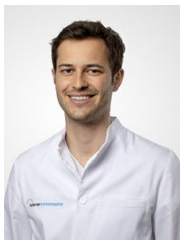


Communication SAKK Network Trial Award

SAKK Network Trial Award for combination therapy in prostate cancer

On 26 June, the Swiss Group for Clinical Cancer Research (SAKK) presented the SAKK Network Trial Award to the specialist Prof. Dr Christian Fankhauser. This highly endowed prize is being awarded for the second time. The prize money of CHF 1 million is of central importance for clinical oncological research in Switzerland. This year's award goes to the young doctor from Central Switzerland, who won the competition with his extraordinary commitment to oncological research and a project on testosterone and PARP1 inhibitor combination therapy for prostate cancer.



Interview with Prof. Dr Christian Fankhauser, MD, MPH, FMH Urology, specializing in surgical urology, Lucerne Cantonal Hospital, Urology

Congratulations on this extraordinary award!

SAKK is an important hub between science and research, patients and industry. We are committed to patient-centered clinical cancer research. What is extraordinary about your project, what scientific question have you answered? What can patients hope for?

Prostate cancer is the most prevalent malignancy in men, with approximately 1.4 million new cases and 375 000 fatalities annually. This imposes significant strains on healthcare resources, with projected cases expected to double by 2040. In 1941, Huggins and Hodges realized that prostate cancer is responsive to androgen manipulation, a breakthrough in prostate cancer treatment honored with the Nobel Prize in 1966. Since then, Androgen Deprivation Therapy (ADT), via surgical castration or luteinizing hormone-releasing hormone (LHRH) agonists or antagonists, was the standard of care, offering a median survival of <4 years. Newer drugs, more potent ADT, chemotherapy, Lu-PSMA, or PARP inhibitors improved survival but still cannot cure the disease and have severe side effects at high financial costs.

What has been ignored since 1941 by most research is that not only castration, but also high-dose testosterone can be used to treat prostate cancer. Researchers from Johns Hopkins showed in several trials that the concept of giving high doses of testosterone does work and improves the quality of life with the main side effect being polycythemia. This is a condition where the body makes too many red blood cells, similar to athletes who use illegal doping to enhance their performance, as the extra red blood cells can improve stamina and strength. Previous studies suggested that testosterone triggers the generation of



double-strand DNA breaks and leads to death of prostate cancer cells. Additionally, testosterone has been demonstrated to modify genes associated with DNA repair. In discussions with Prof. Theurillat (Institute of Oncology Research at the Università della Svizzera italiana), we realized that higher doses of testosterone might be more efficient, and we queried the literature for safe dosages. With this idea, I started 7 years ago but couldn't receive any funding as no pharmaceutical company was interested even after numerous study protocol modifications.

My most recent idea was simultaneous administration of testosterone with a selective PARP1 inhibitor, which is the newest class of PARP inhibitors with fewer side effects. Still, this novel class often leads to anemia, but remember, testosterone leads to the opposite of anemia, polycythemia. Thus, at least the most common side effects of testosterone and PARP inhibitors would level each other off. Interestingly, the combination of PARP inhibitors and testosterone may not only soften side effects but also has a synergistic effect as both drugs target the DNA repair mechanism, and we could hope for better and longer treatment responses. Finally, higher testosterone may improve mood, enable sexual function, improve body image, muscle mass, decrease fat mass, and mitigate many more side effects of castration. Men are likely to improve with only very limited side effects so that patients can live their lives as they prefer, attend birthday parties, weddings, go on holidays, or enjoy other joys in life.

Can you give a rough overview of your study?

We invite 53 men to be treated with testosterone every 2 weeks intramuscularly and a PARP1 inhibitor daily for 12 weeks. Laboratory and clinical visits are planned every 2 weeks. At 12 weeks, we measure prostate specific antigen (PSA), perform imaging. If patients show no adverse events and no clinical progression, this cycle can be repeated.

What do you hope to gain from it for cancer research?

The combination of higher doses of testosterone and PARP1 inhibition is novel, and the efficacy as well as response to subsequent lines of therapy, quality of life, and novel biomarkers remain to be studied.

Please tell us briefly about yourself, what you did before you won the SAKK Network Trial Award, and a little bit about your career.

I studied medicine in Zurich with the initial goal of becoming a general practitioner. I chose to do a thesis in urology to learn how to manage urinary issues early on, as they are common in the aging population. Working with Prof. Tullio Sulser, PD Dr. Thomas Hermanns, Prof. Johann Steurer, and Prof. Jörg Beyer sparked my passion for clinical research. To further improve my research skills alongside my residency, I pursued a Master of Public Health at the Harvard School of Public Health. Following that, I completed a surgical fellowship in Manchester, UK. Here, I am grateful to Prof. Silke Gillissen for connecting me with Prof. Noel Clarke, who I consider one of the most talented open surgeons and academics in urology to date.



In 2021, I was fortunate to secure a position in the department of Prof. Agostino Mattei in Lucerne. Prof. Mattei is, in my opinion, one of the most talented robotic surgeons, and he provided me with two additional intense years of training. The urology team in Lucerne has been incredibly supportive of my research projects, always taking care of patients when I attended conferences to exchange new ideas.

What was the intention for you to participate in the SAKK Network Trial Award? The whole project is usually not individual work, but teamwork. What can you tell us about this?

I started working on this proposal seven years ago and had discussions about drugs and study design with dozens of people in numerous places, facing a lot of pushbacks. A memorable moment was at the European Organization for Research and Treatment of Cancer (EORTC) Course "Methods in Clinical Cancer Research," where Prof. Johann de Bono, one of the brightest translational prostate cancer researchers, called me a "crazy urologist" because of my idea of giving testosterone instead of further castration. Despite this, he strongly supported the concept.

I am especially grateful to Prof. Richard Cathomas and PD Dr. Aurelius Omlin, who were the presidents of the genitourinary group, for allowing me to present my research idea repeatedly at the SAKK group meetings and helping me modify the proposal multiple times. My gratitude also goes to the current president, PD Dr. Ursula Vogl, and vice-president, PD Dr. Alexandros Papachristofilou, who supported my application for the award and will help get this project started.

At our institution, Lucerne Cantonal Hospital, interdisciplinary collaboration is very fruitful not only because of the medical expertise but also due to the friendship as well as the fun we have working together and challenging each other on new potential treatment options for patients. I would like to thank Dr. Philipp Niederberger, Dr. Winfried Arnold, Dr. med. Frederieke Elsinger, and Dr. Wilhelm Nimphius, who, among many others, form an amazing genitourinary specialist team.

What does the prize enable you to do?

Our project is currently not yet fully funded, so I hope that a philanthropist or other funding body will now be more interested in supporting our non-mainstream approach. For me personally, it strengthens my position as a clinician and researcher in the community. I hope this story motivates and illustrates to medical students, residents, and junior faculty that some ideas indeed need more than seven years to develop. One must find the right moment to reapply, but the effort pays off in the end.

Every question answered in science leads to several other questions. Which question will you tackle next and where will it lead to? Do you already have an idea?

As with most cancer drugs, only a subset of patients will respond. Our aim is to study whether we could find any predictive variables so that in the future, we only give the combination of testosterone and PARP inhibitors to men who are very likely to show a response. In addition, sequencing between testosterone and castration could further delay cancer progression.



Thank you very much for your time and your insightful answers.

The winning team

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Specialist in urology, specializing in surgical urology FMH
Clinic for Urology, Lucerne Cantonal Hospital

The team was supported by the SAKK Project Group Urogenital

Project title: A phase II trial of High-dose Androgen Therapy (HAT) and PARP-inhibition in castration resistant prostate cancer patients progressing after novel androgen therapy (ISOTONIC)