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Worldwide Sodium Channel Conference, January 31st - February 2nd, 2024, Grindelwald, Switzerland

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Abstract

The following is a brief report of the inaugural Worldwide Sodium Channels Conference, held in Grindelwald, Switzerland, in January 2024. This excellent in-person conference followed the highly successful online Worldwide Sodium Channel Seminars series which started following the COVID-19 pandemic, in 2021. We present here our highlights of the forty-five presentations delivered over the two-and-a-half-day conference, focusing on key outputs from each of the eight sessions.

Keywords: voltage-gated sodium channels, ion channels, cardiology, excitability, channelopathies

Main text

Voltage-gated sodium channel (VGSC) aficionados gathered at the foot of the Eiger in Grindelwald, Switzerland, in January 2024, for the inaugural in-person Worldwide Sodium Channels Conference (WSCC), organised by a committee led by Professors Angelika Lampert (Uniklinik RWTH Aachen) and Hugues Abriel (University of Bern). The WSCC follows on from the highly successful online Worldwide Sodium Channel Seminars series, organised and hosted by the same team on an approximately monthly basis since 2021 and the heart of the COVID-19 pandemic. A major success of the in-person event, therefore, was to bring the sodium channel community together, for the first time in this unique grouping, to showcase and discuss recent developments in the field. More information can be found on the organizers' formal meeting website (https://sodiumchannelseminars.org/Sodium-Channel-Conference-2024/).

Since the Worldwide Sodium Channel Seminars series started in 2021, twenty cutting-edge presentations have been delivered from researchers spread across all major world continents, stimulating intense and enthusiastic discussions and further cementing this growing research community. However, there was clearly a growing desire for the community to meet in person, out of which came the organisation of the first WSCC. The meeting welcomed 101 attendees, including 45 speakers from fourteen countries, covered within eight sessions, and further represented at eighteen poster presentations. A unique format of the conference was that each presentation was limited to 15 minutes including questions; this arrangement allowed for a wide coverage of topics within the two-day meeting and provided equal opportunity and weighting for proffered presentations from early career researchers alongside leaders in the field. The conference was further supported by presentations, posters, and demonstrations from various sponsors closely integrated within the field. The meeting was held in the Theater- und Kongress-Saal of Grindelwald, which afforded a spectacular view of the mountain scenery and ski slopes surrounding the resort

town, viewed through floor to ceiling windows along one side of the meeting room. The social events for the meeting culminated in a conference dinner at the appropriately named Schweizerhof Romantik Hotel, which has been welcoming guests to Grindelwald since 1892. Although the weather was mild for the time of year, snow was visible on plenty of the slopes, and a number of delegates headed up there to ski at the end of the conference.

Cardiology

The first half-day of the meeting was kicked off by the first of two sessions on Cardiology and the opening presentation was given by Celine Marionneau (Nantes University) on her work into the regulation of cardiac $Na_v1.5$ channel complexes by β-adrenergic stimulation [1]. This was followed by further excellent talks covering topics including $Na_v1.5$ activation in catecholaminergic polymorphic ventricular tachycardia (CPVT)-like arrhythmia from Serena Pozzi (Linköping University), altered response to Class 1b antiarrhythmics in common *SCN5A* variants (Jonathan Silva, Washington University), and high-throughput functional studies of $Na_v1.5$ from Andrew Glazer (Vanderbilt University Medical Center), which accurately revealed significant functional differences between pathogenic and benign *SCN5A* variants [2]. The poster session covered a range of topics, including channel oligomerization, characterization of novel mutations in various channelopathies (e.g. Brugada syndrome), as well as other emerging topics, such as TRPM4 role in prostate cancer hallmarks.

Fast inactivation

Following the poster session, the second set of talks focused on fast inactivation of VGSCs, covering mechanistic representations, molecular modelling, characterization of a novel epilepsy mutation, and an extrapolation to inactivation of the $K_v2.1$ channel delivered by Kenton Schwartz (National Institutes of Health, USA); the latter revealed a novel electromechanical coupling mechanism underlying inactivation which is likely conserved across multiple voltage-gated channels [3]. A unique perspective on VGSC inactivation, and

use of descriptive scientific terminology more broadly, was given by Peter Hull (Friedrich-Alexander Universität Erlangen-Nürnberg), who gave a thought-provoking discussion of the benefits and pitfalls of using metaphor to reconceptualise the VGSC inactivation mechanism. Is the toilet flush mechanism a better analogy than ball-and-chain? The session ended with a presentation of computational studies by Carène Benasolo (Forschungszentrum Jülich). Finally, Elaine Tao (Australian National University) presented data highlighting the effect of a novel epilepsy mutation (N1662D) in the DIII-IV linker of Nav1.2, and revealing the importance of interaction between this linker and the IFM motif for fast inactivation [4].

Pain and CNS

The second day started with a session on pain, covering topics such as the effect of *SCN9A* loss-of-function mutations on action potential shapes, VGSC mutations in small fibre neuropathies (Janneke Hoeijmakers, Maastricht University Medical Center), and the effect of exogenous stimuli including TNF-α and conditioned medium on VGSC function in sensory neurons (Sidharth Tyagi, Yale School of Medicine) [5]. The pain session was followed by a session on VGSCs in the CNS, kicked off by a presentation from Jeanne Nerbonne (Washington University) on the role of iFGF14 increasing neuronal excitability [6]. Subsequent talks covered areas of interest including the mechanism of *SCN2A* variants in autism spectrum disorders from Massimo Mantegazza (University Cote d'Azur), the role of *SCN1A* in Dravet syndrome comorbidities (Moran Rubinstein, Tel Aviv University), and VGSC remodelling in *SCN1A*-associated sudden death in epilepsy (SUDEP) from Przemyslaw Radwański (Ohio State University).

Pharmacology/toxicology and Excitability

Following a lunch break in a nearby hotel, delegates returned for two more sessions on pharmacology/toxicology and excitability. Highlights of these sessions included the functional mechanisms by which stinging nettle toxins modulate $Na_v1.7$ via TMEM233 from Jennifer Deus (University of Queensland) [7], and how channels evade block by toxins (Fayal

Abderemane-Ali, UCLA) as well as delineation of mechanisms of VGSC inhibition by several peptides and fatty acids. Manu Ben-Johny (Columbia University) demonstrated an innovative strategy to reduce arrhythmogenic $Na_v1.5$ current. Further talks within the excitability session focused on linking channel genotype to phenotype via computational modelling approaches, as well as inflammation- and injury-induced changes to VGSCs in peripheral neurons (Michael Gold, University of Pittsburgh). Jenny Tigerholm (Aalborg University) concluded the session, showing how molecular VGSC studies can translate to modulating fibre excitability *in vivo* [8].

Structure

The final half-day started with a session on VGSC structure and was followed by the second session on cardiology. The structure session covered a structural perspective on related Ca^{2+}-selective channel biogenesis and binding to the endoplasmic reticulum membrane protein complex (Daniel Minor, UCSF) [9], and was followed by VGSC regulation by PIP_2 (Yie Chang Lin, Australian National University) [10]. There were also talks on drugging the sodium leak channel complex from Stephan Pless (University of Copenhagen) [11] and the development of novel tools to study channel structure-function (Hendrik Harms, also University of Copenhagen) [12], and a talk on structural basis underlying the hyperpolarisation-dependent opening of the HCN1 channel from Baron Chanda (Washington University) [13]. The session ended with Markos Xenakis' (Uniklinik RWTH Aachen) highly innovative perspective on how VGSC geometry and hydropathicity inform on the biophysical properties of wild-type and mutant channels [14].

The second cardiology session included two talks on $Na_v1.5$ in cancer cells, with one focusing on how $Na_v1.5$ activity leads to glycolytic acidification in breast cancer [15], a talk on β-adrenergic regulation of $Na_v1.5$ from Isabelle Deschenes (Ohio State University), and a presentation exploring $Na_v1.5$ interactions from Jan Kucera (University of Bern). The conference closed with a sponsor talk on how to study compound effects using automated

patch clamping. It is hoped that this highly successful meeting will be the first of many, and that participants may reconvene once more in this beautiful scenic resort town located in the Bernese Alps.

Disclaimer

This description of the WSCC is a selective view of the authors, and it was unfortunately not possible to include all presentations.

Author Disclosure Statement

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