual macrophages within the brain. When these immune cells are activated, they release pro-inflammatory cytokines, which in the case of constant activation, is hypothesized to cause "neuroinflammation".

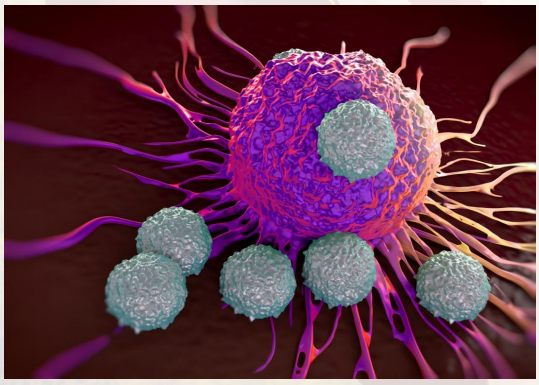
This state of neuroinflammation is thought to influence – amongst many other factors in the brain – the synthesis of neurotransmitters and, via that pathway, cause CNS disorders. If this is indeed the case in COPD, then it needs to be investigated. The effect of cigarette smoke on microglial cells is partially unknown. It has been shown in vitro that nicotine has an anti-inflammatory effect, although the other components in cigarette smoke do cause an inflammatory reaction. This has also been shown in a short-term in vivo model. However, the (sub)-chronic effect of cigarette smoke exposure on microglial cells has not yet been investigated. To investigate the role of microglial cells within COPD, I perform in vitro and ex vivo experiments. In vitro, I investigate the effect of cigarette smoke extract on the inflammatory response of microglial cells. For this, the cells are plated and incubated with cigarette smoke extract and later triggered with LPS. The inflammatory response is measured by an IL-6 ELISA. Preliminary results suggest a dose-dependent anti-inflammatory effect of cigarette smoke, which can be attributed to nicotine, based on literature.

Ex vivo, I will analyze the brains of mice from the different groups from the mouse model. With immunohistochemical staining, I will investigate if there are differences in the abundance and morphology of the microglial cells. Altogether, I hope that my work in this research project will elucidate the role of microglial cells within COPD more.

Polymeric micelles for better administration of hydrophobic drugs

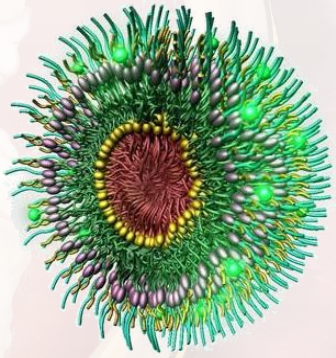
Heleen van Leur

More than one third of newly discovered drugs are poorly water soluble. (1,2) As our body is mostly built of water, this causes problems with administration, circulation, and toxicity of those drugs. A well-known hydrophobic compound is paclitaxel. Paclitaxel is a mitotic inhibitor, an anticancer agent, used for multiple kinds of cancer, such as refractory ovarian cancer, metastatic breast cancer, non-small cell lung cancer, AIDS-related Kaposi's sarcoma, and other cancers. (3,4) Due to its high hydrophobicity, paclitaxel is cleared very rapidly from the body. This leads to a low bioavailability, and thereby, a low therapeutic index. A clinically approved formulation of paclitaxel is Taxol®, which is administered in the solubilization agent Cremaphor EL. However, Cremaphor EL can cause extreme hypersensitivity reactions and other side effects. (4) Solubilization enhancers often cause side-effects. Therefore, another administration vehicle which presents less side effects and possibly makes the drug more effective (by increasing the bioavailability) is desired.



It has been shown that paclitaxel is encapsulated very well in the core of polymeric micelles, specifically, $mPEG_{5000}$-b-p-(HPMAm-Bz) micelles. (3) Polymeric micelles are prepared from amphiphilic polymers, so polymers with a hydrophilic and a hydrophobic block.

When this polymer is put in an aqueous solution, it immediately forms spherical structures. It is possible to encapsulate hydrophobic drugs in these micelles by dissolving the polymer and the drug in the same organic solvent, and adding this dropwise to an equal volume of water. The mechanism by which these drugs stay in the micelles is presumed to be π-π stacking. π-π stacking is a hydrophobic interaction between aromatic rings. (3) Despite this, it seems that this is not the only interaction retaining the hydrophobic drugs in the core of the micelles. (5)



In my internship, I am working with PhD student Aida Varela Moreira in the department of Pharmaceutics on the third floor of DDW. I am testing different hydrophobic drugs in the $mPEG_{5000}$-b-p-(HPMAm-Bz) micelles, and determining the maximum concentration of drug which can be encapsulated by these micelles. Furthermore, I perform release studies with these hydrophobic drugs to see how fast each drug is released from the micelles. In order to perform these experiments, I use dynamic light scattering (DLS) to determine the size of the micelles, and high performance liquid chromatography (HPLC) to determine the amount of drug in each micelle. In the end, the goal is to find which characteristics make a hydrophobic drug suitable for loading in these micelles.

Recruitment for HPPS project

English book project

Dear students,

We are currently looking for new members to join the English Book project. The aim of the book is to provide interested readers with an overview of Pharmaceutical Sciences, which is an interdisciplinary area that incorporates knowledge from disciplines such as biology, chemistry, biochemistry, physiology and others. The book begins with an introduction to pharmacy and continues with pharmaceutical research. From there on, topics related to the action of drugs, for example pharmacokinetics, pharmacodynamics, and related interactions are explained. Focus is given on physiology and cell biology, which are explained in detail to understand disease mechanisms. Neurology, immunology, cardiology-related functions, and several diseases are discussed.

If you are interested please, contact l.chemlal@students.uu.nl to provide you with more information about the project or to answer any questions related to the project.

Kind regards,
Anastasios and Moska

Prix Galien and Nobel Prize award winners

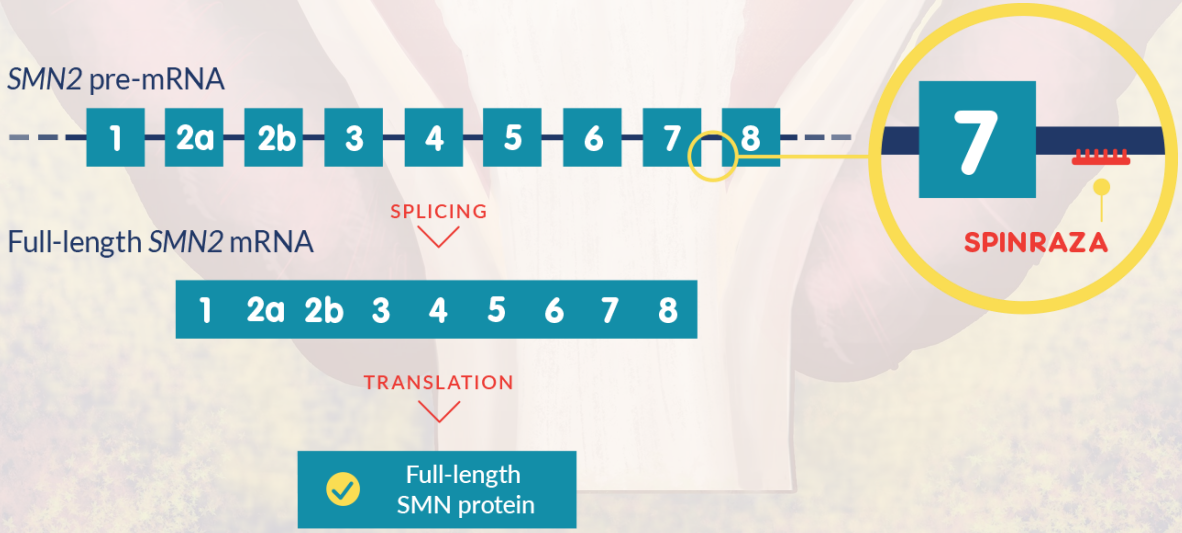
Spinraza wins pharmaceutical Prix Galien

On the 2nd October, the Prix Galien was held in Ede, as part of the Figon DMD. The Prix Galien is awarded by the Galien Foundation, and, in the Netherlands, it is awarded since 1992. This prize is to reward scientific innovation. The Prix Galien has three categories for which an award can be given: pharmaceuticals, researchers, and innovative technologies. This year, Spinraza (nusinersen) received the prestigious award. It is used to treat spinal muscular atrophy (SMA).

Patients with SMA have a mutated or missing SMN1 gene, and can therefore not produce enough SMN protein. This protein is crucial for the communication between the brain and the muscles. Without SMN protein, neurons will degenerate, leading to muscle weakness and paralysis. The closely related gene SMN2 produces small quantities of SMN protein as well, but not enough on its own.

Most of the time, exon 7 will be skipped during transcription, producing shorter SMN proteins that cannot compensate for the insufficient production by SMN1. Spinraza is an antisense oligonucleotide that acts on the splicing of the pre-mRNA. It targets intronic splicing silencer N1, and keeps the intron 7 from being removed during splicing. This eventually leads to translation of a full-length and fully functional SMN protein. It was approved by the FDA on December 23rd of 2016. It is a highly promising drug that allows restoration of the functional protein.

More information can be found on:
Prix Galien: https://www.prixgalien.nl/ & http://new.galienfoundation.org/
Spinraza: *Ottesen EW. ISS-N1 makes the First FDA-approved Drug for Spinal Muscular Atrophy. Transl Neurosci. 2017 Jan;8:1–6.* & *https://www.spinraza-hcp.com/en_us/home/mechanism-of-action.html*



Breakthrough discovery in cancer treatment awarded Nobel Prize

The Nobel Prize in Medicine of 2018 was awarded to James P. Allison and Tasuku Honjo for their research in cancer immunology. Next to chemotherapy and radiotherapy, recent advances have started looking into training the immune system to recognize cancer cells and effectively kill them in the process.

The most important players in the immune system that allow the distinction between self and non-self are T-cells. These T-cells recognize self and non-self antigens, and trigger an immune response. However, in order to initiate this response, a second co-stimulatory signal is needed. Furthermore, other proteins can inhibit the T-cells from initiating an immune response. These signals are called immune checkpoints, and are important for a well-balanced and correct immune response that attacks pathogens and cancerous cells, while keeping tissues unharmed. James P. Allison discovered that a T-cell protein called CTLA-4 acts as a T-cell brake. He developed an antibody against CTLA-4 to study whether inhibition of CTLA-4 could reactivate the T-cells to attack cancer cells. In 2010, a clinical study showed remarkable results of the CTLA-4 antibody in melanoma patients.

On the other hand, Tasuku Honjo discovered a different protein on the surface of T-cells: PD-1. Over a series of meticulous experiments, he discovered that PD-1 also functions as a T-cell brake, but via a different mechanism compared to CTLA-4. Similarly to Allison, Honjo had the idea to inhibit PD-1 with an antibody, which quickly showed promising results in animal cancer models. In 2012, clinical studies proved the employment of a therapeutic anti-PD-1 antibody as a successful method to treat different types of cancer. The mechanisms of anti-PD-1 and anti-CTLA4 treatments are shown in **Figure 7.**

Together, Allison and Honjo paved the way for immune-checkpoint therapy. Their work will be of great importance for future therapies in cancer.

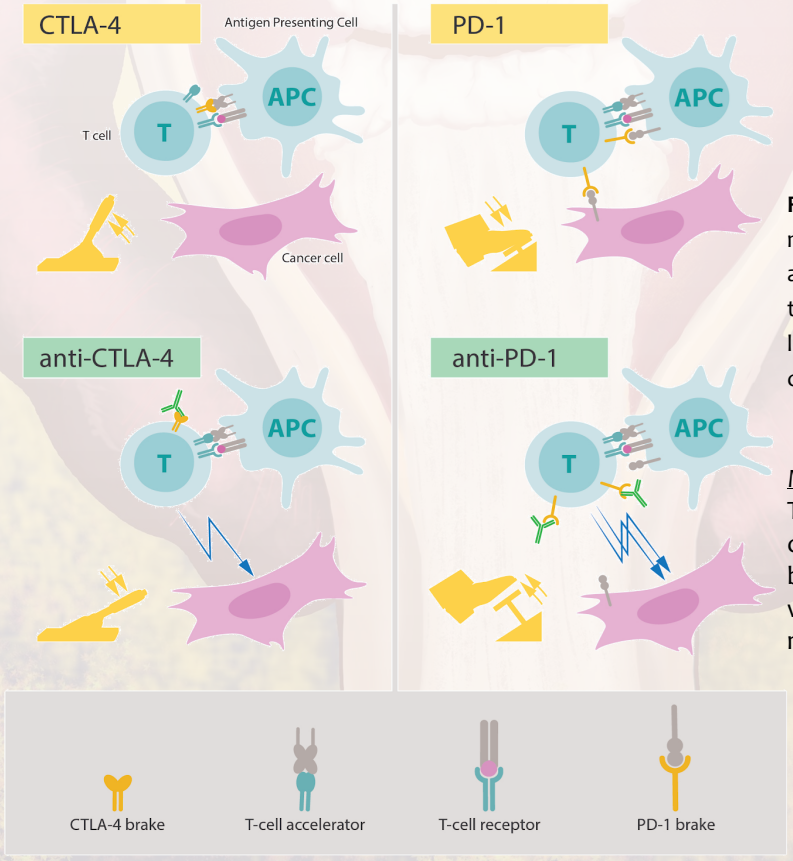


Figure 7: CTLA-4 and PD-1 are immune inhibitors. Anti-CTLA-4 and anti-PD-1 treatments counteract this immunological break, and allow better efficacy in the treatment of cancer.

More information can be found on:
The 2018 Nobel Prize in Physiology or Medicine - Press release - NobelPrize.org [online] https://www.nobelprize.org/prizes/medicine/2018/press-release/

iGEM biotechnology conference

On the 20th of September, the International Genetically Engineered Machine (iGEM) Biotechnology Conference was held in Utrecht. It was organised by the iGEM team of Utrecht, together with the iGEM team of Aachen (Germany).

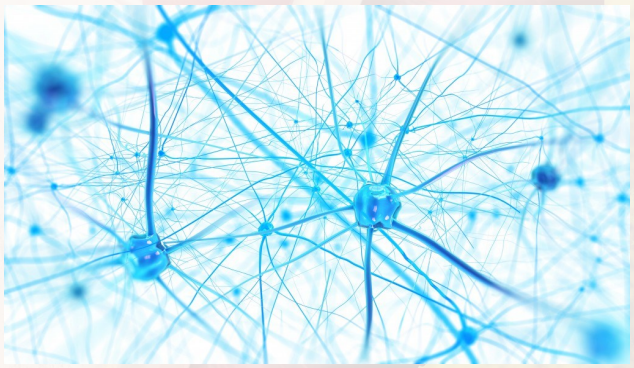
The iGEM competition is the largest synthetic biology competition in the world. It enthused thousands of students from many different countries and studies with the topic synthetic biology. Students that were in the Utrecht iGEM team of last year shared their experiences, along with their ups and downs in doing research. They won the contest; but unfortunately, their research hasn't been picked up by a company.

Additionally, students from Utrecht and Aachen iGEM teams of this year told us about their current ideas, research, and preparation for the great contest in Boston.

It was interesting to see what the possibilities are when you have a motivated and interdisciplinary team of students. Together, you can think of many new technological applications to improve and solve problems in society.

During the conference, not only students from the iGEM teams were present. There were multiple experts invited to share their research related to the theme: 'Valorisation in the biotechnology'. New applications and ideas that can be useful in society were presented. For example, dr. Silvia Mihaila informed us about a kidney on a chip-device that can potentially solve the lack of donated kidneys.

Biotechnology seems to be a new and revolutionary field of life sciences. Even though humankind has already been applying such techniques (such as brewing beer and baking bread) for thousands of years, this field is still growing, and new innovations are appearing everywhere.



UIPS symposium

On the 26th of October, the Utrecht Institute for Pharmaceutical Sciences (UIPS) symposium took place. The theme of the symposium was "Bioinspired therapies". The day was filled with interesting lectures from people within UIPS and invited experts outside UIPS, as well as a PhD poster session. Many people attended the event, teachers and students included. It was an inspiring event that gave an insight into the research that is being done right here in Utrecht, but also included some invited guest speakers who gave interesting talks about their work in other research institutes within or outside of the Netherlands.

The presented work ranged from 3D intestinal organoid models to artificial heart valves made from living tissue, to hydrogels and nanobodies, to immune engineering to fight cancer and regulatory affairs. One less scientific, but nevertheless interesting talk was given by Roland Pierik from UvA on whether vaccines should be made mandatory.

As a philosopher, he discussed the many aspects to consider when it comes to strategies to promote vaccinations, and in which cases vaccines should be made mandatory. Darrel Irvine from MIT discussed methods to engineer immunity in cancer and infectious disease. He presented all the methods that can be used to stimulate the immune system to fight off tumors and infectious agents, such as the immune checkpoint modulators or dendritic cell vaccines.

In addition, a poster session was held in the afternoon, during which PhD students at UIPS displayed many inspiring research topics. At the end of the day, attendees had certainly been introduced to many new inspiring research topics, and had the opportunity to meet aspiring researchers at the PhD poster competition.

HPPS Social Event: Legen-wait for it-dary!!!

On the 27th of September, the first HPPS social event of the academic year took place. After dinner at Stairway's, several thrilling games of laser tag were played at Ozebi. Despite the abundance of competitiveness between teams, there was enough time for socialising during the break. Also, our HPPS coordinator joined the battle, and after a rough start, he was on fire during the second round. We hope the students had a fun evening, and that it was a nice way for the second years to kick off their HPPS journeys!

If you ever get the opportunity to organise such a social event, go for it! It can be a challenge sometimes, especially since not all places can hold a lot of people. However, as long as you start on time, it will be fine at the end. As for all HPPS projects, we are a community that help each other. Therefore, if you have any questions, do not hesitate to ask your fellow students!

AWARENESS CALENDAR

October 2018 - February 2019

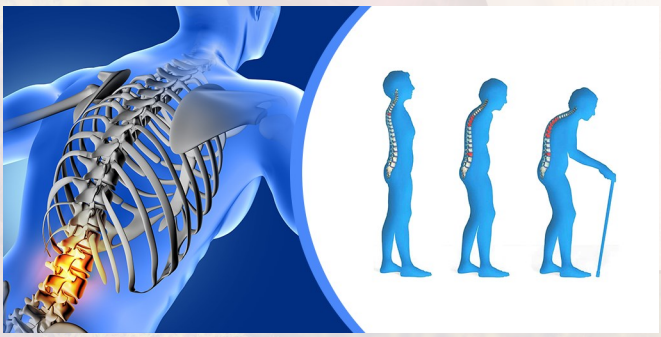
October

- 03-10: World Cerebral Palsy Day
- 22-10: International Stuttering Awareness Day

On the 20th of October, it is World Osteoporosis Day. The International Osteoporosis Foundation (IOF) reaches out to health-care professionals, the media, policy makers, and the public at large to raise global awareness of the prevention, diagnosis, and the treatment of osteoporosis and metabolic bone disease. Osteoporosis causes bones to become weak and fragile, and as a result of that, they break easily. The fractures caused can be life-threatening, possibly leading to long-term disability and pain.

Worldwide, one in three women and one in five men aged 50 years and over can suffer an osteoporotic fracture. However, if action is taken immediately, cases of osteoporosis and fractures can be prevented and reduced. During World Osteoporosis Day, individuals are encouraged to recognize risk factors and to seek testing and treatment if required.

Moreover, only a minority of patients with high risk for osteoporotic fractures actually receive treatment, despite effective medical advances to reduce these fractures. Therefore, IOF calls on health authorities and professionals to prevent osteoporosis from remaining undiagnosed and undertreated. (19)



November

- 12-11: World Pneumonia Day
- 14-11: World Diabetes Day

On the 17th of November each year, World Prematurity Day calls attention to the concerns of preterm babies and their families worldwide. Preterm birth often results in death, due to complications in preterm birth. For the ones that do survive, the additional burden of disability, pain, and suffering awaits; not only for the baby, but also for the family.

Birth is called preterm when the baby is born before 37 weeks of pregnancy. These babies are often very small and have a low-birth-weight (LBW), which is an important and indirect cause of neonatal death. Approximately 15 million babies are born prematurely every year, which accounts for more than one in 10 of all babies born worldwide. This is a very high number, and rates are even increasing. Countries can reduce their neonatal and infant mortality rates by improving the care for the mother during pregnancy and childbirth, and of LBW infants. Appropriate care of LBW infants, including their feeding, temperature maintenance, hygienic cord and skin care, early detection and treatment of infections, and complications can considerably reduce mortality. (20)

December

◊ 03-12: International Day of Persons with Disabilities

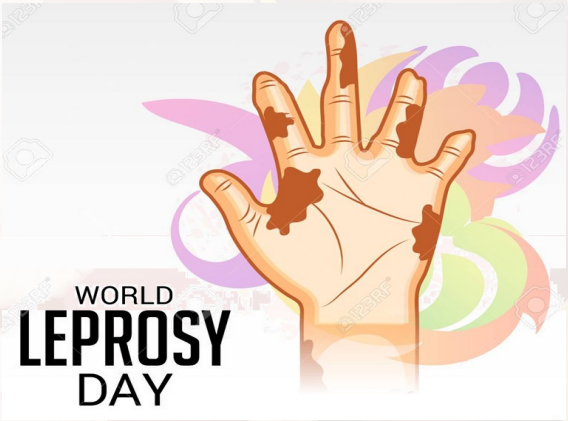
We may all know the red ribbons that are a global symbol for solidarity with HIV-positive people and those living with AIDS. They are shown worldwide on December the first every year, since 1988. At that moment, World AIDS Day reminds the public and government that HIV has not gone away. It is an opportunity for people worldwide to unite in the fight against HIV, to show support for people living with it, and to mourn the ones who have died because of it.

Globally, approximately 36.7 million people are living with HIV, with AIDS having killed between 28.9 million and 41.5 million people. Despite the fact that an HIV treatment exists and that our understanding of the disease has increased, these numbers are still growing. The World Health Organization (WHO) tries to increase awareness, fight prejudice, and improve education by organizing this event each year. (21)

January

◊ 04-01: World Braille Day

World Leprosy Day takes place on the last Sunday of January each year, with it being the 27th of January this year. It increases awareness of the leprosy or Hansen's Disease, one of the oldest recorded diseases in the world. It is an infectious chronic disease that targets the nervous system, especially the nerves in the hands, feet and face.



Many people believe this disease to be extinct, when, in fact, around 210,000 new cases are diagnosed every year. It is also believed that millions more people are living undiagnosed, leaving them at risk of disabilities. Therefore, early detection and treatment is important to prevent disability. By working together and detecting, diagnosing and treating patients with leprosy early, we can all come closer to eliminating the disease worldwide. (22)

February

- 12-02: International Epilepsy Day
- 14-02: Congenital Heart Defect Awareness Day

On the 4th of February each year, World Cancer Day raises awareness and education about cancer, and presses governments and individuals across the world to take action against the disease. It is the one day when the entire world can unite together in this fight. Misinformation is targeted, stigma is reduced, and support is shown to those affected by cancer.

Cancer is the second-leading cause of death worldwide. Round 9.6 million people die from cancer every year, while up to 3.7 million lives could be saved each year by implementing resource-appropriate strategies for prevention, early detection, and treatment. Thereby, at least one third of common cancers are preventable.

World Cancer Day is founded by the Union for International Cancer Control (UICC), and aims to save millions of these preventable deaths. This is also the primary goal of the World Cancer Declaration. (23)

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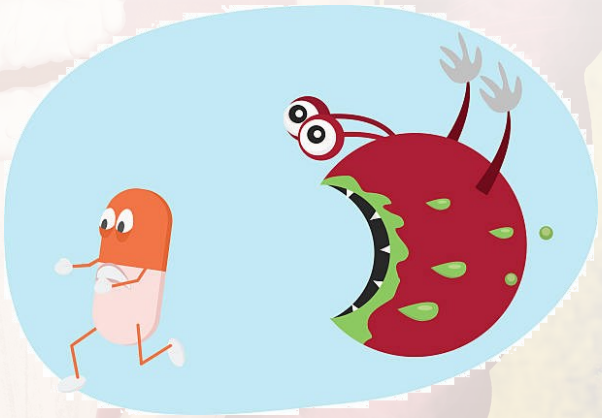
Next time...

That's the end of this issue! We hope you enjoyed it. The next issue of Drugs and Beyond will be released at the end of this academic year before the summer holidays, and will cover one of the most important drug classes: antibiotics. We will take you through the discovery of the first antibiotic, the current state of research in antibiotics development (inter)nationally, and touch upon one of the biggest problems concerning antibiotic use: multiresistant bacteria.

Besides this, you can look forward to many other exciting news, a new awareness calendar, interesting projects from your fellow HPPS colleagues, and more! Don't forget to let us know if you would like to publish your project idea, thesis, abstract, project outcome, etc. You can contact us via our email: **hppsjournal@gmail.com**



See you next time!
The Drugs and Beyond Team