MESI-STRAT

Systems Medicine of Metabolic-Signaling networks -
A New Concept for Breast Cancer Patient Stratification

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We are very pleased to announce that the University Hospital Innsbruck has joined the MESI-STRAT consortium. The team of Christian Marth and Daniel Egle is conducting the WOO2 study, from which we expect important findings which will help us in our search for metabolic markers. You can read about the details in the text below.

We are also happy, that another MESI-STRAT article was published in the scientific journal Cell. We summarise the most important results here. In addition, Mirja Tamara Prentzell, one of the first authors of the publication, introduces herself.

New MESI-STRAT Partner – WOO2 Study

The Innsbruck University Hospital for Gynecology and Obstetrics (Director Christian Marth) has joined MESI-STRAT in July 2020 and is mainly responsible for conducting the WOO2 study. The study is executed in close cooperation with the clinical coordinator of the MESI-STRAT consortium, Christiane Opitz from the German Cancer Research Centre (DKFZ) and the Coordination Centre for Clinical Studies at Heidelberg University Hospital (Director Steffen P. Luntz). Participating patients receive treatment with Anastrozole, a so-called aromatase inhibitor, three weeks before the planned breast surgery. In routine treatment, patients receive this form of endocrine therapy only after the removal of the tumour.

The MESI-STRAT Team at the Univ. Hospital for Gynecology and Obstetrics, from left: Christian Marth, Carmen Albertini, Regina Berger, Daniel Egle; Photo: MUI/Bullock)

The aim of the study is to analyse the effects of Anastrozole in serum (blood), urine, and tumour tissue of patients with hormone receptor-positive breast cancer. In particular the genetic information of the tumour cells (DNA and RNA), the proteins and metabolic products of the tumour, and a cell division marker as well as the changes caused by treatment will be investigated. The study will show if pre-surgical (neo-adjuvant) Anastrozole treatment improves therapy effects and whether markers in the blood can predict the response to a drug. In the long term, we want to find markers that guide therapy decision and help prevent unnecessary therapy.

The study was started in March 2021 and 50 patients will be recruited until April 2022.

New mechanism protects against cancer cell migration

The protein MTOR (Mechanistic Target of Rapamycin) is a sensor for nutrients such as amino acids and sugars. When sufficient nutrients are available, MTOR boosts metabolism and ensures that sufficient energy and building blocks are available for the growth and function of all cells in the body. Because MTOR is such a central switch for metabolism, errors in its activation lead to serious diseases associated with excessive metabolic activity, cell growth and proliferation, such as cancer.

To prevent errors in the MTOR-based signal processing, the cells tightly control its activity, for example by means of the TSC complex. This complex (named after the disease caused by its absence, Tuberous SClerosis) is, together with MTOR, localized at the lysosomes, small cellular structures, where it keeps MTOR in check. Alterations (mutations) changing the TSC complex so that it does no longer remain on the lysosomes, can lead to excessive MTOR activity with severe health consequences.

The teams led by Kathrin Thedieck at the University of Innsbruck and Christiane Opitz at the DKFZ discovered that the G3BP proteins (Ras GTPase-activating protein-binding proteins) form an anchor that binds the TSC complex to the lysosomes. This anchor plays a crucial role in breast cancer. If the amount of G3BP decreases, not only MTOR activity but also cell motility is increased. In breast cancer patients, low G3BP correlates with a worse prognosis. G3BP proteins could therefore be valuable markers

The MESI-STRAT project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 754688.

for personalized therapies and could help to improve the efficacy of drugs that inhibit MTOR.

The study was published in the journal *Cell* and is available open access:https://doi.org/10.1016/j.cell.2020.12.024

Dr. Mirja Tamara Prentzell, PhD

Postdoctoral Researcher
German Cancer Research Center (DKFZ), Heidelberg

Cancer is the second most common cause of death after cardiovascular disease. Despite constantly improving therapies, cancer turns patients' lives upside down and the diagnosis comes with many fears and uncertainties. Breast cancer is the most common cancer in women and although endocrine therapies are an effective treatment, a significant proportion of patients relapse with unclear outcomes. MESI-STRAT questions the Who? Why? and When? of these resistance mechanisms and tries to identify patterns for targeted treatment. I am proud to be involved in MESI-STRAT because I want to give hope and personalised treatment options to the many breast cancer patients with relapse.

I studied biology in Freiburg, Germany and although I had initially chosen a completely different focus in the field of evolutionary biology, ecology and anthropology, I came to protein biochemistry and molecular biology in 2010, and have remained true to it to this day. In 2011, I finished my studies in the group of Kathrin Thedieck with a thesis on the central metabolic regulator MTOR and a new protein, G3BP1, which until then was only known to play a role under cellular stress conditions. In 2012, I received a PhD scholarship from the Spemann Graduate School of Biology and Medicine and in 2014 moved with Kathrin Thedieck's research group to the University Medical Center Groningen (UMCG), The Netherlands. In 2016, I joined the group of Christiane Opitz at the DKFZ in Heidelberg, where I have been a postdoctoral researcher since 2018.

After more than 10 years, I am still fascinated by the complex signalling networks and metabolic pathways in our body. It excites me that we keep unveiling new, surprising connections and diverse interdependencies. I am very pleased that after all those years we identified G3BP1, the protein I started to investigate at the beginning of my career, as the anchor molecule of the TSC complex and successfully published our findings. Also in MESI-STRAT, I decipher the networks that contribute to breast cancer development and resistance to endocrine therapies. In addition to the TSC-MTOR signalling pathway, my work focuses on other key pathways and molecules, such as tryptophan and NAD metabolism, and the role of IL4I1 and AHR.

A major focus of MESI-STRAT are clinical studies to investigate metabolic pathways directly in patient samples and to draw conclusions about the effects of endocrine therapies on the tumour and on the metabolism of the patients. Besides my experimental work, I work at the interface between the clinics and the laboratory. It is my task to implement our clinical studies with the participating clinics, the clinical coordination office, and the PATH Biobank. I find it immensely motivating to directly examine the applicability of our basic research in clinical studies.

Dr. Mirja Tamara Prentzell, PhD
German Cancer Research Center (DKFZ), Heidelberg

I would like to thank all the patients who support MESI-STRAT, but of course also the entire interdisciplinary team behind MESI-STRAT. Without the expertise of each and every one of them, MESI-STRAT could not be successful and I look forward to our continued cooperation.

MESI-STRAT Survey

We have already analysed the first results of our new questionnaire and found interesting differences between cancer patients and the general population. However, we still need more responses to further deepen these findings and to use them to tailor our communication to the needs of patients. If you have not taken part yet, we look forward to your participation and would be grateful if you would share the link with your friends.

Link: Survey in English

Visit www.mesi-strat.eu to learn more about our consortium and follow us on twitter @MesiStrat for the latest news of our project!

If you have not done so yet, please subscribe to receive our newsletter twice a year.

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