MATURE-NK

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Issue 1

MATURE-NK introduces itself

A EUROPEAN CONSORTIUM FOCUSED ON THE MANUFACTURING OF TUMOUR REACTIVE NK CELLS (MATURE-NK)

Since 2018, 13 European academic institutions and companies have been taking part in MATURE-NK, a European consortium. The consortium is receiving funding in the amount of a 3.51 million Euro contribution from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No. 765104.

The consortium led by Prof Ulrike Köhl from Hannover Medical School and Fraunhofer-IZI will run until 30 November 2022. The project's objective is to work on developing novel methods to manufacture tumour reactive NK cells. The consortium consists of nine academic centers covering basic and translational research, as well as three leading biotech companies (Innate Pharma, Miltenyi and Glycostem) and Fraunhofer IZI as a world leading applied research institute. The objective is to educate selected top level selected PhD candidates not only in science, but also with a strong focus on business and management activities as well as on basic and advanced knowledge in strategies around intellectual property.

Prof. Ulrike Köhl, PhD, MD, at University Clinical Center Leipzig and Hannover Medical School as well as director of Fraunhofer IZI in Leipzig, states: "I am very excited, that we have the chance to continue educating highly talented PhD candidates in the field of NK cell immunotherapy. I am proud to have the top academic NK cell researchers and most important NK cell related biotech companies of Europe in one consortium, which generates a great momentum to develop new NK cell products for the coming years, to help cancer patients."

Written with the contribution of Glycostem

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FOUNDATION OF THE CONSORTIUM

The MATURE-NK consortium was created in 2017 as a follow-up to the NATURIMMUN consortium that had been ongoing from 2012 to 2016.

The partners had wished to pursue their efforts in immunotherapies of cancer with a focus on NK cell therapies and to educate a new group of young researchers, who would continue work on novel cellular and molecular therapies during their future careers.

The consortium partners are among the best known NK cell researchers and include several leading institutions from Europe.

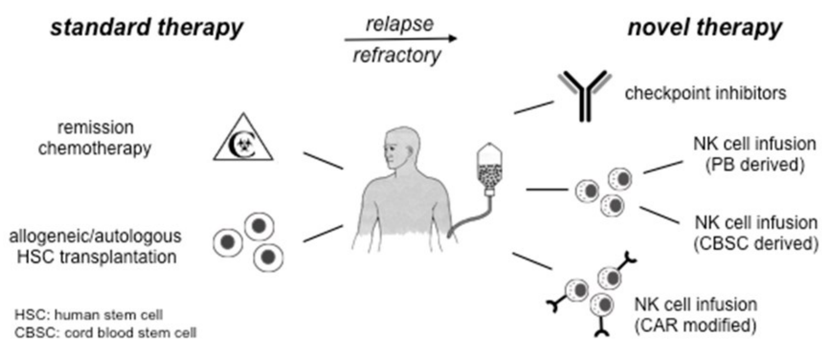
- Coordinator:
  Hannover Medical School
- Oslo University Hospital
- University Hospital Basel
- University Hospital Genoa
- Institut Pasteur, Paris
- Ruprecht-Karl University Heidelberg
- University Pompeu Fabra, Barcelona
- The Hebrew University of Jerusalem
- Medical University Vienna
- Innate Pharma
- Miltenyi Biotec B.V. & Co KG
- Glycostem Therapeutics B.V.
- Fraunhofer-Institute for Cell Therapy and Immunology IZI

AN UNMET NEED

Despite substantial progress in the last decades, mortality in most malignant diseases remains high representing a major threat to the European population and health care system. Many efforts are undertaken to develop innovative therapies especially in the field of immunotherapy.1 * Approaches based on boosting CAR T lymphocytes have recently yielded promising clinical results.

However, supplementary therapeutic strategies are urgently needed since tumors often escape from T cell-based therapies. Moreover, T cell therapies frequently have been associated with off-target toxicities and severe side effects including graft-versus-host-disease and autologous CAR T cells are partly limited in viability.

Thus, there are now great hopes on the application of donor NK cells, because of their efficient direct cytotoxic anti-tumour activity and their potential to bridge the innate to the adaptive immune response. According to our experience, NK cell-based therapy is generally well tolerated at high doses and no severe adverse effects have been observed to



A NOVEL THERAPY

The rapidly developing knowledge on molecular regulation of the innate immune system and its complex interplay with adaptive immunity has spurred interest in exploring its potential in cancer therapy. NK cells have been first described 40 years ago as a separate, heterogeneous group of innate lymphocytes capable to kill transformed and infected cells without prior sensitization.

Small-scale clinical trials using polyclonal allogeneic or autologous NK cells for infusion have demonstrated promising results in leukaemia, significantly increasing 5-year survival rates of Acute Myeloid Leukaemia (AML) patients.9-11 However, only a fraction of AML patients responded and moderate response rates were observed with other malignancies. Thus, the anti-tumor efficacy of NK cells needs to be enhanced.

Furthermore, the cost-and labour-intensive semi-automated Good Manufacturing Practice (GMP)- compatible manufacturing process limits the number of patients that can benefit from NK cell therapies. There is an urgent need to develop GMP-compliant expansion strategies for optimized NK cells and an automated pipeline for advanced cell manipulation. This is essential to improve treatment success and decrease production costs to make therapies available to higher numbers of patients, thereby overcoming a key bottleneck in clinical NK cell therapy.

Recently, major advances have been made in elucidating the fine-tuned interplay between activating/inhibiting NK cell receptors that regulate anti-tumour cytotoxic activity, immune modulation and crosstalk with the adaptive immune system. NK cell subsets have been identified which mediate the clinically relevant killing of transformed cells, whereas other subsets exert immune regulatory functions. In addition, NK cell cytotoxicity can be enhanced by bi-/trivalent reagents or by genetic modification of NK cells with CARs directing NK cells to cancer cells.

The aim of our consortium, consisting of basic and clinical NK cell experts, Europe-based industry and SMEs, is to integrate the recent discoveries in NK cell biology into novel concepts and harmonized protocols for immunotherapy of cancer within an extensive training program. The link between clinical, company and research partners will guarantee the translation to clinical work. This will address the future needs and technology transfers critical to the innovative development of "next generation NK cell ATMPs".

THE OBJECTIVES

Our consortium aims to improve NK cell-based ATMPs for the treatment of cancer. The tools and technologies to be refined stepwise in the work program will be instrumental for the development of next generation NK cell-based therapy. This will lead to the fully automated manufacturing of functionally improved NK cell products ready for use in European and international clinics.

The manufactured NK cell products will be preclinically characterized according regulatory requirements. So far, NK cell manufacturing was low-throughput and involved safety challenges. Our proposed fully automated process aims to be more effective, faster and safer, thereby enabling treatment of larger numbers of patients and application of higher numbers of NK cells. In addition, highly specific and genetically manipulated NK cells will be included. The program will foster interaction of basic research with clinical translation and product development in European industry/ SMEs. As such it is interdisciplinary and intersectorial.

The overall objective of this project is to form a research training network of 13 fellows to i) improve NK cell anti-tumor cytotoxicity, ii) develop NK-enhancing technology and a manufacturing process for NK cell products and iii) prepare for follow-up clinical trials. This should be done in a training network exemplary for the training of experts for bench to bedside translation of upcoming cellular therapies.

Prof. Dr. Dr. Ulrike Koehl, Coordinator

"I am very excited, that we have the chance to continue educating highly talented PhD candidates in the field of NK cell immunotherapy. I am proud to have the top academic NK cell researchers and most important NK cell related biotech companies of Europe in one consortium, which generates a great momentum to develop new NK cell products for the coming years, to help cancer patients."
Prof. Dr. Dr. Ulrike Koehl

THE CONSORTIUM

The MATURE-NK Consortium is led by Prof. Dr. Dr. Ulrike Koehl, Director of the Institute for Cellular Therapeutics at the Hannover Medical School. Prof. Ulrike Koeh is also Director of the Fraunhofer-Institute for Cell Therapy and Immunology IZI in Leipzig, Director of the Institute for Clinical Immunology at the University Leipzig and of the University Hospital Leipzig .

The current consortium consists of four groups which are extensively involved in clinical therapies of leukemia, four basic molecular immunotechnology laboratories, one bioinformatics unit and four companies. As such the consortium is interdisciplinary and intersectorial. Within each group, the partners bring in complementary expertise and tools that lead to significant synergistic effects.

Thus, each partner has a unique role in research and training and the network as a whole gains its strengths through the combination of the complementary expertise of all partners. As this is a training network, we have incorporated a business school and a patent consultant/training company to deliver specific training courses in business development and patent rights to our Early Stage Researchers.

Not only does this configuration benefit our PhD students but also the consortium partners expect to create knowledge and foresee a future collaboration between the companies and the clinical partners in the exploitation and commercialization of their products.

LET'S MEET SOME OF OUR EARLY STAGE RESEARCHERS

The MATURE-NK consortium is excited to have a very talented pool of young researchers. Today, we have the pleasure to get to know some of them.

ANNA THALLER, INSTITUT PASTEUR, PARIS

Hello,

My name is Anna Thaller and I am from Germany. I studied biology and did both, my Bachelor and Master degree at the Ludwig Maximilian University (LMU) in Munich. During my master I started to get into the field of immunology through my internship at Roche Diagnostics GmbH in Penzberg and my master thesis in the group of Edgar Meinl at the Biomedical Center (BMC) in Munich.

After my studies I wanted to do an internship abroad and I was able to do a project on stem cells in the group of Thomas Graf at the Center for Genomic Regulation (CRG) in Barcelona with the ERASMUS+ program.

Following this experience, I decided to apply mainly for international PhD programs in the field of Immunology and joined the MATURE-NK international training network in January 2019 to do my PhD at the Institut Pasteur in Paris. Here, I am currently developing a pre-clinical model to study the interaction of human Natural Killer (NK) cells and Innate Lymphoid Cells (ILCs) with cancer cells in vivo.

Outside of the lab I like to do crafts, like for example pottery and wood working. Further, I enjoy sharing time with friends and doing outdoor activities, like cycling, snorkeling, hiking and skiing.

MARTIN FAHRENBERGER, MEDICAL UNIVERSITY OF VIENNA

Hi, I'm Martin a PhD student in the von Haeseler lab in Vienna.

During my PhD I'm working on bioinformatics method development with application in single cell RNA-seq.

However, my path here was not always clear. When I was 16, I finished school and went on to do an apprenticeship as a Mechatronics Engineer. I had a great time during my apprenticeship, but also realised that I wanted to continue learning and studying. I went on to get my "Abitur", with the plan of studying Mechatronics Engineering which then changed to studying Physics and then again to Computational Science, the subject I finally studied at the University of Regensburg for my bachelor's and master's.

I enjoyed my time at university and was lucky enough to gain a full scholarship from the "German Academic Scholarship Foundation". This reassured me in my path and gave me the opportunity to spend a year abroad at the University of Nottingham.

Throughout my studies I worked on multiple bioinformatics projects and became very interested in the subject. So, when my master's came to an end I decided to apply as a PhD-student in the field.

SONYA CIULEAN, FRAUNHOFER—IZI, LEIPZIG

My name is Sonya Ciulean and I joined the Fraunhofer IZI in Leipzig as a Marie Curie Fellow on the MATURE NK consortium in February 2019. I

am originally from Romania and did my studies in Bucharest where I majored in Veterinary Medicine. I began transitioning from the clinics to the lab during my studies by doing volunteer work in a research institution. In research, I found different ways to apply my medical knowledge and skills and to build upon the excitement of learning how things work. This was driven by the thought that the research being done is leading to the development of treatments meant to aid certain afflictions. Today, I work with the same enthusiasm on developing CAR-NK cell therapies for solid tumors like head and neck cancer.

When I am not busy in the lab, I like to spend my time outdoors biking and hiking. Taking care of my plants and drawing is where I find my peace, going to concerts and art exhibitions is where I get my fuel

RONJA WIEBOLDT, UNIVERSITY OF BASEL

Hi,

I am Ronja and I currently work as a PhD candidate at the University of Basel, Switzerland. I am originally from Germany and received my Master's from the University of Marburg with a major in cancer biology. My bachelor thesis got me hooked on translational research and I enjoy working close to the clinic and patients ever since.

My PhD project aims to further investigate the potential of NK cell adoptive immunotherapy in the setting of hematopoietic cancer in an ongoing clinical trial. Thus, I already learned a lot about clinical trial conduct, GMP production and how to coordinate work efficiently. I hope that my work can help to improve our current NK production protocol so that more patients can benefit from NK cell therapies.

I like Basel a lot. It is a lively town with lots of restaurants, theatres and museums. I enjoy hiking, dancing and cooking and I am looking forward to travel again.

NATALIA COLOMAR, UNIVERSITY HOSPITAL GENOA

Hi, I am Natalia!

I was born in Barcelona, Spain, where I obtained my bachelor's degree in Biotechnology and then my MSc in Biomedical Research at Pompeu Fabra University in Barcelona. During my master's thesis, I got the opportunity to attend national and international conferences, in which I got the chance to share and talk about my research. At that moment, I discovered my passion for biomedicine, which is why I applied for this position.

I am now pursuing my PhD in Genoa, Italy, where I have been focused on providing deeper insights on receptor/ligand interactions that occur between NK and leukemia cells, and possible strategies to enhance the NK cell-mediated anti-leukemia activity.

Besides science, I love being outdoors in nature, discovering new places and being around friends. During my stay in Italy, I visited beautiful cities and magical places all around the country, learned a new language, met a lot of people, and of course, I enjoyed the food.

PAST EVENTS

- Kick-Off Meeting & Winter School 1.
  Bergisch-Gladbach, 2-5 April 2019
- Summer School 1.
  Barcelona, 16-20 September 2019
- Summer School 2.
  Online, 8-10 September 2020
- Consortium Meeting.
  Online, 15-16 September 2020
- Winter School 2 & Consortium Meeting.
  Online, 19-23 April 2021
- Summer School 3.
  Online, 14-15, 19 October & 26-29 October 2021
- Consortium Meeting.
  Online, 25 October 2021

NEWS

PUBLICATIONS

Meazza, Raffaella et al. "Phenotypic and Functional Characterization of NK Cells in αβT-Cell and B-Cell Depleted Haplo-HSCT to Cure Pediatric Patients with Acute Leukemia." *Cancers* vol. 12,8 2187. 5 Aug. 2020, doi:10.3390/cancers12082187

REVIEWS

Chauhan, Sachin Kumar Singh et al. "Harnessing NK Cell Checkpoint-Modulating Immunotherapies." Cancers vol. 12,7 1807. 6 Jul. 2020, doi:10.3390/cancers12071807

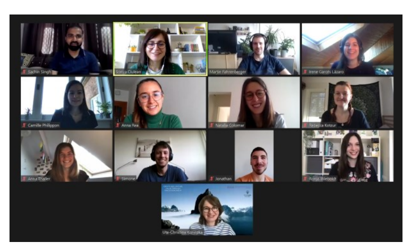
PAST WORKSHOPS

The MATURE-NK consortium organized a recruiting event in Leipzig at the Fraunhofer-Istitute for Cell Therapy and Immunology IZI in September 2018. 32 highly talented candidates were selected and invited to a marathon recruitment day. Some of the candidates from Asia and Sout America were able to introduce themselves and participate in interviews with our partners online.

The kick-off meeting and the first winter school took place at Miltenyi Biotec in Bergisch-Gladbach and brought together the newly recruited 13 Early Stage Researchers and our consortium partners.

In summer 2019, a summer school and consortium meeting. Were organized by our partner, University Pompeu Fabra, in Barcelona. After long days presenting their research projects and attending workshops, lectures and course modules, the participants were able to enjoy the late summer in the beautiful city of Barcelona.

Unfortunately, the winter school 2, which was planned to take place in Marseille, had to be cancelled when countries closed their borders in an effort to limit the propagation of the COVID-19 pandemics. All other consortium meetings have been held since then online.



UPCOMING EVENTS

Nevertheless, we stay optimistic and hope that we will be able to meet in person at our next two meetings in 2022. We are currently planning to hold our last consortium meeting and winter school at the beautiful Kleivstua resort in Norway on 14-16 March 2022. A Satellite Symposium will be organized by our Early Stage Researchers, who will present our consortium as well as some of their research project's results at the NK2022 Meeting in Florida on May 14.

We look eagerly forward to meeting again at those events and hope that the Omikron variant will not come in our way.

Hannover Medical School

UPCOMING EVENTS

- Winter School & Consortium Meeting.
  Kleivstua, Norway 14-16 March 2022
- Satellite Symposium at the NK2022, The 19th Meeting of the Society for Natural Immunity.
  Bonita Springs, FL 14-17 May 2022

Consortium MATURE_NK
Hannover Medical School
Institute of Cellular Therapeutics
Feodor-Lynen-Str. 21
D-30625 Hannover
Telefon: +49 511 532 8253
Fax: +49 511 532 7961
E-mail: MatureNK@mh-hannover.de