HUMAN & BIOTECHNOLOGY

Fields of Expertise TU Graz

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Gabriele Berg and Christian Baumgartner
Human & Biotechnology
Source: Lunghammer – TU Graz

Since our last issue, there have been some new and interesting things to report from our FoE. Robert Kourist and team celebrated the success of a new lead project at TU Graz entitled Learn & Predict: Digitalization of Biotechnology (DigiBioTech), which was selected from five shortlisted projects.

CBMed GmbH, a center for biomarker research in medicine of which TU Graz is a shareholder, recently became the first Comet center to enter into a strategic collaboration with Boehringer-Ingelheim without the need for further K1 funding. As part of this collaboration, both partners want to jointly accelerate the translation of cancer treatment approaches into new therapies. TU Graz researchers are also invited to get involved in CBMed's joint projects.

In the fall, two scientific conferences in the field of biomedical engineering will again be held at TU Graz. One is the 9th Graz Brain-Computer Interface Conference 2024 from 9-12 September, organized by Gernot Müller-Putz, and the annual conference of the Austrian Society for Biomedical Engineering (ÖGBMT) from 24-25 October, organized by Kerstin Lenk and Theresa Rienmüller. We congratulate Manuel Kainz of the Institute of Biomechanics and Catarina Lopes Dias, formerly of the Institute of Neural Engineering, for the best paper and PhD thesis prizes, respectively, from the Styrian Brain Research Initiative (Initiative Gehirnforschung Steiermark). In addition, the FoE is also planning to award science prizes for the best publications of our young researchers in order to give the high level of scientific publications more visibility to partners of TU Graz.

Last but not least, a new FoE team, Gabriele Berg and Christian Baumgartner, has been in place since January and is looking forward to a lively exchange within the FoE and asks all colleagues to register with the FoE if they are interested. This will provide access to all important information within the FoE. We would also be delighted to receive new input from you and are open to any new ideas.

Sonja Langthaler

Illuminating the Electrical Signature of Cancer

Cancer, a multifaceted disease characterized by uncontrolled cell growth, remains one of the greatest health challenges of our time. While extensive research has focused on genetic mutations and biochemical pathways that drive cancer progression, emerging evidence suggests that the bioelectrical properties of cancer cells play pivotal roles in tumorigenesis.

THE ACTION BEYOND THE ACTION POTENTIAL

Cells are characterized by a unique composition of ion channels responsible for their bioelectric properties. In addition to action potential generation in excitable cells, ion channels play essential functional roles in almost all basic cellular processes of non-excitable cells such as proliferation, apoptosis, motility or differentiation. Unlike healthy cells, which maintain a stable electrical environment, cancer cells exhibit aberrant electrical activity, characterized by dysregulated ion channel expression and disrupted membrane potentials. These alterations in electrophysiological properties contribute to the hallmark features of cancer, including uncontrolled proliferation, evasion of apoptosis, and metastatic dissemination.

THE BIOELECTRIC SIDE OF PROLIFERATION

Our research focuses on the question of how alterations in electrophysiological properties influence the proliferation of cancer, in particular A549 cells, an adenocarcinoma cell line of the lung. During the cell cycle, in general, the membrane potential undergoes rhythmic oscillations from hyperpolarized (more negative) to depolarized (less negative) states caused by ion channel activation and deactivation. These characteristic changes are able to trigger the transition and drive the cells through the distinct phases, thus serving as a key bioelectric signal for cell proliferation. Using patch-clamp experiments and novel voltage indicators (Figure 1), we are able to measure the ion channel activity and membrane potential dynamics in distinct phases of the cell cycle to understand their role in cell behavior and fundamental mechanisms underlying cancer growth.

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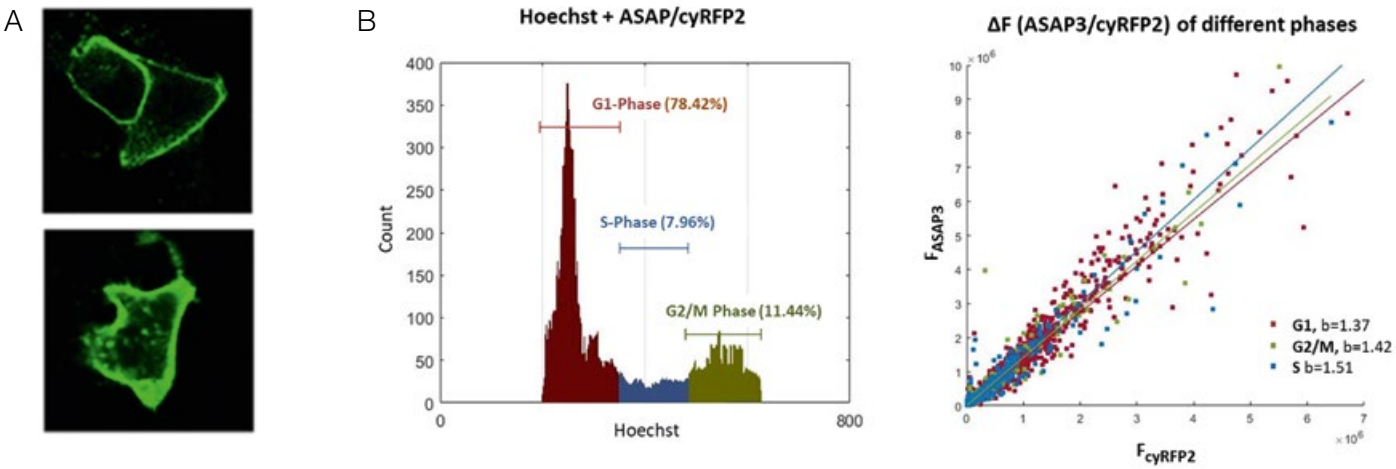

Figure 1: Optical measurement of the membrane potential during distinct phases of the cell cycle using voltage sensitive dyes and cell cycle indicators. (A) Laser scanning microscope image of cells using ASAP (voltage-indicator), (B) flow cytometry experiments combining ASAP and Hoechst for simultaneous measurement of the cell cycle dependent membrane potential in a large population of cells.

Source: Sonja Langthaler

DIGITAL CANCER CELL – ELECTRIFYING INSIGHTS INTO THE CELL CYCLE

While computational modeling of biophysical and bioelectric phenomena in excitable cells is an indispensable complement to experimental studies, modeling the "action beyond the action potential" is still underrepresented in the field of computational electrophysiology. However, in-silico tools can provide a comprehensive view and open up deeper insight into the complex ion channel interaction and roles of the bioelectric properties in cancer, supporting oncological research and development of novel therapeutic strategies. Our experimental data serves as a fundamental basis for building digital models aimed at outlining the bioelectric mechanism underlying cell proliferation. By developing the first whole-cell model of a cancer cell, particularly A549 cells, we are able to simulate membrane potential changes of the cell cycle, based on corresponding ion channel modulation [1,2], as illustrated in Figure 2. Additionally, various hypotheses on channel blockage or activation and their consequences on cell proliferation can be tested. Figure 2D for instance shows the artificial block of KCa3.1 by TRAM-34, a proven cell cycle modulator and attractive therapeutic target, leading to a decrease of the membrane potential which might arrest the cell in G1 phase, consistent with experimental data showing a reduced proliferation rate. Thus, despite a high level of abstraction, the model enables a methodologically reliable and physiologically reasonable prediction of ion channel-mediated changes in membrane potential, opening the door for new model-based instruments in cancer research. >

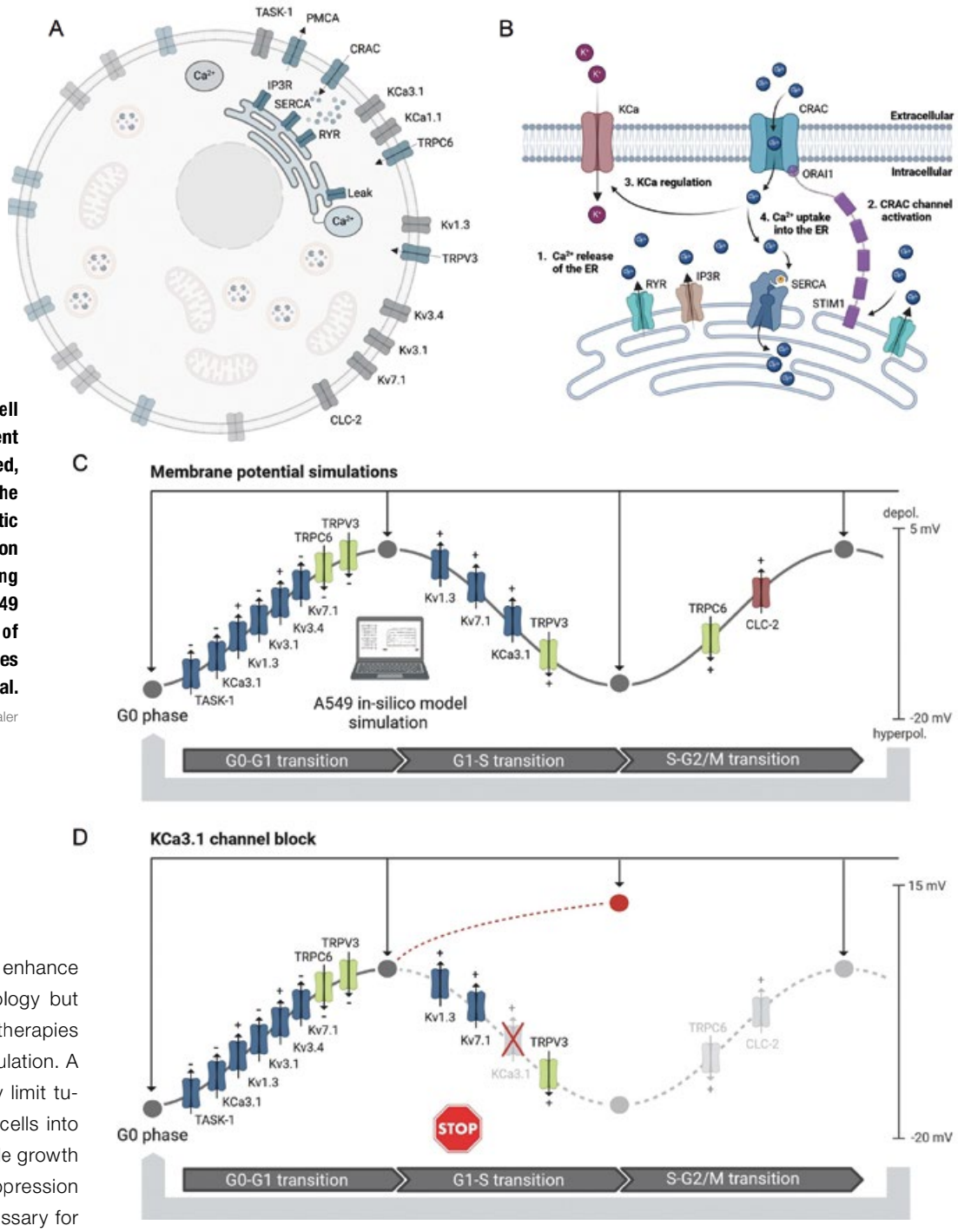

Figure 2: (A) A549 whole-cell ion current model with different ion channel types considered, (B) implemented concept of the calcium dynamics and (C) schematic illustration of the simulated ion channel activity and resulting membrane potential during the A549 cell cycle. (D) Computational block of KCa3.1 channels and its consequences on the membrane potential.

Source: Sonja Langthaler

INDUCED CELL CYCLE EXIT AND ARTIFICIAL CANCER AGEING

Our research not only seeks to enhance our understanding of cancer biology but also the development of targeted therapies aimed at disrupting cell cycle regulation. A promising approach to effectively limit tumor growth is to artificially drive cells into senescence – a state of irreversible growth arrest, implicated in tumor suppression (Figure 3). The mechanisms necessary for manifestation of senescence are highly complex and not fully understood. So far, it has only been considered from the molecular biological level, but in view of the crucial role of the membrane potential on proliferation, it may also play a key role in the formation of senescence. To this end, in close cooperation with our partners from the Medical University of Graz and ZMF, we investigate the interplay between bioelectric properties and cell aging (senescence) in order to gain deeper insights into the mechanisms underlying drug-induced cell cycle exit for cancer therapy.

UNVEILING THE ELECTRICAL SIGNATURE: A PATH TO THERAPEUTIC INTERVENTION?

Indeed, a major breakthrough for the development of effective and physiologically applicable treatment modalities could be to link different approaches together and tackle cancer cells from multiple directions. Hence, a profound understanding of cancer biology at multiple levels considering molecular as well as electrophysiological aspects therefore might afford novel therapeutic strategies to effectively fight and cure this disease. Beyond diagnosis and prognosis, decoding the electrical signature of cancer offers promising avenues for therapeutic intervention. Modulating ion channel activity emerges as a novel approach with potential applications in overcoming drug resistance, preventing cancer growth or inducing cancer cell apoptosis. Through computational modeling, we try to navigate the intricate terrain of cancer electrophysiology, giving advanced insights on fundamental mechanisms driving tumor progression.

Sonja Langthaler

is a project assistant at the Institute of Health Care Engineering with European Testing Center of Medical Devices and works in the field of experimental and computational cancer electrophysiology. The goal is to understand basic cellular process and mechanisms involved in tumor development and progression.

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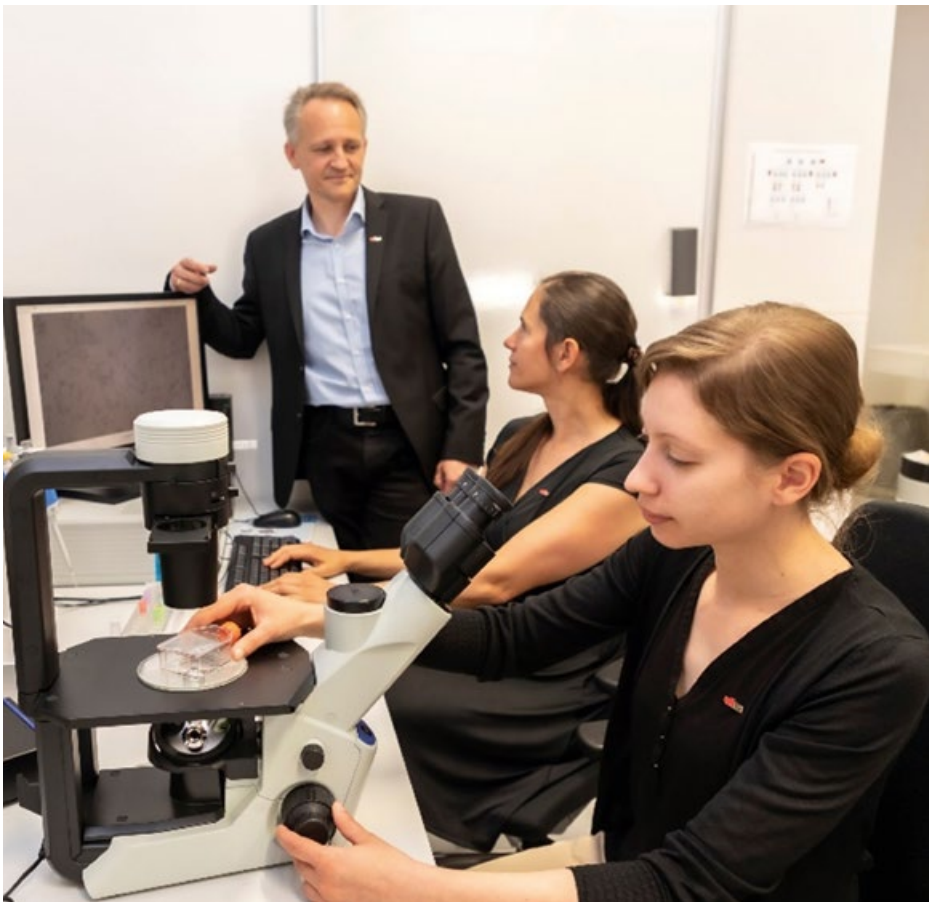

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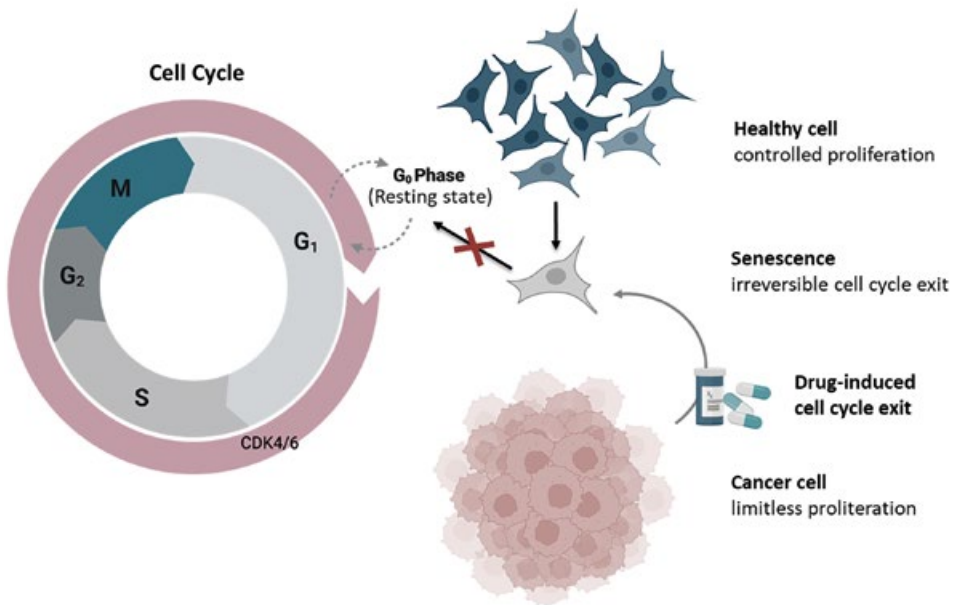

Figure 3: Process of cellular senescence. Healthy cells undergo controlled division as they progress through the cell cycle. After a certain number of divisions, the cell ages and enters a state of senescence. By contrast, cancer cells bypass the natural ageing process and divide rapidly, ultimately leading to the formation of tumors. Drug induction of cellular senescence could therefore be a promising therapeutic approach for limiting tumor growth.

Source: Sonja Langthaler

REFERENCES

[1] Langthaler S, Rienmüller T, Scheruebel S, Pelzmann B, Shrestha N, Zorn-Pauly K, et al. (2021) A549 in-silico 1.0: A first computational model to simulate cell cycle dependent ion current modulation in the human lung adenocarcinoma. PLoS Comput Biol 17(6): e1009091. https://doi.org/10.1371/journal.pcbi.1009091

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