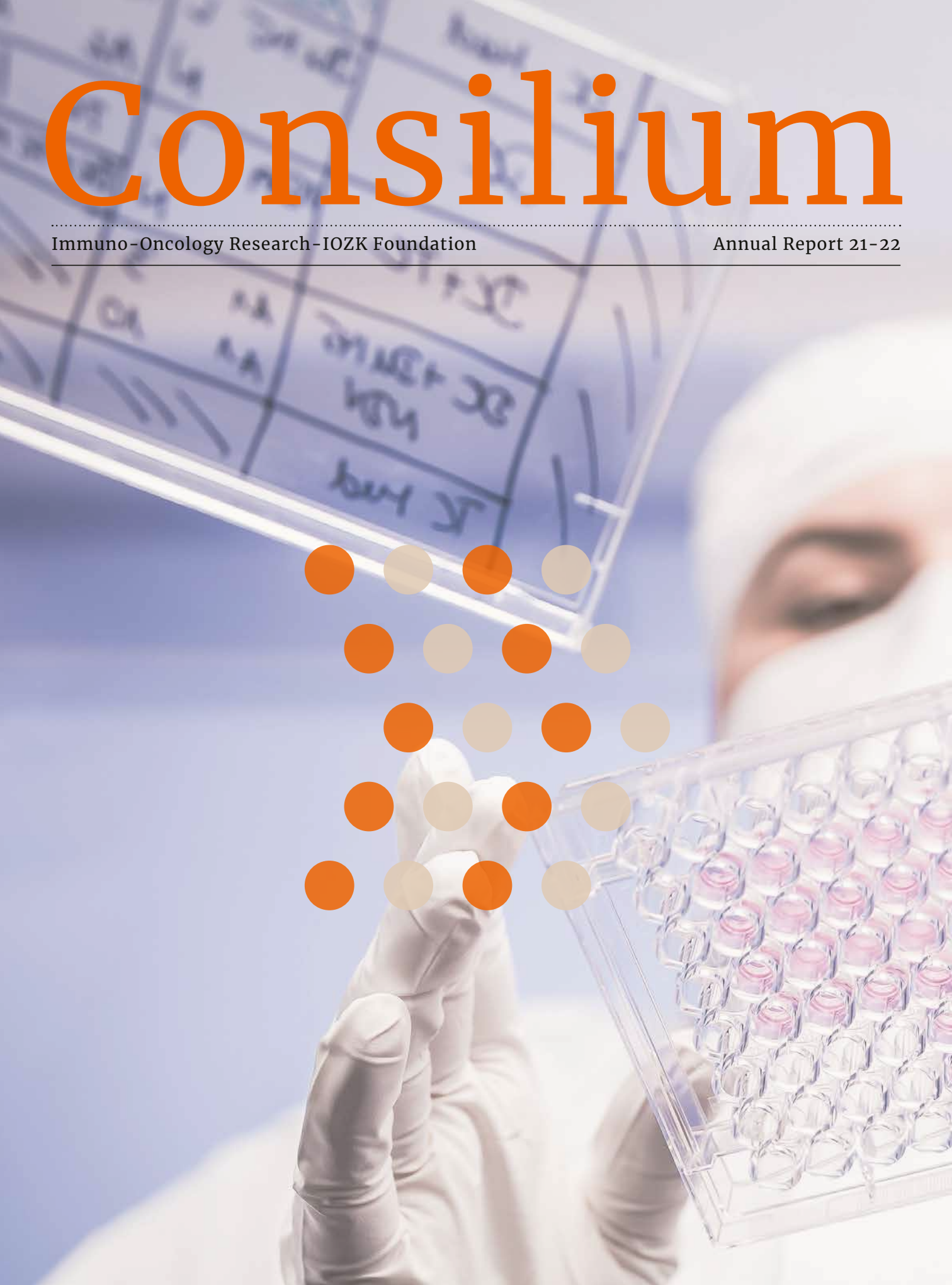
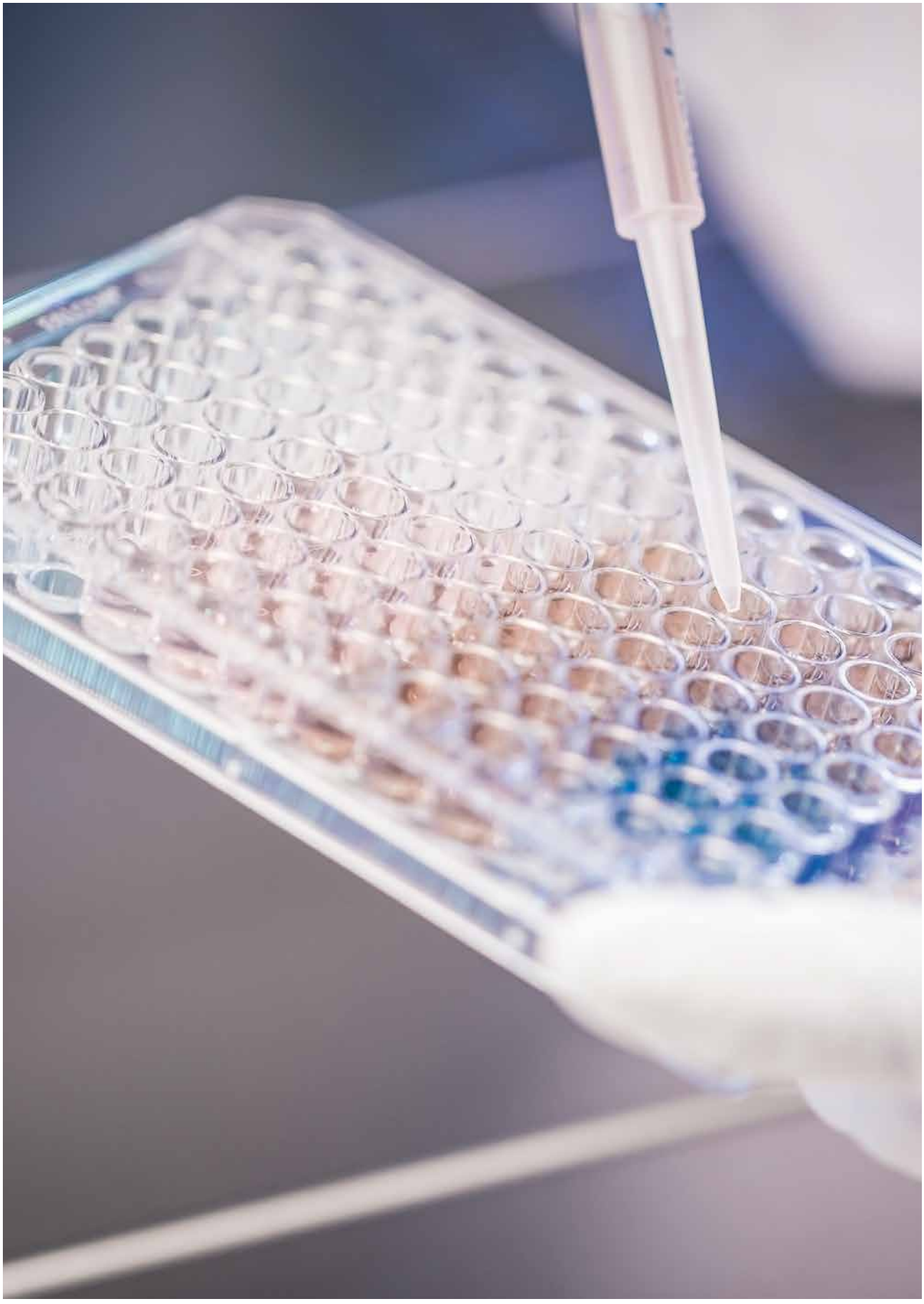
Consilium

Immuno-Oncology Research-IOZK Foundation

Annual Report 21-22





COLOGNE, JUNE 2023

Dear Readers

with great pleasure we present you the current annual report, in which we would like to inform you about new developments in the field of immuno-oncology.

This issue features reports on study projects by young researchers in the context of bachelor's and diploma theses. These were scientifically supervised at the IOZK by Dr Bitar and Dr Van Gool. We are content to be able to support young colleagues in this emerging field of science with these projects. Furthermore, these activities intensify networking with universities and other research institutions. This corresponds to our claim to actively stimulate public awareness, scientific exchange and research.

Also, you will find presentations of various laboratory methods for the analysis of immunological functions as well as information on the topic of "immunogenic cell death" - a concept that is crucial for the effectiveness of immunotherapy in the fight against cancer.

The contribution to the scientific discourse by Dr Van Gool deals with the topic of randomised controlled trials, with particular reference to research into malignant brain tumours. Recent findings on „extracellular vesicles" have opened up new perspectives. These are tiny particles that all cells in our body, especially cancer cells, secrete in considerable quantities, and whose molecular signatures promise diagnostic and therapeutic benefits. We are also active in this field and hope to report exciting news in the next issue of Consilium.

We appreciate your interest and wish you pleasant reading.

Sincerely, Dr. Wilfried Stücker

Managing Director of the IOZK Foundation

THE IDEA BEHIND THE FOUNDATION

Immuno-oncology in focus

The mission: More education and targeted research for the benefit of patients

Immunotherapies are now recognised treatment options in oncology. They target the body's self-healing powers in order to mobilise the immune system against the growth of tumour cells. Considerable progress has been made in recent years and there is still much to be explored. New findings are constantly being added that can be integrated into therapy.

At present, however, most people know far too little about these innovative forms of treatment; they have the idea that cancer can only be treated with the classical methods such as surgery, radiation or chemotherapy - this is also the view of many doctors. Therefore, intensive and and broad-reaching efforts to provide information are needed.

The Foundation for Immuno-Oncological Research - IOZK Foundation gGmbH – was established to advance research on immunotherapy and to disseminate knowledge about the methods. Its scientific and communicative work is financed exclusively by donations. It is recognised as a non-profit organisation.

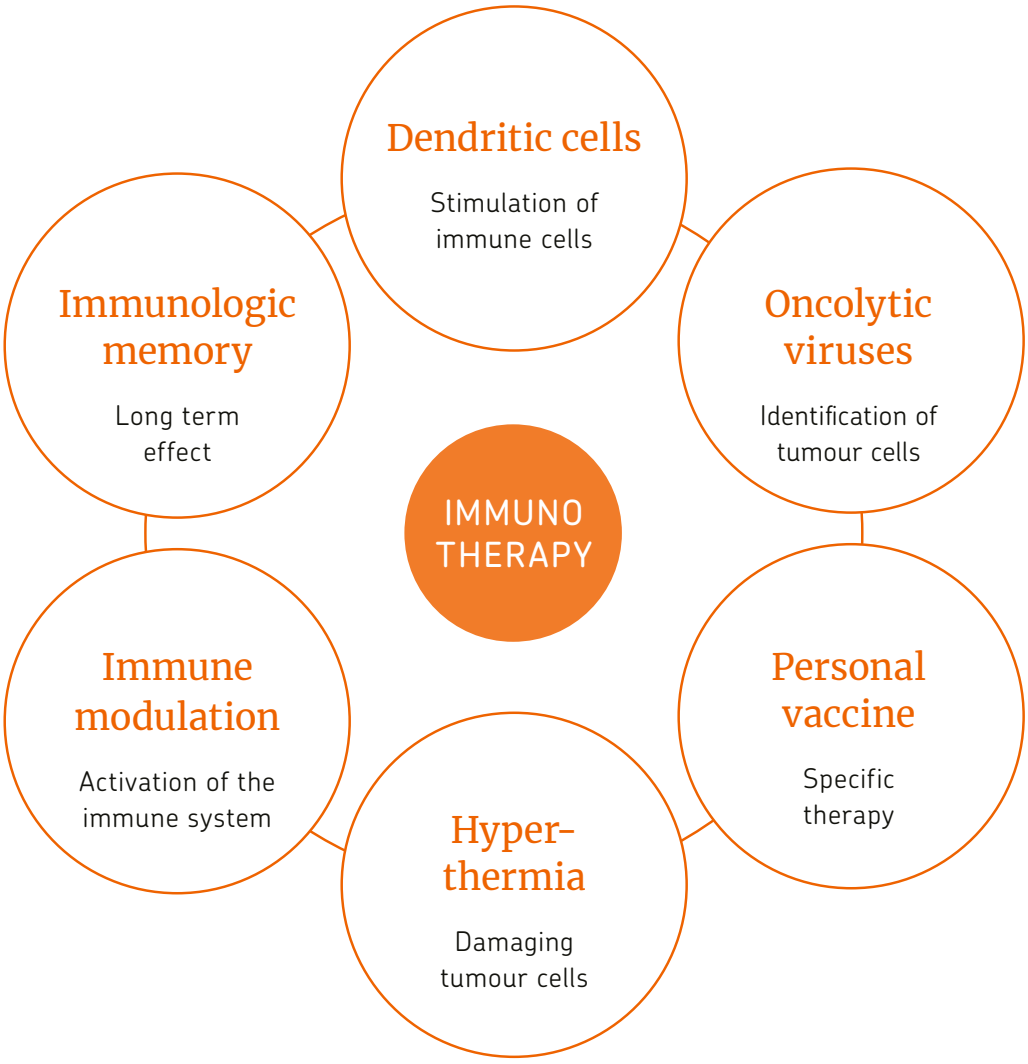
The therapy: A cancer treatment that helps the body to help itself

The IOZK is a translational institution in the field of immunological oncology, where promising results of basic research are promptly transferred into medical therapies.

Founded in 1985, the centre was the first institute in Europe to receive approval for the production of the individual IO-VAC® vaccine for the treatment of tumours in 2015.

The vaccination is carried out with the patient's own cells and tumour antigens in combination with oncolytic viruses and, in conjunction with appropriate hyperthermia procedures, serves to activate the immune system specifically to fight against the tumour. The hyperthermia puts the tumour tissue under "stress" and the immune cells are activated more strongly.

What is special about this therapy is that some of the informed immune cells migrate into the bone marrow and form an immunological memory there. It can prevent the development of metastases and thus ensures a lasting effect of the immunotherapy.


Dendritic cells
Stimulation of immune cells
Immunologic memory
Long term effect
Oncolytic viruses
Identification of tumour cells
IMMUNO THERAPY
Immune modulation
Activation of the immune system
Personal vaccine
Specific therapy
Hyper-thermia
Damaging tumour cells

SCIENTIFIC PROJECT WORK

Targeted research and funding

These exemplary projects not only serve the scientific advancement of active immunotherapy, but also the practical experience and profiling of young academics in modern courses of study such as bioanalytics or technomathematics.

The students were supervised in their scientific work by Dr. rer. med. Michael Bitar, the technical director of the diagnostics IOZK laboratory, and Stefaan Van Gool, MD. PhD, the medical director of the IOZK.

Project 4006

A novel method to monitor T cell responses upon DC vaccination.

Andreas Markolwitz
Bachelor thesis Bsc Biology,
Faculty of Mathematics
and Natural Sciences,
Rheinische Friedrich-Wilhelms-
Universität, Bonn

The aim of the thesis was to investigate the ability to measure T cell activation in the context of vaccination. This required the development of analytical techniques to measure (the increase in) pSTAT5 proteins in tumour-specific T cells.

The method is now used in routine diagnostic analyses in the IOZK laboratory to measure the activation properties of patients' T cells.

More about this project on page 6

Project 4010

In vitro CMV-expanded T cells as adaptive T cell therapy

Golnaz Rajabpour
Bachelor thesis Bsc Medical Engineering,
Department of Medical Technology
and Technomathematics,
Aachen University of Applied Sciences

This project focused on the further development of immunotherapeutic strategies for patients with glioblastoma multiforme (GBM), an aggressive, malignant disease of the brain. Studies have shown that human cytomegalovirus (CMV) contributes to the progression of glioma.

Various criteria and properties of T lymphocytes were investigated, including the duration of T cell expansion, the number of mononuclear cells required to initiate expansion, and the appropriate concentration of CMV peptide to stimulate the cells. The result is a precise protocol for the activation of CMV-specific T lymphocytes in vitro, which will now be tested in clinical practice.

More about Golnaz Rajabpour on page 23

Project 4010

Enrico Kolb
Bachelor thesis - Bioanalytics Coburg University of Applied Sciences

Enrico Kolb
Bachelor thesis - Bioanalytics
Coburg University of Applied Science

This project describes the approach of loading activated peripheral blood lymphocytes from healthy donors with the Newcastle Disease Virus (NDV) in vitro, in order to use them as a means of transport to the tumour target cells. For this purpose, various concentrations of NDV were tested for loading. Peripheral blood lymphocytes (PBL) are mature lymphocytes that circulate in the blood and do not settle in organs.

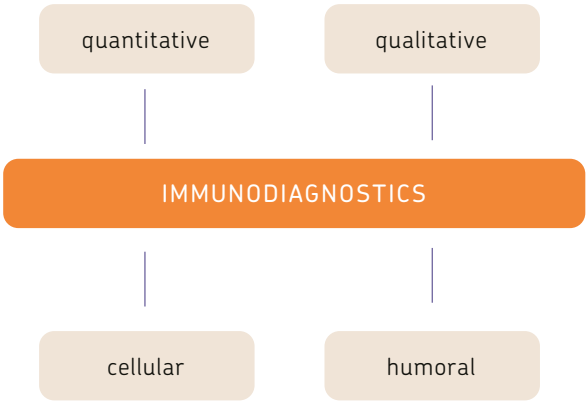
The results show that NDV loading of PBL is possible, and the survivability of tumour cells was significantly reduced. It could be shown that the onco- lytic viruses reach the target cells of the tumour. These results represent a new approach for tumour treatment.

IMMUNODIAGNOSTICS

Immunodiagnostics provide the basis for precise interventions

Immunodiagnostics is an area of laboratory medicine. For example, the number and composition of special subgroups of immune cells can be tested (“quantitative cellular immune status”) or the functional ability of relevant immune cells (“qualitative cellular immune status”). In addition, immunodiagnostics allows a targeted look at, for example, the antibodies in the blood, the so-called humoral immune status.

.



Immunological diagnosis as a pillar of therapy

We harness and condition the immune system The basis is the knowledge of how the patient’s immune system works: What can it do, what can it not yet do? How does it communicate with the tumour cells? Where does the system have a problem? The data from immunodiagnostics provide answers to these questions.

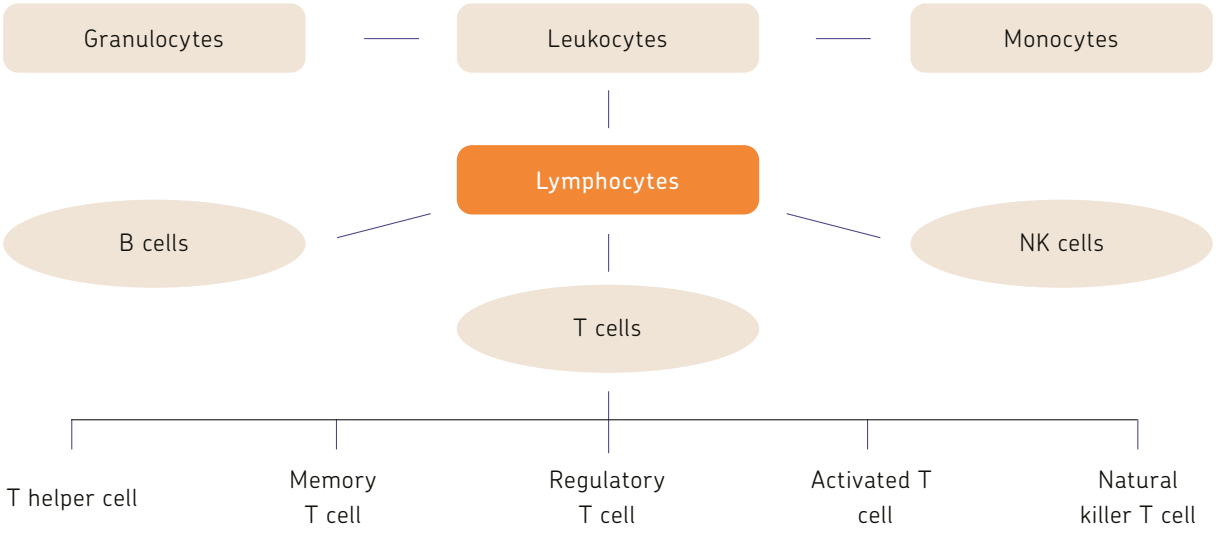
Treatment planning begins with a site assessment of immune system function and what can be done to ensure that an immune response occurs. The treatment should provide the greatest possible benefit to the patient, so we need to take appropriate measures to determine the optimal timing. Some patients also take advantage of other treatments, so the IOZK therapy must be integrated accordingly. The diagnostic data provide a scientific basis for assessing of the further course of action.

Immunophenotyping

In the quantitative cellular immune status, the different cell populations are examined. Each immune cell has a very specific task and belongs to a group. Depending on their characteristics, they can become active themselves or they inform other immune cells so that, for example, a concerted action can start. One can imagine the immune defence as in a state: there are informants who report to a public prosecutor's office who reports back, a police force that executes or a secret service that provides information to protect society.

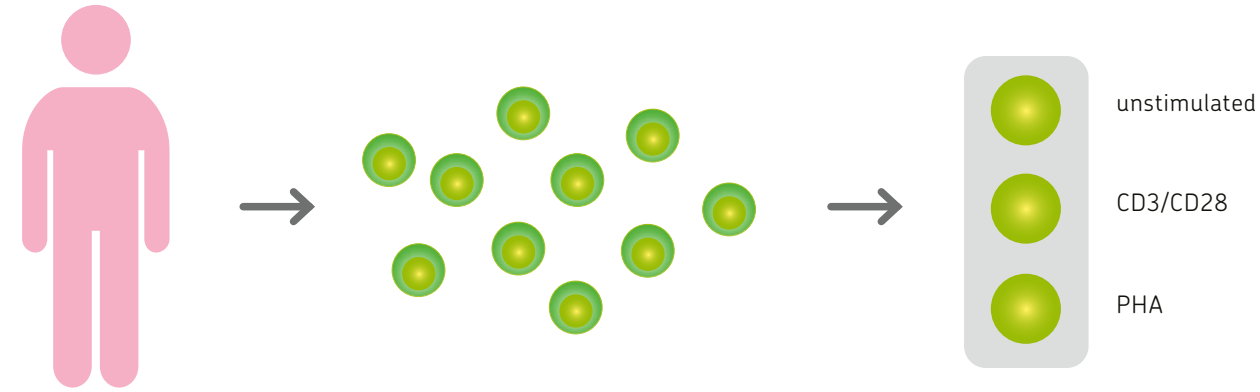
Whether T-helper cell, regulatory T-cell, T killer cell or T memory cell - all T cells belong to the lymphocytes, a subgroup of white blood cells. These T cells make up about 70 % of the lymphocytes in the blood. Their special feature is that they carry an antigen on their surface and that they perform very different tasks.

Here are some examples of cell subtypes. Regulatory T cells ensure that the tissue is not attacked by other immune cells so that no auto-immune reaction occurs. Tumour cells take advantage of this phenomenon; they are protected from attack by other immune cells by the regulatory cells. Gamma delta T cells, which make up only up to 2 % of blood lymphocytes, fulfil potent tasks in the transmission of information. They activate other cells or kill those that are not in order - they are "guiding cells" in the system. They recognise tissue injuries and can prevent the spread of infection by lysis (dissolution) of affected cells.



IMMUNODIAGNOSTICS

STAT5 analysis to check the proliferative capacity of T cells



Blood collection

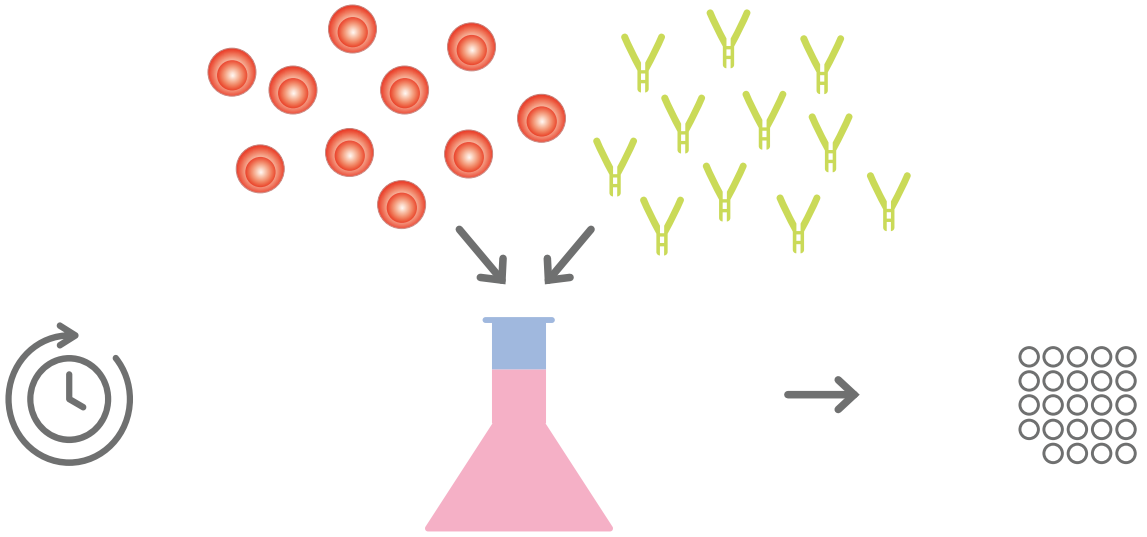
Isolated PBMCs

Stimulation of T cells within PBMCs by CD3 and CD28 antibodies

By analysing STAT5 in the laboratory, we can see how active or how sensitive the T-cells react when confronted with certain irritants. Only if the T-cells can be stimulated can a defence process be set in motion by the vaccination.

We can see, for example, whether the cells are already exhausted and have reached the end of their life span or whether they are very active and work effectively, a lot can be read about the quality of the immune system. In a few patients, these cells do not react or react too weakly - often after a strong chemotherapy.

An essential prerequisite is that the immune system is able to process information correctly, so the main thing is to create the optimal conditions in this regard before treatment begins.



After 20-24 h

Staining of the cells with fluorescently

Measurement of the STAT5 signal

ICD THERAPY

The new combination of chemotherapy and immunotherapy

Over the course of 3 to 12 months, 3 to 12 cycles

CHEMOTHERAPY

Time course →

Day 1–2

The tumour cells and all rapidly multiplying cells are blocked in their growth by the chemotherapy. Since rapid growth is a characteristic of tumour cells, these should be damaged the most by chemotherapy. Since the haematopoietic cells also belong to the rapidly dividing cells, they are also temporarily damaged or blocked.

On the day of chemotherapy administration, haematopoiesis production in the bone marrow stops.

On the following day, there is more blood formation – to make up for the shortfall in production on the previous day, so to speak.

NEW: ICD THERAPY

ADJUVANT IMMUNOTHERAPY

the time between chemotherapies is used to support the immune system in its self-help.

Beginning of the next chemotherapy cycle

Day 8

CYCLE: 5 DAYS

START: DAY 8–12

Day 13 | Day 15 or Day 21

INDUCTION OF IMMUNOGENIC CELL DEATH OF TUMOUR CELLS (ICD)

+ MODULATED LOCO-REGIONAL HYPERTHERMIA

The tumour cells are additionally stressed, then infected.rt.

+ NEWCASTLE DISEASE VIRUS

Tumour cells die immunogenic cell death.

Day 10: Lowest cell count in the blood because production in the bone marrow stopped on day 1 for chemotherapy administration.

IMMUNE RESPONSE

From day 11 onwards, new immune cells sprout up again in the bloodstream. (rebound effect). These newly regenerated immune cells take up the information about the now immunogenic tumour cell components and form cytotoxic T cells.

These cytotoxic T cells attack the tumour cells. Thus, in addition to chemotherapy, the immune system also creates a tumour growth inhibition

STEFAAN VAN GOOL - SCIENTIFIC DISCOURSE

On the problem of studies in individual immunotherapy

Stefaan Van Gool, Medical Director of the Immuno-Oncology Centre in Cologne, is intensively involved with the question of which scientific methods are best suited to prove the effectiveness of a complex, multi-modal immunotherapy.

Glioblastoma multiforme (GBM) is a malignant form of brain tumour with very limited treatment options. Extensive clinical trials have shown that dendritic cell vaccines can prolong the life of patients. However, a successful randomised controlled clinical trial (RCT) has not yet been conducted. Stefaan Van Gool wants to find out why. His extensive literature review shows the reasons why conducting a successful trial for GBM patients is so difficult. Building on this work, the IOZK team is developing promising combination strategies for cancer immunotherapy that can be integrated into first-line treatment to improve patients' prognosis.

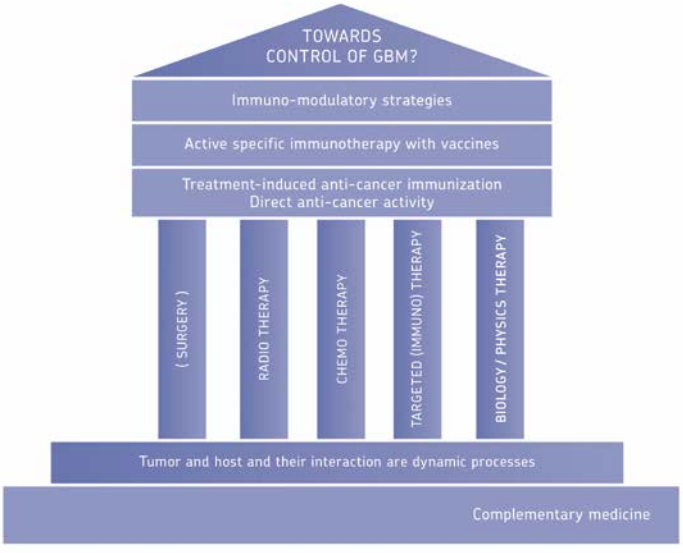
The IOZK is developing active and specific immunotherapies, which, in combination with other cancer therapies, offer promising therapeutic potential.

Cancer is the second most common cause of death in humans worldwide, accounting for one in six deaths. Cancer is the subject of intensive clinical research into its treatment and possible cure. There are many forms of serious cancer, but one of the most difficult to treat is glioblastoma multiforme (GBM).

There is a need for improved treatments for GBM patients, such as the inclusion of first-line immunotherapy to combat their cancers. Meta-analyses (i.e. examining data from many independent studies to determine overall trends) have examined the effectiveness of specific immunotherapy for GBM. These studies show that immunotherapy can significantly increase survival.

What makes GBM so threatening?

Brain tumours are the most common cause of cancer deaths in men aged 20-39 and the fourth most common cause in women of the same age. However, GBM is a particularly dangerous form of cancer and the most common malignant brain tumour in adults. It is a fast-growing tumour of the brain and spinal cord that causes rapid progression of symptoms. The number of deaths caused by GBM is the highest of all cancers, partly due to its occurrence at a young age and poor prognosis. Despite this, GBM is considered a rare disease for which there has not been much interest from drug manufacturers in developing a treatment. The current standard treatment after a diagnosis of GBM includes neurosurgery, radiochemotherapy and maintenance chemotherapy. Unfortunately, these treatments do not fully control the disease, which contributes to its poor prognosis.



! INTELLIGENT COMBINATIONS!
DYNAMIC ADAPTATION!
INDIVIDUALISATION!

1. Molecular biology
2. Tumour antigens
3. Interaction between tumour and host
4. Immune system/inflammation
5. Combination of treatments
6. Response to treatment

An analytical look at the research design of a randomised trial

With immunotherapy against Glioblastoma

(GBM) Unfortunately, the treatment options for people with GBM have not changed in recent years. However, there have been innovative treatment options have been explored, including tumour-targeting agents, anti-angiogenic treatments (designed to curb the formation of blood vessels in tumour disease), targeted therapies, oncolytic virus therapy or immunotherapies.

One example of targeted immunotherapy is dendritic cell (DC) vaccines. They help the immune system to recognise and attack foreign cells, such as cancer cells. To produce the vaccine, researchers grow dendritic cells together with cancer-specific antigens in the laboratory. The vaccine then stimulates the patient's own immune system to fight the cancer.

Systematic reviews of phase I and phase II trials have shown that giving DC vaccines to people with GBM leads to a significant improvement in long-term overall survival (two to five years). The efficacy of DC-vaccines in GBM reached evidence levels 2a and 1c (Oxford Centre for Evidence-Based Medicine).

Why have the neuro-oncology experts not been able to conduct an RCT? Stefaan Van Gool gives several reasons in his comprehensive literature review.

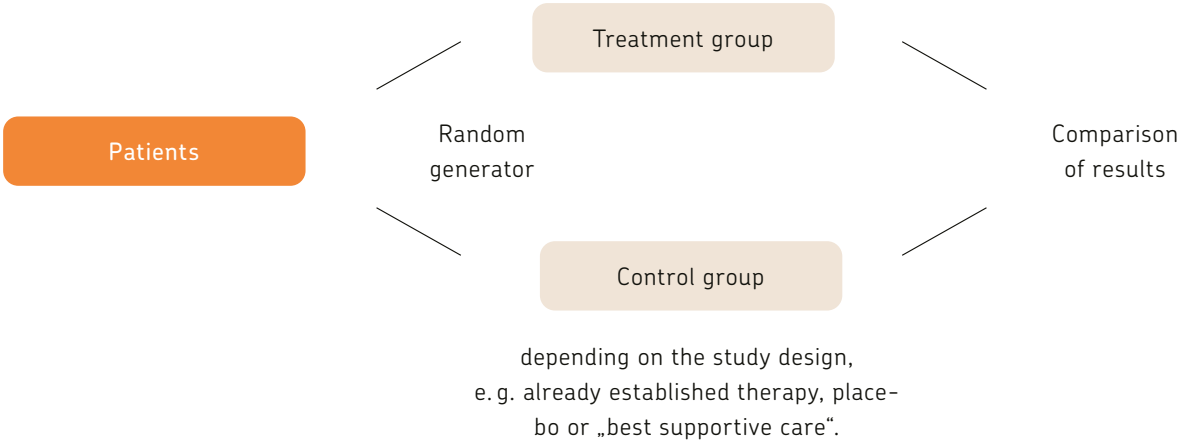
How does a randomised controlled trial (RCT) work?

Well-designed and properly conducted studies can compare the effectiveness of different treatments. For this purpose, selected patients are divided into groups and treated with different procedures.

In order to compensate as far as possible for all other factors on the success of treatment (individual characteristics such as age, mental state, social factors or concomitant diseases) are statistically balanced out, the largest possible groups are formed to which the patients are randomly assigned.

RCTs are considered the most reliable form of proof of efficacy in the hierarchy of research methods, as they are most likely to reduce error and bias. In some areas, great progress has been made through randomised controlled trials. These trials usually compare a new experimental treatment with the best currently available treatment.

However, the implementation is associated with high costs (tens of millions) and often takes many years. It is difficult to achieve the very large sample sizes required for meaningful results. Moreover, due to the high costs, it is not always possible to test all variables and provide a complete picture of complicated medical situations.



The randomised controlled trial (RCT) is considered the best study design.

Randomisation means randomly assigning patients to a treatment group – this is to exclude any possible influence. This prevents arbitrary manipulation or random distortions on the results are minimised.

STEFAAN VAN GOOL - SCIENTIFIC DISCOURSE

Randomised studies and immunotherapy

Stefaan Van Gool reviewed the literature on the suitability of randomised clinical trials (RTCs) for evaluating the effectiveness of immunotherapies. He concluded that there are many reasons why their implementation can be problematic.

RCTs are well suited to compare two methods in large, homogeneous patient collectives. However, with a large number of prognostic factors (clinical condition, tumour biology, chemosensitivity of tumour cells, tumour-host interaction, systemic immunity), RCTs are almost unfeasible: to statistically balance these variables, a very large number of patients would have to be included in the study, which would be impossible to recruit in rare diseases (such as GBM).

In addition, patients react very differently to radiochemotherapy. Some require larger amounts of cortisone, which affect the immune system, so that the pre-determined study protocol may not be adhered to.

In reality, the dynamic behaviour of the tumour and the immune system is not well compatible with a fixed treatment protocol that requires a randomised trial.

Since glioblastoma muliforme can lead to death within a few months, it is ethically unjustifiable to deprive patients in the control group of an effective therapy. Therefore, for example, a "cross-over" is introduced, which also allows patients in the control group to receive the immunotherapy during the course. But this makes the statistical proof of their effectiveness more difficult.

In summary, for GBM, an RCT is not the best scientific method for proving the efficacy of an individualised immunotherapy. This is due to the rarity of the disease, the multitude of influencing factors and the complexity of immunological methods.

Evidence of efficacy for individualized multimodal immunotherapy (IMI) for glioblastoma multiforme

Since RCTs are not feasible at the IOZK, we chose another method for scientific evaluation: retrospective analysis. It is considered less reliable than the RCT, but it also allows a systematic evaluation of immunotherapy.

We evaluated the course of 50 consecutively treated adults with IDH1 wild-type GBM at initial diagnosis. All patients received IMI in addition to standard treatment (surgery, radiochemotherapy and maintenance chemotherapy). The latter included vaccination with autologous dendritic cells (DC) loaded with tumor antigens, oncolytic virotherapy with Newcastle disease virus, and modulated electrohyperthermia (mEHT).

It is well known that certain markers are relevant to the prognosis of glioblastoma, such as the methylation status of the MGMT promoter. MGMT is involved in the repair of alkylated DNA and therefore attenuates the effect of alkylating chemotherapeutic agents such as Temodal. An unmethylated promoter is associated with a worse outcome. Therefore, patients were divided into different groups according to this characteristic.

MGMT promoter-unmethylated (*„unmeth“*, 10 women, 18 men) and MGMT promoter-methylated (*„meth“*, 12 women, 10 men) patients were treated and retrospectively analyzed between May 27, 2015, and Jan. 1, 2022, with July 1, 2022, as the cutoff date for follow-up. The mean age was 48 years (range 18-72), the mean Karnofsky index was 80 (range 50-100). Complete resection was not possible in more than half of the patients.

Dynamic changes in tumor biology and immune response were documented during treatment. In unmeth patients, a median survival of 22 months was documented and a two-year survival rate of 42 %. Both parameters were clearly better in meth patients at 38 months and 81 %, respectively. All treatments were performed on an outpatient basis. No serious treatment-related adverse events occurred.

Since these data were not collected in the context of a clinical trial but on the basis of individual curative trials, there was no direct comparison group. However, in order to assess the impact of IMI, the survival data were compared with clinical trials whose patients were very similar to those treated in the IOCC. In these studies, standard therapy was compared with other interventions.

STEFAAN VAN GOOL - SCIENTIFIC DISCOURSE

Randomised studies and immunotherapy

The following table shows the median overall survival in months (mOS) and the two-year survival rate in percent (2y OS) in meth and unmeth patients for the current standard of care. The bottom row shows data for standard treatment with additional IMI. Shaded in orange are the respective best survival times or rates that could be documented under standard therapy. The difference therefore represents the additional benefit of IMI, which is shown in the bottom row (in each case with an indication of the percentage by which the baseline value was improved).

		Unmethylated		Methylated	
First author	Intervention	mOS (m)	2y OS (%)	mOS (m)	2y OS (%)
Stupp 2009	S + RCT + CT	12,6	14,8	23,4	48,9
Stupp 2017	S + RCT + CT	14,7	22,1	21,2	37,7
Liau 2023	S + RCT + CT	14,6	21	21,3	42
Van Gool 2023	S + RCT + CT + IMI	22,1	39	37,7	80,5
Additional benefit of IMI		**7,4 (50,3 %)**	**16,9 (76,5 %)**	**14,3 (61,1 %)**	**31,6 (64,6 %)**

S: Surgery
RCT: Radiochemotherapy
CT: Chemotherapy
IMI: Individual, multimodal Immunotherapy (DC, NDV, mEHT)

In summary, there is a substantial improvement of all parameters by at least 50 %, even if the best data for the efficacy of the standard therapy from the various studies are used as a basis. This is the highest additional benefit published since the standard therapy was established in 2005. IMI is a therapy with particularly few side effects, for which considerable additional benefit has now been demonstrated.

Literature
Liau LM, Ashkan K, Brem S, et al. Association of Autologous Tumor Lysate-Loaded Dendritic Cell Vaccination With Extension of Survival Among Patients With Newly Diagnosed and Recurrent Glioblastoma: A Phase 3 Prospective Externally Controlled Cohort Trial. JAMA Oncol 2023;9:112-21.
Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009;10:459-66.
Stupp R, Taillibert S, Kanner A, et al. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial. JAMA 2017;318:2306-16.
Van Gool SW, Makalowski J, Van de Vliet P, et al. Individualized multimodal immunotherapy for adults with IDH1 wild-type GBM: a single institute experience. Cancers (Basel) 2023;15.

The future of glioblastoma treatment

These combination strategies led to a remarkable improvement in overall survival. Stefaan Van Gool explains this innovative concept: "Neurosurgery, radiotherapy, chemotherapy, targeted (immune) therapies and immunogenic cell death therapies are all anticancer strategies that can partially induce cancer immunity and prolong patient survival. However, in most cases, this is not sufficient and active, specific immunotherapy is required to build anticancer immunity. Finally, modulatory immunotherapy (such as checkpoint inhibitors) may be needed to facilitate the actively induced immune response against cancer.

The philosophy is that immunotherapy specifically strengthens and activates the patient's own defence system to help them fight their cancer. This protective immunotherapeutic cancer treatment shows great promise for treating patients with GBM.

How close is the goal of bringing multimodal immunotherapy for immunotherapy for GBM patients into routine practice?

"Clinically and technically, I would say very close," says Stefaan van Gool . "The treatment takes place on an outpatient basis and does not involve major side effects. Patients can be referred to a few specialised centres in each country where this part of the treatment can be done in close cooperation with the local oncology centre.

The HGG Immuno Group has brought together neuro-oncologists from many countries to build a network in Europe for the delivery of DC vaccination. HGG, by the way, stands for High Grade Glioma.

"However, at the level of legislation and health insurance, I have to remark," says Van Gool, "that we are still very far from that. Everyone needs to work together to overcome these hurdles, with the aim of improving quality of life and prolonging life for patients with GBM."

THE ORGANISATION

The people behind the foundation

Executive Board

Dr. Wilfried Stücker

Stefaan Van Gool, MD, PhD

Foundation Council

Prof. Dr. Dieter Müller

Management

Dr. Felix Li

Arnd Slegers

Jacob Hösl

Scientific Advisory Board

Prof. Dr. rer. nat.
Volker Schirrmacher

Elisabeth Arrojo, MD, PhD

Abhishek D. Garg, MSc, PhD

Dr. Wilfried Stücker
continues to develop a therapy that, instead of administering a substance from without, strengthens and activates the body's own defence mechanisms to proceed against the tumour tissue.

Stefaan Van Gool, MD, PhD
is medical director of translational oncology. He is backed by over 25 years of experience in clinical oncology and tumour immunology, including basic research on these topics.

Prof. Dr. Dieter Müller
is an entrepreneur and scientist dedicated to preventive medicine in the sense of salutogenesis. His scientific base is the Proviita Institute. Dieter Müller is the Chairman of the Board of Trustees of the IOZK Foundation.

Dr. Felix Li
graduated with a PhD in Economics from Cologne University. He sucessfully held leadership roles across Germany and Asia in Retail and Private Equity. He is married and is father of three adult children.

Arnd Slegers
looks after the financial needs of the foundation. He has over 20 years of experience in financial management in companies around the world. He is also researching in the area of health economy.

Jacob Hösl
is a lawyer with 30 years experience in the area of foundation and company law. He has constantly worked on matters regarding health and patient care – thereby producing various publications.

Prof. Dr. rer. nat.
Volker Schirrmacher
is an internationally renowned pioneer of cellular immunology and immune therapy specialized in the scientific work with oncolytic viruses.

Elisabeth Arrojo, MD, PhD
sis medical director of the Institute of Advanced Oncology in Madrid and professor of oncological hyperthermia at University of Murcia. She was awarded best oncologist of the year in spain in 2020 and 2021.

Abhishek D. Garg, MSc, PhD
is the assistant professor at KU Leuven, Belgium, and head of the Cell Stress & Immunity Lab. He is an expert in cellular and molecular immunology, especially in the field of immunogenic cell death in cancer.

PERSONAL

Congratulations to Dr. rer. med. Bitar

We are very pleased that Dr. rer. med. Michael Bitar has been awarded by the Medical Faculty of the University of Leipzig in November 2021: His doctorate is one of the best theses in the class of 2020/21.

As a clinical immunologist and pharmacist, Dr Michael Bitar is the technical head of our diagnostics laboratory, and at the same time he is responsible for the method development department. Our patients benefit from his expertise. The topic of the doctoral thesis is STAT5 analysis, which helps to identify how sensitive T-cells react when confronted with irritants, i.e. whether they can be stimulated. This is an important aspect before starting the immunotherapy - the analysis serves to create the optimal conditions for the vaccination against cancer.

Offspring in the lab: Golnaz Rajabpour

Even as a little girl, Golnaz wanted to help people; today she puts this wish into practice in her scientific work. With the support of the IOZK Foundation, she was able to participate in a research project that serves new perspectives in cancer therapy.

The fact that she can enjoy a university education in Jülich is thanks to her mother in Tehran, whose greatest wish was to enable her daughter to study abroad. After graduating from high school in Iran, Golnaz Rajabpour moved to Germany all by herself at the age of 16. She has just finished studying biomedical engineering at Aachen University of Applied Sciences. The subject combines mathematics, physics, engineering and computer science to solve medical problems in diagnostics and therapy.

A practical project was compulsory for the Bachelor's degree. Golnaz decided against the option of doing this at the university because she really wanted to get to know "real laboratory work". She found the IOZK by researching on the internet. "Everything was new to me, we had internships but in the first month I had to practice and learn a lot, whether pippetting or centrifugation," says the 22-year-old, "but the people at the IOZK were very nice and helpful."

The project focused on the CMV virus, which is often found in the bodies of cancer patients. In the in vitro experiment, T cells were specifically stimulated for this virus so that they could later target it in the patients' bodies. A standard protocol was to be developed as a basis, that was the actual bachelor project.

What is her conclusion from her time in the lab? "It takes a lot of discipline and a high level of concentration, and above all you must not be afraid to ask questions," says Golnaz Rajabpour. Her dream would be to work at the IOZK after graduation. Incidentally, her professor at the university is very pleased with the results of the research series; for the university, the new standard protocol is so interesting that it will be integrated into the academic work there.

GRANTS, FUNDS AND PROJECTS

The financial side of the foundation

The IOZK Foundation was established in 2016 as a result of a donation from a Canadian family whose child was treated at the IOZK for a brain tumour. With their generous donation, the family wanted to make a contribution to promote research into cancer in order to spare future families the suffering caused by the loss of loved ones.

Since then, the IOZK Foundation has collected donations of around 210,000 euros, which have been used to support various research projects over the past six years. The researchers working on these projects have also been supported to participate in the scientific discourse. Of the grants, around 55,000 euros were earmarked for multi-year research projects at the end of 2021.

The IOZK Foundation conducts these research projects in the laboratories at the IOZK in Cologne.

Research projects until the end of 2021 – beginning of 2022

These projects have been successfully carried out since the beginning of the Foundation's activities. In the future, the work will continue to focus on the subject areas of immuno-therapy.

Dr. Matthias Domogolla

Testing and validation of antigen production and presentation

Stefaan Van Gool, Michael Sobotta

Antibody generation in oncolytic virotherapy

Andeas Markowitz

Development of a FACs protocol for measure-ment of STATS phosphorylation and T cell proliferation after stimulation with CD3/CD28 antibodies

Maria Schuldt

Evaluation of specific activation markers of human dendritic cells for tumour immuno-therapy

Lisa Hannapel

Cancer stem cell-like antigens from fetal xenogeneic trafficking

Dr. Michael Bitar

Investigation on natural killer cells in vitro and in vivo

Dr. Michael Bitar, Golnaz Rajapbour, Enrico Kalb

In vitro CMV-expanded T cells as adaptive T cell therapy

DONATIONS

Endowments and donations welcome

Supporting cellular immuno-oncology research and communicative activities requires appropriate funding, resources and opportunities. Successful implementation of these requirements and objectives cannot be achieved from within our own organisation alone, i. e. the IOZK Treatment Centre.

Therefore, we rely on the support of private individuals or companies who want to support immunological research against cancer and contribute financial resources to the Foundation for this purpose.

With a donation, you support, for example, innovative immunotherapy projects and contribute to advancing cancer research.

Whether a small amount or a larger sum - everything helps our vision of fighting cancer with the help of the immune system in such a way that people gain more quality of life and longevity as a result.

To the online-donation

Donation account
IOZK Stiftung gGmbH
Volksbank Köln Bonn
IBAN: DE29 3806 0186 8304 2140 16
BIC: GENODED1BRS

Paypal: donation@iozk-stiftung.org

WHAT'S NEXT?

Translation into the future

What does translational medicine actually mean? Translational medicine transfers the results from basic research into patient care as quickly as possible. "From the laboratory bench to the bedside" is the motto, a new paradigm in medical research, which is known in the international professional world under the slogan "Bench to bed - and back".

Benefit orientation

From the very beginning, the IOZK has functioned as a translational institution, this topic is not new to the team. The therapy system for cancer vaccination has already been used in practice for many years and it has been able to show over time that it is effective. The aim of the research activities within the framework of the foundation is to understand the immunogenic microparticles(*) even better in their mode of action and to use them in an even more targeted manner. "The more precisely we detect the steps, the higher the efficiency of the vaccine and the quality of the treatment," says Stefaan Van Gool, "in translational research, what counts is the benefit for each individual patient."

Orientation towards networking

In addition to the current and planned research projects, there are already promising prospects for the future. For example, a cooperation with a globally operating institute is currently underway, which, among other things, provides the reference diagnostics for large research projects. The company approached the IOZK because the therapeutic concept that is being implemented in Cologne was able to convince with its innovative strength. In the context of scientific networking, a longer-term cooperation with a university hospital is also planned. More on this topic soon.

(*) Immunogenic microparticles, apoptotic corpuscles or exosomes are the smallest components of cells that have recently been discovered and whose significance is a new focus of research. Several university research groups are conducting research in this field.

REFERENCES 2022

Conferences

Poster presentation
3RD GLIOBLASTOMA DRUG DEVELOPMENT, 01/2022, BOSTON.
Synergy between TMZ and individualized multimodal immuno-therapy to improve Overall Survival of IDH1 wild-type MGMT promoter-unmethylated GBM patients
Stefaan Van Gool, Jennifer Makalowski, Michael Bitar, Peter Van de Vliet, Volker Schirrmacher, Wilfried Stuecker

Oral presentation
16 ROSTOCK SYMPOSIUM FOR TUMOR IMMUNOLOGY AND BRAIN TUMOR RESEARCH in paediatrics Synergy between TMZ and individualized multimodal immunotherapy to im- prove Overall Survival of IDH1 wild-type MGMT promoter- unmethylated GBM patients
Stefaan Van Gool, Jennifer Makalowski, Michael Bitar, Peter Van de Vliet, Volker Schirrmacher, Wilfried Stuecker

ORAL PRESENTATION
SIOPE HGG WORKING GROUP MEETING, 04/2022, MILAN
Individualized multimodal immunotherapy for glioblastoma multi-forme
Stefaan Van Gool

Poster presentation
CIMT (CANCER IMMUNOTHERAPY), 05/2022, MAINZ
Integration of individualized multimodal immunotherapy for adults with IDH1 wild-type GBM
Stefaan Van Gool, Jennifer Makalowski, Michael Bitar, Peter Van de Vliet, Volker Schirrmacher, Wilfried Stuecker

Poster- and oral presentation
ISPNO (INTERNATIONAL SOCIETY FOR PEDIATRIC NEURO-ONCOLOGY); 06/2022, HAMBURG
Synergy between TMZ and individualized multimodal immuno-therapy to improve Overall Survival of IDH1 wild-type MGMT promoter-unmethylated GBM patients
Stefaan Van Gool, Jennifer Makalowski, Michael Bitar, Peter Van de Vliet, Volker Schirrmacher, Wilfried Stuecker

Oral presentation
34TH ANNUAL MEETING EUROPEAN SOCIETY FOR HYPER-THERMIC ONCOLOGY, 09/2022, GÖTEBORG
Contralateral transient contrast enhancement in a patient with IDH1wt MGMT promoter-methylated GBM responding to TMZ and individualized multimodal immunotherapy
Andrii Matiashchuk, Jennifer Makalowski, Michael Bitar, Peter Van de Vliet, Wilfried Stücker, Stefaan Van Gool

Oral presentation
DEUTSCHER FUNDRAISING KONGRESS, 09/2022, BERLIN
Transnational giving Europe – Praxisbeispiel
Stefaan Van Gool

Oral presentation
HYPERTHERMIE-KONGRESS, 10/2022, BERLIN
Loko-regionale Hyperthermie zur Induktion des immunogenen Zelltods als adjuvante Therapie zur Chemotherapie
Wilfried Stücker

Oral presentation
BRNO ONCOLOGY DAYS, 10/2022, BRNO
Anticancer vaccines in pediatric oncology
Stefaan Van Gool

Oral presentation
MEDIZINISCHE WOCHE 2022, 10/2022, BADEN BADEN
In vitro CMV-expanded T cells as adoptive T cell therapy
Golnaz Rajabpour, Stefaan Van Gool, Jennifer Makalowski, Peter Van de Vliet, Wilfried Stuecker, Michael Bitar

Publications

SCHIRRMACHER V.
Molecular mechanisms of anti-neoplastic and immune stimulatory properties of oncolytic Newcastle Disease Virus. Biomedicines 2022;10:562

VAN GOOL SW, MAKALOWSKI J, BITAR M, VAN DE VLIET P, SCHIRRMACHER V, STUECKER W.
Synergy between TMZ and individualized multimodal immuno-therapy to improve overall survival of IDH1 wild-type MGMT promoter-unmethylated GBM patients. Genes & Immunity 2022; https://doi.org/10.1038/s41435-022-00162-y

WOLFF JE, VAN GOOL SW, KUTLUK T, DIEZ B, KEBUDI R, TIMMERMANN B, GARAMI M, STERB J, FULLER GN, BISON B, KORDES UR.
Final results of the choroid plexus tumor study CPT-SIOP-2000. J Neuro-oncol 2022;156:599-613

SCHIRRMACHER V, VAN GOOL SW, STUECKER W.
Counteracting immunosuppression in the tumor microenvironment by oncolytic Newcastle Disease Virus and cellular immunotherapy. Int J Mol Sci 2022;23:13050

Immun-Onkologische Forschung

IOZK Stiftung

www.iozk-stiftung.org

Publisher:
Stiftung für immunologisch-onkologische Forschung
IOZK gemeinnützige GmbH

Hohenstaufenring 30–32
50674 Köln

Donation account:
IOZK Stiftung gGmbH
Volksbank Köln Bonn
IBAN: DE29 3806 0186 8304 2140 16
BIC: GENODED1BRS

Paypal:
donation@iozk-stiftung.org

Cologne, june 2023