PANACHE

Production of next generation modulators of pannexins and connexins as novel therapeutics in the treatment of inflammatory cardiovascular, hepatic and joint diseases

Funded by the Horizon 2020 Framework Programme of the European Union

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Deliverable number:	D1.11 (D11)
Deliverable title:	Workshop organized in Geneva, Switzerland
Work package:	WP1
Leading partner:	UNIGE
Participating partners:	VUB / FPNS /PROTOQSAR
Due date:	28/02/2022
Submission date:	21/12/2021
Dissemination level:	Public

1. Introduction

The second PANACHE/Science Xpression workshop was organized on 22 November 2021 as an online event because of ongoing travel difficulties due to the COVID-19 situation. The program (attachment 1) consisted of 3 sessions, which are outlined in this report. Throughout the day, 70 participants from 15 different universities/institutes attended the workshop (attachment 2). Thirteen flash presentations were given by young investigators based in 6 different countries. The workshop was highly visible and abundantly discussed on social media (attachment 3). The welcome address, initially intended to be presented jointly by Brenda Kwak (UNIGE) and Mathieu Vinken (VUB), was presented solely by Mathieu Vinken due to unforeseen circumstances in Geneva.

2. Session 1

Session 1 consisted of 4 half-hour presentations by experienced researchers from 3 different countries, followed by a general discussion. This session was chaired by Filippo Molica (UNIGE).

Christoph Scheiermann. University of Geneva, Switzerland.

Christoph Scheiermann is an associate professor in the Department of Pathology and Immunology at the University of Geneva. His lab studies circadian rhythms in the immune response recruitment of leukocytes, their regulation by neural influences and promigratory factors, and potential modulation by surgical, pharmacological, or genetic interventions.

Title: Circadian rhythm in inflammation.

Summary: Circadian rhythms are a behavioral adaptation of organisms to the anticipation of the regular rotation of the Earth's axis. White blood cells count changes dramatically during the course of the day, lowering during active hours and raising during sleep hours, with lymphocytes migrating out of the blood and to the lymph nodes and other organs before those active hours. The Scheiermann group's research has explored the rhythmicity of migration and trafficking dynamics and the underlying mechanisms of this circadian response.

Hester den Ruijter. University Medical Center Utrecht, Netherlands.

Hester den Ruijter is a professor in the Laboratory of Experimental Cardiology at UMC Utrecht, as well as the vice-chairwoman of the Young Academy of the Royal Netherlands Academy of Sciences and specialty chief editor of the journal Frontiers in Cardiovascular Medicine in the Sex and Gender section. Her research focuses

on understanding sex-specific biomarkers of heart disease to facilitate better diagnosis of heart disease in women.

Title: Sex differences in atherosclerotic mechanisms.

Summary: Atherosclerosis is caused by cholesterol plaque buildup causing narrowing of the blood vessels. Women are understudied in Acute Coronary Syndrome and Coronary Artery Syndrome studies, and generally across clinical trials, cohort studies, and even basic research where male tissues are used more frequently. Sex stratification of studies is important for several reasons. Younger women are more likely to experience erosion of the plaque while men are more likely to experience plaque rupture – in general atherosclerotic plaques tend to be more stable and collagen-heavy in women. Women had less chance of plaque bleeding, and plaque bleeding was only linked to worse outcome in male patients. A biobank containing samples from atherosclerotic aorta and mammary artery from bypass patients was used to quantify differences between 160 female and 160 male patients. Gene connectivity in atherosclerosis varied greatly between men and women, with Prof. den Ruijter's group identifying several key drivers of atherosclerosis in women.

Simone Becattini. University of Geneva, Switzerland.

Title: Impact of inflammatory stimuli on the function of the gut microbiota.

Simone Becattini is currently an assistant professor at the University of Geneva, having received the Swiss National Science Foundation (SNSF) Eccellenza Professorial Fellowship in 2020. He completed his PhD at ETH Zurich in 2014 and did his postdoctoral studies at the Memorial Sloan-Kettering Cancer Center in New York prior to his professorial appointment. His work focuses on the microbiota of the gastrointestinal system and its effect on immune response.

Summary: The interaction between the immune system, gut microbiota and pathogens is important to understand in the context of treating disease. The gut microbiota is incredibly rich and diverse, with 10x unique genes from the other microbes present on the body compared to the human genome, and dysregulation of these biota is linked to many diseases including allergies, diabetes, and atherosclerosis. Cues sent from the microbiota communicate with the immune system and vice versa, but the exact method of communication is not understood. Instead of looking at overall genetic makeup like most gut microbiota studies, the Becattini group used RNA sequencing to look at function of the gut microbiota of mice exposed to specific gut-colonizing bacteria, the response of this microbial transcriptome to external modulators, including immune stimuli and host factors, and the effect of the variation of this transcriptome.

Paul C Evans. University of Sheffield, United Kingdom.

Title: Blood flow and vascular inflammation.

Paul Evans is currently professor and Chair of Cardiovascular Science at the University of Sheffield. In 2000 he won the Medawar Prize from the British Transplantation Society for his discovery of deubiquitinating enzymes that suppress inflammation through inhibition of NFkB. More recently, this year he was awarded the Outstanding Achievement Award from the European Society of Cardiology, their highest award for outstanding achievement in scientific research. His research focuses on the biomechanical mechanisms underlying the development of atherosclerosis.

Summary: Blood flow patterns influence vascular form and function; the carotid artery bifurcation is a particular point of disturbed flow. Shear stress on endothelial cells controls the initiation and progression of atherosclerosis, with plaques often forming only on points of bifurcation or curvature, associated with low shear stress and oscillatory flow. Imaging of patients prior to treatment allows clinicians to map shear stress and predict plaques vulnerable to rupture, finding that shear stress outside the physiological norm predicts disease. The Evans group looked at transcriptome profiling of endothelial cell samples from porcine blood vessels in high and low shear stress regions to explore the different gene response patterns that may drive disease development in these regions.

3. **Sessions 2 & 3**

Sessions 2 & 3 consisted of 2 keynote lectures and several flash presentations presented by young researchers from different research groups that are studying the role of pannexins and connexins in health and disease (attachment 4). These young researchers were affiliated to both PANACHE partners or non-PANACHE partners. Session 2 was moderated by Paula Carpintero (INIBIC), while session 3 was moderated by Steven Ballet (VUB).

Session 2

Keynote lecture 1:

Arantxa Tabernero. Professor. University of Salamanca, Spain.

Arantxa Tabernero is a professor at the Institute of Neurosciences of Castilla y León (INCYL) in the Department of Biochemistry and Molecular Biology at the University of Salamanca. Her work has primarily focused on the brain, looking at astrocytes and connexin43 in the context of glioblastoma.

Title: Therapeutic applications of Src inhibitory peptides based on connexin43.

Summary. Malignant gliomas are a highly aggressive form of cancer in the brain with a very low survival rate. Malignant gliomas often express significantly less connexin43 (Cx43), and inducing glioma cells to express Cx43 or simply the c-terminal domain of cx43 reduces their rate of proliferation. Additionally, c-Src is often overactivated in gliomas and Cx43 specifically inhibits the oncogenic activity of Src. However, Cx43 can also confer TMZ chemoresistance and enhance glioma invasion. A Cx43 mimetic peptide TAT-Cx43266-283, which contains the Src binding domain on the c-terminus of Cx43 and recapitulates the native protein's inhibitory capacity without the pro-tumorigenic potentials of the full-length protein, was developed by the Tabernero lab and its potential effectiveness in cancer treatment was explored.

Session 2: Flash presentations

Axelle Cooreman. Department of Pharmaceutical and Pharmacological Sciences. Vrije Universiteit Brussel, Belgium**.**

Title: Effect of COVID-19 drugs on connexin43.

Summary: Inflammation is one of the clinical features of COVID-19. Cx43 hemichannels are involved in inflammation as they seem to open by pathological stimuli and release ATP in the extracellular environment which exacerbates inflammation. Drugs used to treat COVID-19 were examined for effects on Cx43 hemichannels to examine whether modulation of Cx43 is a path to successful anti-inflammatory treatment of COVID-19.

Harry Scott. University of Glasgow, United Kingdom.

Title: The human Discs large protein (Dlg1) controls Connexin 43 (Cx43) trafficking to the plasma membrane and gap junctional communication in keratinocytes.

Summary: Cx43 is involved in many processes including chronic wound healing, where it is upregulated, and also in human papillomavirus-associated cancer progression, where it is downregulated. Cx43 interacts with hDlg, a suspected tumor suppressor. This study looked at Cx43/Dlg1 interaction in vitro and in vivo to examine its potential role in trafficking of Cx43.

Jade Montgomery. Department of Pathology and Immunology. University of Geneva, Switzerland.

Title: Ain't nothing but a heartbreak: Effects of chronic hypoxia on cardiac ischemic injury response.

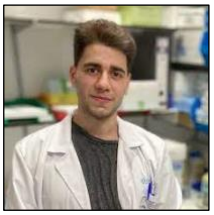
Summary: Connexin43 is an important protein in the context of cardioprotection. This study looked at variability of the connexin43 protein and its alternate translation fragments in response to ischemic injury in the context of chronic hypoxia.

Marc Mesnil. Laboratoire Signalisation et Transports Ioniques Membranaires. University of Poitiers, France.

Title: Implication of connexin43 in glioma invasion.

Summary: Connexin43 is localized in the invadopodia of U251 glioblastoma cells and participates in their formation and invasive activity. Studies on C6 glioma cells suggest that Cx43 expression is correlated with cell migration, secretome composition, and exosome amount. New glioblastoma cell models with different Cx43 constructs (entire, truncated, mutated) will help to understand how Cx43 is involved in these processes, specifically as to whether it is the absence of the carboxyl tail that decreases invasive capacity. The use of these models will permit verification of the link existing between invadopodia and exosome through Cx43 expression and their involvement in glioblastoma invasion.

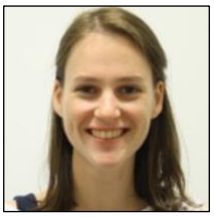
Session 3: Flash presentations



Alejandro Garcia-Yuste. CellCOM Research Group. Institute for Biomedical Research of A Coruña, Spain.

Title: Role of connexins in intervertebral disc degeneration.

Summary: Chronic lower back pain is one of the leading causes of disability. Connexin43 has been shown to regulate the senescence of osteochondrocytes. This study sought to characterize healthy and diseased human intervertebral disc samples through immunohistochemistry and enzymatic digestions.



Kaat Leroy. Department of Pharmaceutical and Pharmacological Sciences. Vrije Universiteit Brussel, Belgium**.**

Title: Connexin-based channel activity is not specifically altered by hepatocarcinogenic chemicals.

Summary: Carcinogenic compounds are chemicals that can lead to the development of cancer. Hepatocytes typically express Cx32 & Cx26 but not Cx43. This expression pattern is switched in various liver diseases. This study explored the connexin mRNA and protein expression as well as the functionality of the connexin (hemi)channels in liver cells after treatment with various hepatocarcinogenic chemicals.

Andrea Álvarez Vázquez. Institute of Neurosciences of Castilla y León. University of Salamanca, Spain**.**

Title: Effect of the Src inhibitory peptide TAT-$Cx43_{266\text{-}283}$ in neural stem cells with EGFR overexpression or EGFRvIII mutation.

Summary: Glioma stem cells can regenerate glioma after surgical removal and are very resistant to chemotherapy. Neural stem cells are theorized to be the origin of glioma stem cells, with altered EGFR amplification overactivating Src, leading to tumor development. This study aimed to look at the effect of the TAT-$CX43_{266\text{-}283}$ peptide on neural stem cells with altered EGFR expression.

Teresa Rodrigues. Faculty of Medicine. University of Coimbra, Portugal**.**

Title: USP8 modulates Cx43 homeostasis in endothelial cells.

Summary: Ubiquitination of connexin 43 acts as a triggering signal for internalization and degradation of gap junctions. This study examines the effects of deubitiquination by USP8 and AMSH on the life cycle of connexin 43 and correlates it with vascular endothelial cell flow type exposure.

Pietro Cacialli. Department of Pathology and Immunology. University of Geneva, Switzerland.

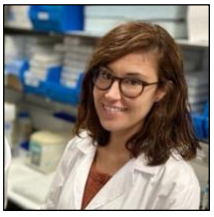
Title: A connexin/ifi30 pathway bridges HSCs with their niche to dampen oxidative stress.

Summary: Hematopoetic stem cells, the progenitor of liver in fetal development, develop in zebrafish in an area called the CHT. Mutation of cx41.8 or inhibition of this connexin resulted in modulated hsc development, a phenotype that could be rescued by antioxidant treatment or overexpression of ifi30.

Laureano Carpio. ProtoQSAR SL, Spain.

Title: AlphaFold: a revolution in biology and medicine. Examples in the case of Connexins and Pannexins.

Summary: AlphaFold is an AI that predicts the shape of 3D protein structure with a high degree of accuracy. It works by building off of similar sequences with known protein structure, building a potential structure for the given sequence iteratively and then providing a degree of confidence for the predicted output structure. This study reviewed the use of AlphaFold on connexin and pannexin structures.



Paula Carpintero-Fernandez. CellCOM Research Group. Institute for Biomedical Research of A Coruña, Spain.

Title: Targeting drug resistance in breast cancer.

Summary: Cellular senescence is an age-associated procession, but also linked to fetal development and is an interesting target for eliminating cancers. Pro-senescent therapies encourage the death of cancer cells and the recovery of normal tissues, however maintaining senescence for too long can cause cancer recurrence. This study examined the role of Cx43 in senescence in breast cancer cells.

Malaury Tournier. Department of Pathology and Immunology. University of Geneva, Switzerland.

Title: Studying Pannexin1 channel function in cardiovascular diseases.

Summary: Ischemic heart disease is the leading cause of death worldwide. A key actor in inflammation is the Pannexin 1 (Panx1) channel, whose release of ATP causes a cascade that results in the release of proinflammatory cytokines. Panx1 channel inhibition could therefore be a strategy to treat cardiac ischemia/reperfusion injury. This study looked at optimizing high throughput in vitro methods for studying Panx1 channel inhibition.

Anne Caufriez. Department of Pharmaceutical and Pharmacological Sciences. Vrije Universiteit Brussel, Belgium**.**

Title: Effects of drugs for the treatment of COVID-19 on pannexin1 channels.

Summary: Inflammation of patients in COVID19 is key, often inducing pyroptosis. Patients who end up hospitalized with COVID19 often have highly dysfunctional immune response to infection. Panx1 being a known part of the inflammatory cascade, this study examined whether COVID-19 drugs affect human Panx1 channels in vitro.

Session 3

Keynote lecture 2:

Brant Isakson. Professor of Molecular Biology and Biological Physics, Resident Faculty of the Robert M. Berne Cardiovascular Research Center, & UVA School of Medicine Pinn Scholar. University of Virginia, USA.

Brant Isakson is a professor in the department of Molecular Biology and Biological Physics at the Robert M. Berne Cardiovascular Research Center at the University of Virginia. In 2016 he was the recipient of the Pinn Scholar award, given to UVA faculty members on the basis of research accomplishments and proposed future research. He is also current editor-in-chief of the Journal of Vascular Research (impact factor 1.9). His lab's work focuses on understanding the role of signaling microdomains in mediating cellular communication within the microvasculature and disfunction of these microdomains in disease states.

Title: Dunning-Kruger Effect in Pannexin Biology

Summary: Of the 3 pannexin channels, Panx1 is the most studied because of how ubiquitous it is. The Isakson lab has previously studied Panx1 in great detail and has uncovered much of importance about how Panx1 functions in the body. Panx2 and Panx3, meanwhile, are very localized to specific cells and thus much less studied. In this talk, Isakson covered much of the work his lab has undertaken recently in pivoting to explore the role and function of Panx3.

Closing remarks

Closing remarks were delivered by Brenda Kwak to conclude the workshop.

Attachment 1

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

PANACHE

Second PANACHE workshop

Monday November 22, 2021:
on-line meeting, free of charge
registration required at: https://forms.gle/pirF6QN2M9vwaeXC9

8.50h: **Welcome** (Brenda Kwak / Mathieu Vinken)

Session 1: Points of attention in biomedical research
Chair: Brenda Kwak (UNIGE, Switzerland)

9h: **Circadian rhythm in inflammation** – Christoph Scheiermann (University of Geneva, Switzerland)

9.30h: **Sex differences in atherosclerotic mechanisms** – Hester den Ruijter (University Medical Center Utrecht, the Netherlands)

10h: **The influence of the gut microbiome on the course of inflammatory disease** – Simone Becattini (University of Geneva, Switzerland)

10h30: **Blood flow and vascular inflammation** – Paul C. Evans (University of Sheffield, UK)

11h-11h20: General discussion and wrap-up

COFFEE BREAK (11h20-11h35)

Session 2: Connexins in health and disease
Chair: Maria Mayan (INIBIC, Spain)

11.35h: **Keynote Lecture 1**

Arantxa Tabernero (University of Salamanca, Spain) -
Therapeutic applications of Src inhibitory peptides based on connexin43

12.20h-13h: **Flash presentations** (7 min presentation, 3 min discussion)

Axelle Cooreman (VUB, Belgium) -
Effect of COVID-19 drugs on connexin43

Harry Scott (University of Glasgow, UK) -
The human Discs large protein (Dlg1) controls Connexin 43 (Cx43) trafficking to the plasma membrane and gap junctional communication in keratinocytes

Jade Montgomery (University of Geneva, Switzerland) -
Ain't nothing but a heartbreak: Effects of chronic hypoxia on cardiac ischemic injury response

Marc Mesnil (University of Poitiers, France) -
Implication of connexin43 in glioma invasion

LUNCH BREAK (13h-14h15)

Session 3: Connexins/pannexins in health and disease

Chair: Steven Ballet (VUB, Belgium)

14h15-16h: **Flash presentations** (7 min presentation, 3 min discussion)

Alejandro Garcia-Yuste (INIBIC, Spain) -
Role of connexins in intervertebral disc degeneration

Kaat Leroy (VUB, Belgium) -
Connexin-based channel activity is not specifically altered by hepatocarcinogenic chemicals

Andrea Álvarez Vázquez (University of Salamanca, Spain) -
Effect of the Src inhibitory peptide TAT-Cx43$_{266-283}$ in neural stem cells with EGFR overexpression or EGFRvIII mutation

Theresa Rodrigues (University of Coimbra, Portugal) -
USP8 modulates Cx43 homeostasis in endothelial cells

Pietro Cacialli (University of Geneva, Switzerland) -
A connexin/ifi30 pathway bridges HSCs with their niche to dampen oxidative stress

Laureano Carpio (ProtoQSAR SL, Spain) -
AlphaFold: a revolution in biology and medicine. Examples in the case of Connexins and Pannexins

COFFEE BREAK (15h15-15h30)

Paula Carpintero-Fernandez (INIBIC, Spain) -
Targeting drug resistance in breast cancer

Malaury Tournier (University of Geneva, Switzerland) -
Studying Pannexin1 channel function in cardiovascular diseases

Anne Caufriez (VUB, Belgium) -
Effects of drugs for the treatment of COVID-19 on pannexin1 channels

16h-16.45h: **Keynote Lecture 2**

Brant Isakson (University of Virginia School of Medicine, USA) -
Dunning-Kruger experiences with pannexins in the vasculature

Funded by the Horizon 2020 Framework Programme of the European Union

Grant agreement number 858014

Attachment 2


Kirk Taylor (he/him)
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CJ Morado-Díaz
Julia D Zajac, Project Manager, V...
Prashant Kadam
Malaury Tournier
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Olga Rusiecka
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Marina Rguez-Candela
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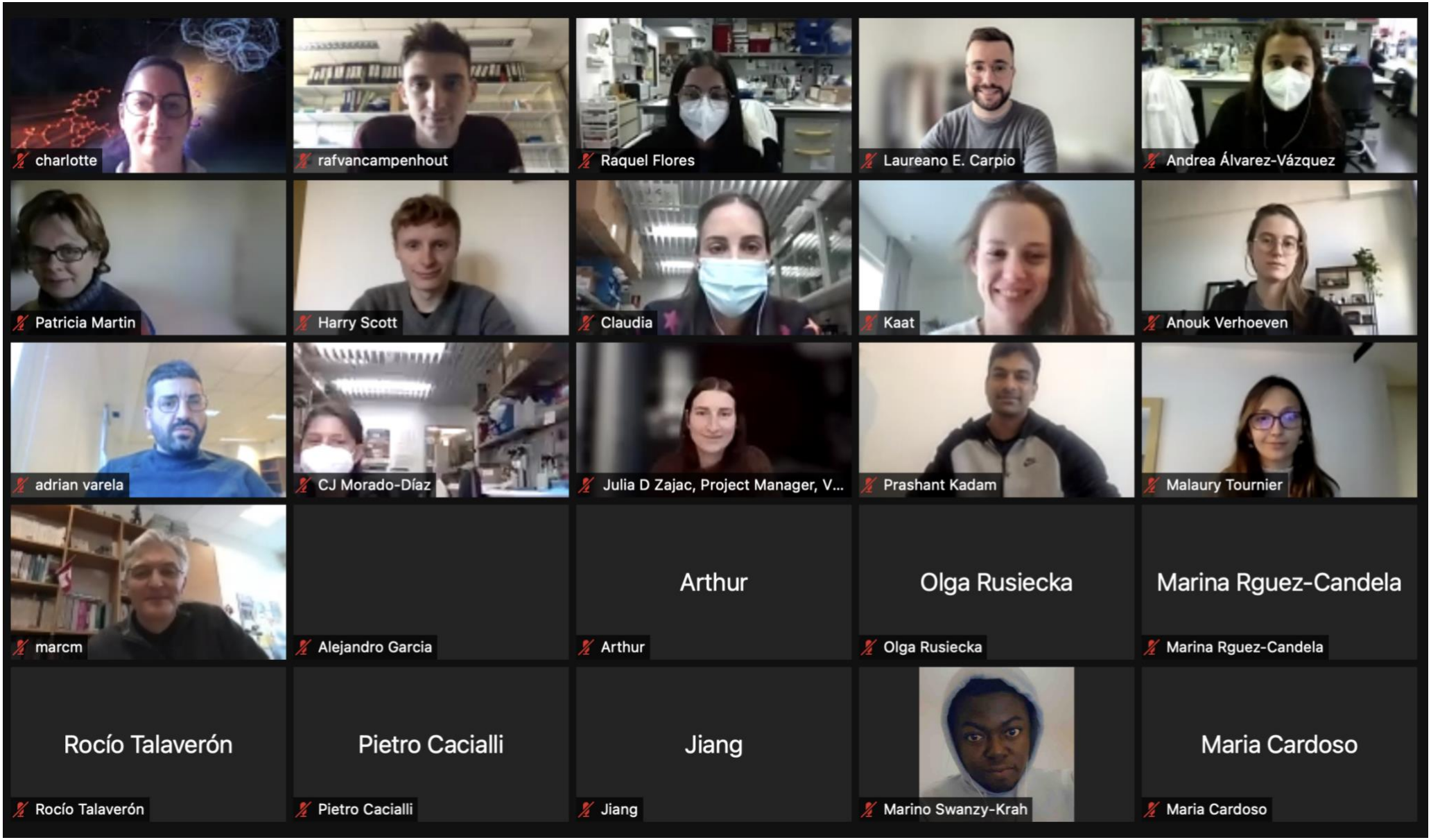
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Pietro Cacialli
Pietro Cacialli
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Marino Swanzy-Krah
Maria Cardoso
Maria Cardoso

Attachment 3

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Filippo Molica • 1st
Maître-assistant chez Université de Genève
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Great PANACHE workshop ahead. Now open for registration. Link:
https://lnkd.in/dd--QjWe

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ProtoQSAR
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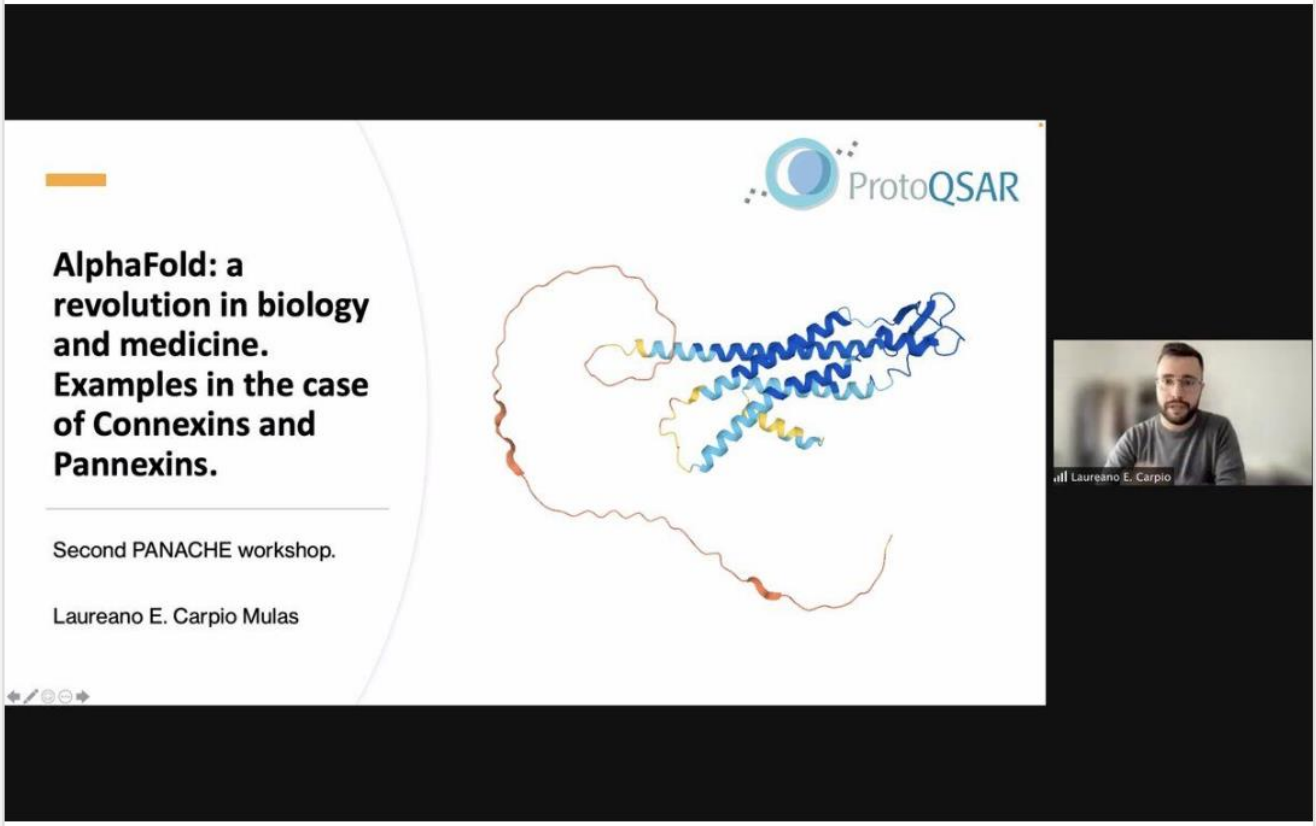
Yesterday our #PhD student **Laureano Emilio Carpio Mulas** presented a #FlashPresentation in the second #PANACHE workshop organized by Université de Genève and de #PANACHE consortium. In his short ta ...see more



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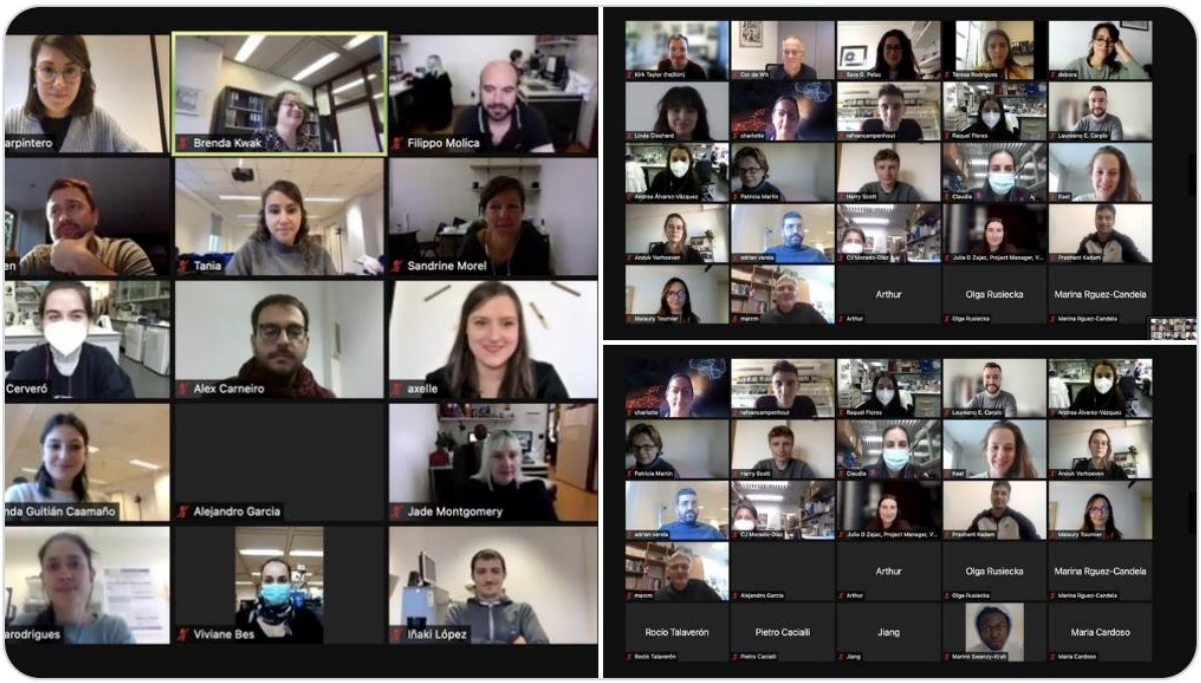
FET_PANACHE @FET_PANACHE · 22 Nov

We want to thank you all for being at this PANACHE workshop again! Every year we have the pleasure of attending amazing and innovative projects from very talented researchers. We hope to see you next year. 🙌



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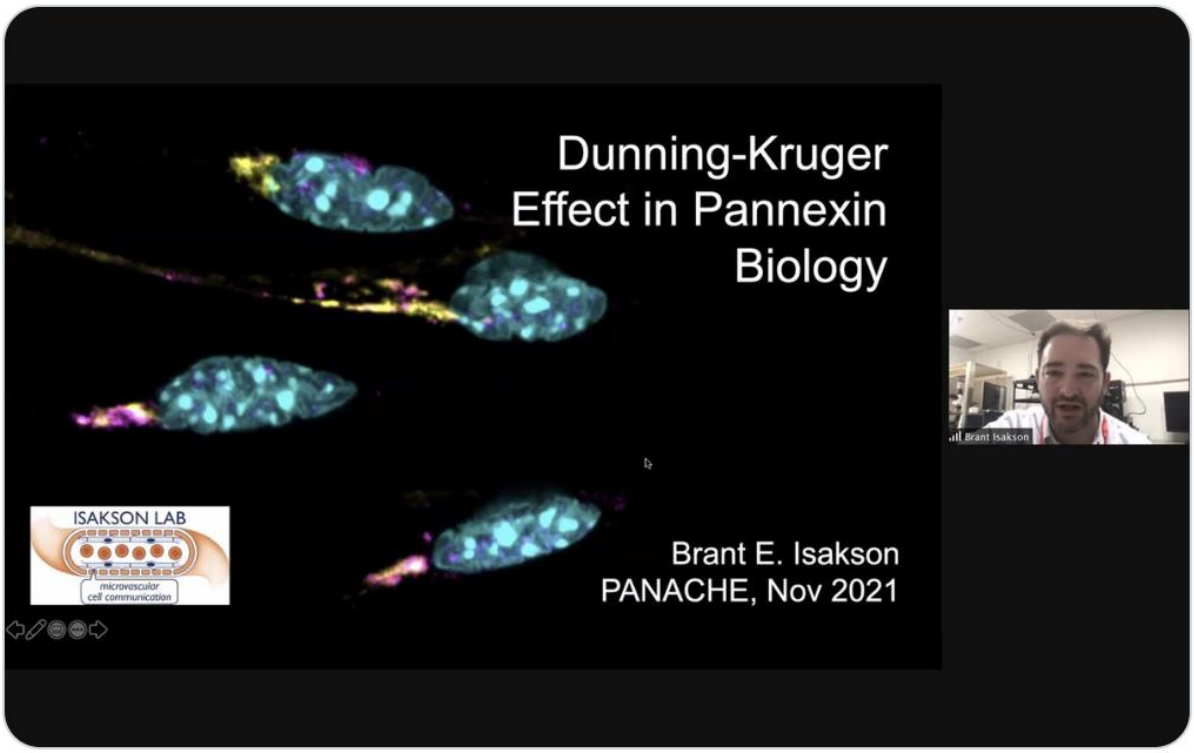
FET_PANACHE @FET_PANACHE · 22 Nov

As last intervention of this Panache workshop, we have the pleasure to attend to @conn_pann_fun as keynote speaker!

His work is about Dunning-Kruger experiences with pannexins in the vasculature 👏👏



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FET_PANACHE @FET_PANACHE · 22 Nov

Anne Caufriez, from @VUBrussel, is the last speaker of this flash presentations TOP

She is talking about the effects of drugs for the treatment of COVID-19 on pannexin channels.

2 8

Dr. María D. Mayán

21.9K Tweets

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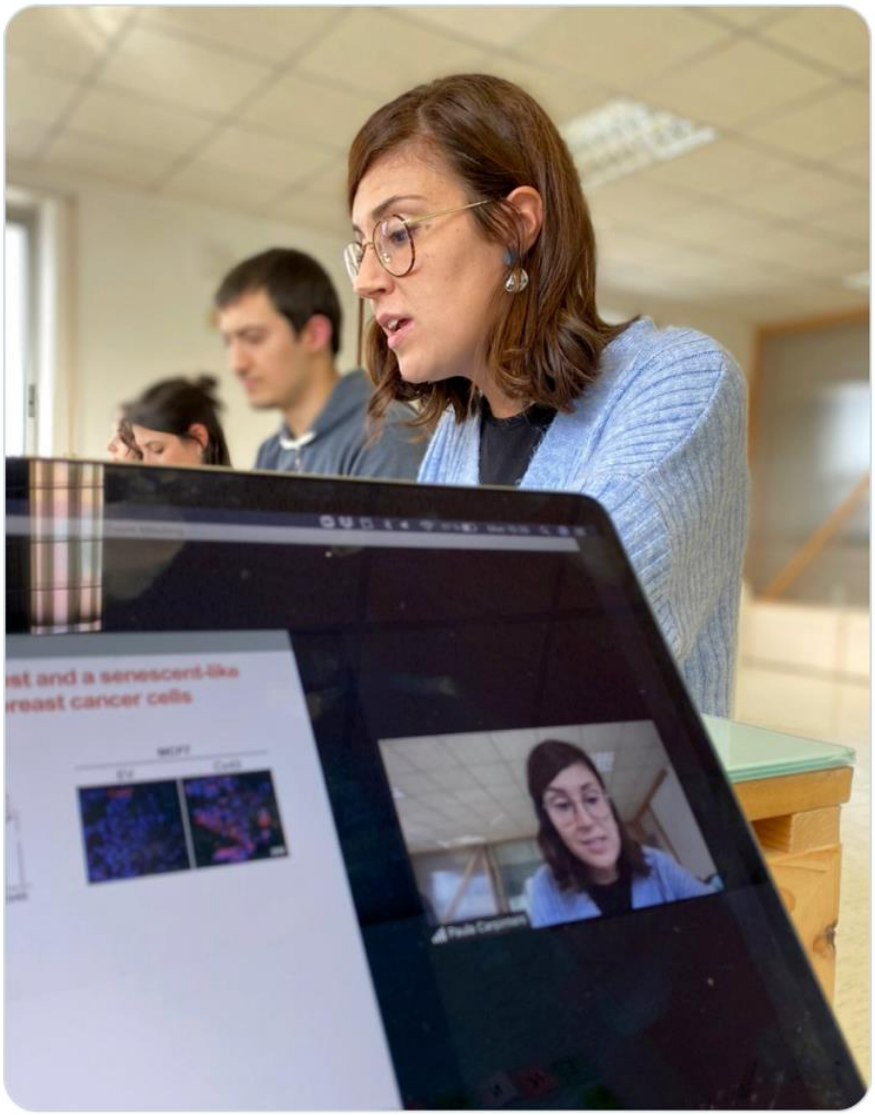
Dr. María D. Mayán @MariaDMayan · 22 Nov

Great talk and results! 👌

Fantastic as usual @PaulaCarpintero 🤩👏🏻#ProudPI❤️



FET_PANACHE @FET_PANACHE · 22 Nov

We're back from the coffe break and we have renovated energy to continue with our last flash presentations 👏⚡

@PaulaCarpintero is our next speaker, and she is ...

3 20

Alejandro García-Yuste @AlexgYuste · 22 Nov

Thank you very much for the opportunity and the visibility to young researchers 👨‍🔬💥 @FET_PANACHE

> **FET_PANACHE** @FET_PANACHE · 22 Nov
>
> After an exiting first session of this second PANACHE workshop, we begin with flash presentations for our young researchers 👏
>
> @AlexgYuste is the first one presenting his work about the role of Cxs in intervertebral disc degeneration! ⬆️TOP

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