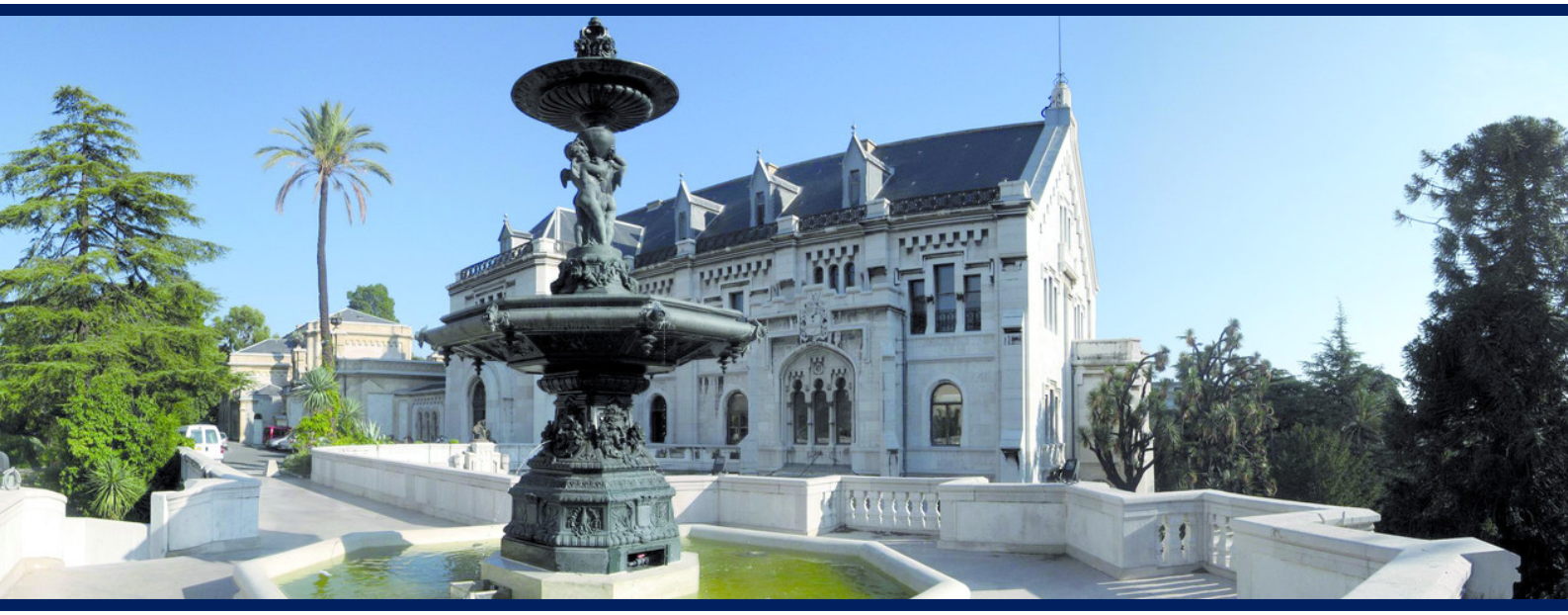
JEDNs 85

Journées de l'École Doctorale de Nice

26th, 27th and 28th of May 2025

ABSTRACT BOOK



Grand Château - Valrose Campus
Avenue Joseph Vallot, 06100 NICE

GUEST SPEAKERS

Pr. Jette LENGEFELD
Center for Hematology and Regenerative Medicine, Karolinska Institute, Sweden

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BOEGLIN Laure	*Plant Ecophysiology*
CALCAGNO Vincent	*Evolutionary Biology, Ecology, Insects*

JEDNs TEAM

CLARY Raphaëlle (3rd Year, C3M), **LUBRANO DI SCAMPAMORTE Hélène** (2nd Year, IPMC), **MARCHANDISE Sophia** (1st Year, iBV), **BOUVET Océane** (4th Year, C3M), **COURTOIS Marine** (3rd Year, ISA), **LABORY Justine** (3rd Year, ISA), **LAGHRISSI Hiba** (2nd Year, iBV), **OUERTANI Amira** (4th Year, iBV), **RIBERA Aurore** (3rd Year, IPMC), **WURTZ Mickael** (2nd Year, IRCAN)

KEYNOTE SPEAKER

Pr. Jette LENGEFELD,

Jette is a tenure-track Assistant Professor at the Helsinki Institute of Life Science - University of Helsinki (Finland) since 2021 and the Center for Hematology and Regenerative Medicine at Karolinska Institutet (Sweden) since 2023. Jette did her graduate studies at the ETH Zurich with Prof. Yves Barral (Switzerland) and her postdoctoral studies at MIT (USA) in the lab of Prof. Angelika Amon, supported by the SNF, the Jane Coffin Childs Memorial Fund and HHMI. Her independent research team studies how cellular size affects stem cell function during aging and cancer using mice and patient samples and to evaluate whether these discoveries are evolutionarily conserved.

Jette was awarded the prestigious European Research Council (ERC) Starting Grant in 2023, FEBS Excellence Award 2024, along with funding from Research Council of Finland (Fellow funding and project grant) and Research Council of Sweden (Starting grant). She is a member of the Center of Excellence MetaStem at Helsinki University.

Current Research

We discovered a new aspect of stem cell ageing *in vivo*: cellular enlargement. With age and damage, stem cells increase in size causing their functional decline. However, we are only beginning to understand how size impacts stem cell fitness and the physiological importance of this process remains unsolved. My team addresses these fascinating questions:

- What pathways cause stem cell dysfunction during their enlargement?
  We use blood (hematopoietic) stem cells of mouse models to identify the molecular mechanisms impairing fitness of large stem cells from a metabolic perspective.

- Can we rejuvenate stem cells after aging and damage?
  We explore approaches to rejuvenate stem cells and investigate the effects on cellular ageing and organismal health.

- Does deregulation of size lead to cancer?
  We utilize blood stem cells from mice and humans to identify factors that facilitate leukemia *in vivo* and to investigate the underlying mechanisms.

Representative Publication :

- **Lengefeld J†** and Zatulovskiy E† (2023) Cell Size Regulation: Molecular Mechanisms and Physiological Importance, Front Cell Dev Biol 11, 1219294
- Davies D, van der Handel K, Bharadwaj S**, Lengefeld J†** (2022) Cellular enlargement - a new hallmark of aging?, Front Cell Dev Biol **10**, 1036602
- **Lengefeld J†,** Cheng CW, Maretich P, Blair M, Hagen H, McReynolds MR, Sullivan E, Mayors K, Roberts C, Steiner J, Kang JH, Miettinen TP, Manalis SR, Antebi A, Rabinowitz JD, Morrison S, Lees J, Boyer L, Yilmaz O, Amon A "Cell size determines stem cell potential during aging", **Science Advances**
- Neurohr G, Terry R**, Lengefeld J**, Bonney M, Brittingham G, Moretto F, Miettinen T, Pontano Vaites L, Soares L, Paulo J, Harper W, Buratowski S, Manalis S, van Werven F, Holt L, Novak B, Tyson J, Amon A "Excessive cell growth causes cytoplasm dilution and contributes to senescence", **Cell**
- **Lengefeld J,** Hotz M, Rollins M, Baetz K, Barral Y "Budding yeast Wee1 distinguishes spindle pole bodies to guide their pattern of age-dependent segregation", **Nature Cell Biology**

INVITED SPEAKERS ROUND TABLE

Dr. BOULET Nathalie

Assistant Professor at Université Côte d'Azur

Recently appointed Assistant Professor at Université Côte d'Azur, Dr. Nathalie Boulet has built a research career at the intersection of adipose tissue biology and metabolic disease. After completing her PhD at I2MC (Toulouse), where she contributed to defining key progenitor populations in human adipose tissue, she pursued postdoctoral training at Stockholm University and again at I2MC. Her work across these positions explored the impact of immune and nutritional environments on stromal cell function and thermogenesis.

She joined the Centre Méditerranéen de Médecine Moléculaire (C3M) two years ago, where she is now part of Team IROD, focusing on the molecular mechanisms of adipose tissue remodeling in obesity and insulin resistance. Her academic path reflects a steady commitment to fundamental research with strong translational relevance.

Main research interests: Adipose tissue progenitor cells, adipogenesis, stromal cell heterogeneity, obesity, metabolic dysfunction.

Dr. DANI Vincent

CEO/CTO of ExAdEx-Innov, Private Sector Research

Dr. Vincent Dani leads strategy and technological innovation at ExAdEx-Innov, a deeptech company he founded to advance human adipose tissue research. With a dual background in science and startup development, he combines scientific expertise with entrepreneurial vision.
He holds a PhD in Cellular and Molecular Biology from Université Côte d'Azur and completed clinical research associate (CRA) training at the Faculty of Medicine of La Timone in Marseille. As co-inventor of the company's two patent families, he has been instrumental in translating cutting-edge bioengineering concepts into clinically relevant tools.Dr. Dani's work focuses on creating human-relevant, sustainable models for use in drug development, dermo-cosmetics, and aesthetic medicine.

Key areas of expertise: DeepTech entrepreneurship; Bioengineering of human adipose tissue

About: ExAdEx-Innov

ExAdEx-Innov is a deeptech company specializing in 3D ex vivo platforms based on real human adipose tissue. Through its patented technology, the company delivers reliable, human-relevant data that address the limitations of traditional in vitro and animal models in early-stage research. The ExAdEx platform is designed to bridge the gap between preclinical testing and clinical outcomes by offering physiologically accurate models for pharmaceutical and dermo-cosmetic applications. This approach supports more predictive, cost-effective, and ethical development processes.

Dr. KOZLOWSKI Djampa

Data Scientist & ML Engineer at Doriane, Private Sector Research

Djampa Kozlowski completed his PhD in 2020 at Université Côte d'Azur, with a dissertation entitled *"Contribution of transposable elements to crops pests adaptability in absence of sexual reproduction."* He continued his research with a six-month postdoctoral position in the same lab, before joining the university's MSI department as an AI engineer. There, he pursued his work on artificial intelligence applied to plant health, building on the foundations laid during his doctoral studies. After two years in academia, Djampa transitioned to the private sector. He is now a Data Scientist at Doriane, a company that provides innovative, data-driven solutions to stakeholders in agronomy undergoing digital transformation. His main role is to strengthen Doriane's expertise in AI and data processing across diverse use cases, from plant breeding to the implementation of agroecological practices such as biocontrol and biostimulation.

About: Doriane

Pioneer and leader in crop innovation software, Doriane develops digital solutions that empower agronomy teams to tackle modern research challenges. By fostering collaboration, organizing complex data, and optimizing resource management, the company supports smarter, more sustainable agricultural practices.
With a strong foundation in both technology and agronomy, Doriane is recognized for its reliability, expertise, and long-standing commitment to innovation. The company continues to evolve alongside the agricultural sector, driven by a multicultural team dedicated to delivering on its promises with agility and integrity.

Doriane's mission is to enable researchers and practitioners to make informed decisions through powerful data collection and interpretation tools—enhancing efficiency, openness, and resilience in the field of crop science.

PROGRAM

MONDAY 26th of MAY

8 : 30 AM – REGISTRATION

9 : 00 AM	OPENING
9 : 30 AM	PARTNERS & SPONSORS – ULYSSEUS
9 : 45 AM	3rd YEAR PhD TALKS 1. **HAMAI Amazigh** *(IPMC) - Biochemistry* 2. **MIGEVENT Tiffany** *(IPMC) - Physiopathology* 3. **CHESSEL Emilie** *(C3M)* - Cancer 4. **LAI Quynh-Huong** *(IRCAN) – Biochemistry/Development*

10 : 45 AM – COFFEE BREAK (30min)

11 : 15 AM	3rd YEAR PhD TALKS 5. **FRAISSARD Kéren** *(IPMC)* - Cancer 6. **STRAZZULLA Axelle** *(C3M) - Physiopathology* 7. **COURTOIS Marine** *(ISA) - Biomodelling*
12 : 00 PM	2nd YEAR PhD POSTERS TEASINGS Posters 1 to 18

12 : 45 PM – LUNCH BREAK (1H)

1 : 45 PM	KEYNOTE SPEAKER **Dr. Jette LENGEFELD**, Karolinska Institute, Sweden
2 : 30 PM	3rd YEAR PhD TALKS 8. **BASTISTIC Ludovic** (C3M) - Immunology 9. **LABORY Justine** (ISA) – Bioinformatics/Omics 10. **PROTEAU Sarah** (C3M) - Cancer 11. **RIBERA Aurore** (IPMC) – Neurobiology/Physiopathology
3 : 30 PM	2nd YEAR PhD POSTERS SESSION (+COFFEE BREAK) Posters 1 to 18
4 : 30 PM	ULYSSEUS – Talks **GARCÍA RODRÍGUEZ Diego** – Plant Biology **LUQUE PÉREZ Manuel** – Cancer
4 : 45 PM	3rd YEAR PhD TALKS 12. **KAHIL Mira** (C3M) - Cancer 13. **CLARY Raphaëlle** (C3M) - Physiopathology 14. **VAYANKARA EDACHOLA Sreeparvathy** (iBV) - Developmental Biology

PROGRAM

TUESDAY 27th of MAY

9:00 AM – REGISTRATION

9 : 30 AM	**3rd YEAR PhD TALKS** 15. **ABDEL SATER Alice** (IPMC) – Biochemistry/Immunology 16. **REZAPOVA Valeriia** (LP2M) – Bioinformatics/Immunology 17. **PUJALTE MARTIN Marc** (C3M) - Cancer 18. **NOGUÈRES Margot** (iBV) – Developmental Biology

10 : 30 AM – COFFEE BREAK (30min)

11 : 00 AM	**3rd YEAR PhD TALKS** 19. **ECHAVIDRE William** (CSM) - Cancer 20. **SCRIBE Célia** (IPMC) - Physiopathology 21. **DUSSUTOUR Ange** (ISA) – Plant Biology
11 : 45 PM	**2nd YEAR PhD POSTERS TEASINGS** Posters 19 to 37

12 : 15 PM – LUNCH BREAK (1H)

1 : 15 PM	**3rd YEAR PhD TALKS** 22. **MENUET Killian** (ISA) – Biochemistry/Plant Biology 23. **LOPES GONÇALVES Rafael** (IPMC) - Cancer 24. **GERARD Alexandre** (LP2M) – Immunology/Physiopathology 25. **HABBOUCHE Lama** (C3M) - Physiopathology
2 : 15 AM	**ROUND TABLE** **BOULET Nathalie** **DANI Vincent** **KOZLOWSKI Djampa** **LENGEFELD Jette**
4 : 00 PM	**2nd YEAR PhD POSTERS SESSION** (+ COFFEE BREAK) Posters 19 to 37
4 : 45 PM	**ULYSSEUS – Talks** **MORA ROMERO Bella** – Neurobiology/Developmental Biology **GONZALEZ ROVIRA Maria** - Host/Patho Interactions
5: 15 PM	**3rd YEAR PhD TALKS** 26. **DEBORD Juliane** (IPMC) – Physiopathology/Neurobiology 27. **VU-TO Giang** (IRCAN) - Immunology 28. **OUAHMI** Hajar (LP2M) – Physiolopathology/System Bio

7 : 00 PM – EVENING PARTY AT LE TOWN BAR !

PROGRAM

WEDNESDAY 28th of MAY

9 : 00 AM – REGISTRATION

9 : 30 AM	PARTNERS & SPONSORS – EUR LIFE
9 : 45 AM	3rd YEAR PhD TALKS 29. **SALADINI DI ROVETINO Marlen** (ISA) – Biochemistry/Plant Bio 30. **MANGEL Anthony** (iBV) - Neurobiology 31. **SIRERA Jessy** (IRCAN) - Cancer 32. **FYTILI Eirini Maria** (IPMC) – Structure Biology

10 : 45 AM – COFFEE BREAK (30min)

11 : 15 AM	Thesis Prize 2024 Nicolas ROBY
11 : 45 AM	3rd YEAR PhD TALKS 33. **BELLOUTI Ouafaa** (IRCAN) – Bioinformatics/Omics 34. **LAMGHARI Noura** (IPMC) – Cancer/Immunology 35. **GARNIER Mathilde** (RETINES) - Physiopathology
12 : 30 PM	2nd YEAR PhD POSTERS TEASINGS Posters 38 to 55

1 : 00 PM – LUNCH BREAK (1H)

2 :00 PM	ULYSSEUS – Talks **PARADELA LEAL Carmen** - Neurobiology **DE LA PENA NOYA Javier** - Microbiology
2 : 30 PM	3rd YEAR PhD TALKS 36. **PENG Siyong** (C3M) – Cancer 37. **AZOULAY Benjamin** (IPMC) - Neurobiology 38. **MAMJOUD Iman** (C3M) - BioModelling
3 : 15 PM	2nd YEAR PhD POSTERS SESSION (+ COFFEE BREAK) Posters 38 to 55
4 : 15 PM	3rd YEAR PhD TALKS 39. **DUBOIS Margaux** (MICORALIS) – Immunology/Microbiology 40. **ANGOT Brice** (C3M) - Physiopathology 41. **ABOU-ALI Mélanie** (IRCAN) – Biochemistry/Structure Bio
5 : 15 PM	AWARDS & CLOSING CEREMONY

POSTERS SESSIONS - PROGRAM

MONDAY 26th of MAY

P-1	**FAKIH Ibrahim**	*C3M*	Immunology/Structural Biology
P-2	**SEÇKIN Ercan**	*ISA*	Bioinformatics
P-3	**DELLA CROCE Laetitia**	*IPMC*	Cancer
P-4	**LERAY Chloe**	*iBV*	Developmental Biology
P-5	**LEBEL Quentin**	*IPMC*	Biochemistry/Neurobiology
P-6	**GAO Yuan**	*ISA*	Biological modeling
P-7	**SAÏSSI Margot**	*C3M*	Immunology/Microbiology
P-8	**CRUSSET Floricia**	*iBV*	Physiopathology
P-9	**FIERVILLE Morgane**	*IPMC*	Bioinformatics/Omics
P-10	**ARTIERES Lydia**	*IRCAN*	Cancer
P-11	**CASADO Doïna**	*ISA*	Developmental Biology/Neurobiology
P-12	**BROGUET Clarisse**	*C3M*	Physiopathology
P-13	**CARLEA Federica**	*IRCAN*	Microbiology
P-14	**MADY Ahmed**	*IRCAN*	Biochemistry
P-15	**ROSENTHAL PEREIRA LIMA Marina**	*ISA*	Plant Biology
P-16	**CHAPEAU Mélissa**	*C3M*	Cancer/Immunology
P-17	**GARCIA GARCIA Raquel**	*Ulysseus*	Neurobiology/Immunology
P-18	**HERRERO GOMEZ Irene**	*Ulysseus*	Plant Biology

POSTERS SESSIONS - PROGRAM

TUESDAY 27th of MAY

P-19	**BENACEUR Oumayma**	*C3M*	Biochemistry/Cancer
P-20	**LUBRANO DI SCAMPAMORTE Hélène**	*IPMC*	Physiopathology/Neurobiology
P-21	**TRAN Nghia**	*IRCAN*	Developmental Biology/Immunology
P-22	**OUALI Safae**	*TIRO/MATOs*	Bioinformatics/Omics
P-23	**MARTIN James**	*C3M*	Cancer
P-24	**FINKELSTEIN Jade**	*ISA*	Microbiology
P-25	**MCANDREW Eamon**	*IPMC*	Omics/System Biology
P-26	**RAVEL Nils**	*iBV*	Developmental Biology/Neurobiology
P-27	**GONÇALVES Diogo**	*C3M*	Cancer
P-28	**WURTZ Mickael**	*IRCAN*	Marine Biology
P-29	**GUILLEBON Claire**	*ISA*	Immunology/Microbiology
P-30	**ALEXOPOULOU Zampeta-Sofia**	*CoBteK*	Physiopathology
P-31	**MUKESHA Kabandana Dany**	*CoBteK*	Bioinformatics/Omics
P-32	**BANCILHON Déborah**	*IPMC*	Biochemistry/Microbiology
P-33	**SEGUI Fabien**	*CSM*	Cancer
P-34	**JABAUD Laure**	*ISA*	Structural Biology
P-35	**DJEBBOUR Hyame**	*IPMC*	Cancer/Immunology
P-36	**REVERTE PAGOLA Gonzalo**	*Ulysseus*	Cancer
P-37	**GARCIA BERNARDO Lorena**	*Ulysseus*	Biochemistry/Cell Cycle

POSTERS SESSIONS - PROGRAM

WEDNESDAY 28th of MAY

P-38	**KARAULIC Arthur**	*IRCAN*	Biochemistry/Cancer
P-39	**DA CUNHA Eloise**	*CoBteK*	Physiopathology
P-40	**GOSSET Clément**	LP2M	Bioinformatics
P-41	**RIVAULT Adèle**	*C3M*	Cancer
P-42	**HOFMÄNNER Kai**	*IRCAN*	Developmental Biology/Marine Biology
P-43	**BALDUZZI Jonathan**	*IPMC*	Neurobiology
P-44	**MARION Valentine**	*C3M*	Immunology/Microbiology
P-45	**AUSSEL Anais**	*C3M*	Cancer
P-46	**KHATIR Wassila**	*IPMC*	Bioinformatics/Omics
P-47	**MARTINELLO Chiara**	*C3M*	Cancer/Immunology
P-48	**LAUGIER Simon**	*IRCAN*	Microbiology
P-49	**GIROLET Camille**	LP2M	Immunology/Physiopathology
P-50	**ROUSSET Zoé**	*ISA*	Plant Biology
P-51	**DELABY Chloé**	*C3M*	Cancer/Immunology
P-52	**LELIEVRE Quentin**	LP2M	Physiopathology/Neurobiology
P-53	**LAGHRISSI Hiba**	*iBV*	Bioinformatics/Omics
P-54	**GALLEGO LOPEZ Maria Del Carmen**	*Ulysseus*	Physiopathology
P-55	**AZOGUE PALMA Carlos**	*Ulysseus*	

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-1	*Biochemistry*	HAMAI Amazigh	*IPMC*

Sfh3 Is A Sec14-Homolog Protein With A PI/PI4P Transfer Function Controlled By Sterol

Amazigh Hamaï and Guillaume Drin#
Institut de Pharmacologie Moléculaire et Cellulaire, UMR 7275 CNRS/Université Côte d'Azur. 660, Route des Lucioles, 06560 Valbonne, France.
#Corresponding author drin@ipmc.cnrs.fr

Sfh3 is a yeast protein of the Sec14 superfamily, able to bind phosphatidylinositol (PI) and sterol in a mutually exclusive manner. Sfh3 is recruited at the lipid droplet (LD)/vacuole contact site by LDO45 (Lipid Droplet Organization) and seems involved in regulating the,utilization of energy stored in LDs by the yeast. To date, how Sfh3 translates its ability to bind PI and sterol into a cellular function remains elusive. To gain insights into this, we analyzed in real-time by fluorescence how it captures and transfers lipid ligands in controlled in vitro systems using artificial membranes and recombinant proteins. We found that Sfh3 does not have the features of an efficient sterol/PI exchanger but can transfer PI between membranes to promote PI4P synthesis. We also found that, unexpectedly, it can transfer PI4P between membranes. We next found that ergosterol and lanosterol levels regulate the ability of Sfh3 to transfer PI and PI4P. We conclude that Sfh3 distinguishes itself from the well-known PC/PI exchanger Sec14 as it has the unique capacity to regulate PI4P signaling processes in a sterol- dependent manner. The biochemical characterization of several Sfh3 mutants associated with particular phenotypes in yeast supports this idea. Notably, our data suggest that Sfh3 might provide yeast with resistance against azole treatment via PI4P-dependent signaling processes. Collectively, our data indicate that Sfh3 ensures functional links between sterol metabolism and PI4P signaling by unanticipated lipid transfer modalities.

Keywords: Sfh3, Sec14, lipid transfer protein, sterol, phosphatidylinositol, PI4P, membrane contact sites

Acknowledgments
This work was supported by the CNRS. AH is supported by ANR-21-CE13-0014 grant from the Agence Nationale de la Recherche.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-2	*Physiopathology*	MIGEVENT Tiffany	IPMC

Mechanisms Of Sudden And Unexpected Death In Epilepsy (SUDEP) In A Mouse Model Of Epileptic And Developmental Encephalopathy: Dravet Syndrome.

Tiffany Migevent, Fabrice Duprat, Sylvain Rheims and Massimo Mantegazza

Sudden and unexpected death in epilepsy (SUDEP) is a cause of death affecting people with epilepsy of all ages, and is a major problem because of its dramatic consequences and unpredictability. Its risks is particularly high in Dravet syndrome (DS), a severe epileptic and developmental encephalopathy caused by a loss of function genetic mutation of the Scn1a gene encoding the alpha subunit of sodium channel NaV1.1. Seizure repetition, a major clinical factor involved in SUDEP, alters the autonomic nervous system and would cause cardio-ventilatory dysfunctions such as apneas and arrhythmias potentially leading to SUDEP. The Scn1a gene involved in DS is also expressed in the heart, but its involvement in cardiac dysfunction (calcium homeostasis, electrical activity, etc) is still unclear. In addition to peripheral autonomic dysfunctions, dysfunctions of serotoninergic (5-HT) pathway in the brainstem have been proposed in DS. These serotoninergic dysfunctions would increase ventilatory dysfunction related to seizure and potentially increase the risk of SUDEP. However, the mechanism linking the seizure repetition and these cardio-ventilatory dysfunctions remains unknown. A possible mechanism of SUDEP could be the propagation of « cortical spreading depolarization » (CSD), a slow depolarizing wave arising in the cortex after a seizure, which could propagate to the brainstem and temporarily block cardio-ventilatory control centers. In this thesis project, we use the Knock-In (KI) Scn1a R1648H/+ mouse model reproducing DS. The host team has shown that this KI model is not spontaneously epileptic but that the induction of short seizures by a convulsant agent, fluorethyl, (1 seizure/day for at least 5 consecutive days) causes the appearance of a phenotype close to DS and increases the risk of SUDEP (30% SUDEP after 10 seizures) (Salgueiro-Pereira et al.). Our model is appropriate to study if seizure repetition impacts autonomic nervous system control, leading to cardio- ventilatory dysfunctions that would increase the risk of SUDEP. We are studying the dysfunctions at several levels : i) on cardiomyocytes' features (calcium homeostasis) by calcium imaging and ii) performing an in vivo pathophysiological study with simultaneous recordings of video (behavioral characteristics), brain activity (ElectroCorticoGram, ECoG), ventilation (nasal thermistor) and heart rate (ElectroCardioGram, ECG), in relation to SUDEP events and 5-HT modifications in the brainstem(expression of receptors measured after brain sampling or use of molecule acting on 5-HT receptors).

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-3	*Cancer*	CHESSEL Emilie	C3M

Role Of The Arginine Synthesis Pathway And ASS1 In ICI Resistance In Melanoma

Emilie CHESSEL[1,2], Patricia ABBE[1,2], Wassila KHATIR[1,2], Issam BEN-SAHRA[3,4], Caroline ROBERT[5,6], Thierry PASSERON[1,7], Shensi SHEN[8,9], Stéphane ROCCHI[1,2], Michaël CEREZO[1,2]

[1] Université Côte d'Azur, INSERM U1065, C3M, Nice, France
[2] Equipe labellisée Fondation pour la Recherche Médicale
[3] Department of Biochemistry and Molecular Genetics, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA
[4] Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL 60611, USA
[5] Université Paris Saclay, Le Kremlin Bicêtre, France
[6] Dermatology Unit, Department of Medicine, Institute Gustave Roussy, Villejuif, France
[7] Department of Dermatoloy, University Côte d'Azur, Centre Hospitalier Universitaire de Nice, Nice, France
[8] National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, China
[9] Department of Thoracic Surgery, West China Hospital of Sichuan University, Chengdu, China

Despite the breakthrough of immune checkpoint inhibitors (ICI) in melanoma treatment, their efficacy is reaching a plateau. Understanding molecular mechanisms driving resistances is essential to identify patients susceptible to respond to ICI and explore strategies preventing or abrogating resistance. ICI target the crosstalk between immune and tumors cells, then, understanding the complex interactions in the tumor microenvironment (TME) is crucial to improve clinical response. Elevated resources consumption by cancer cells and limited vascularization of the TME drive competition between cancer and stromal cells. Using metabolomic and fluxomic we have identified, in melanoma resistant to ICI, alterations at the corner of urea cycle and *de novo* pyrimidine synthesis and especially arginine synthesis upregulation. Interestingly, the rate limiting enzyme of arginine synthesis, ASS1, is upregulated in patients resistant to ICI compared to patients that respond. We have demonstrated that arginine synthesis modulations lead to translational adaptations that could be involved in ICI resistance. Our hypothesis is that this upregulation of arginine synthesis could give advantages to tumor cells, to proliferate and bypass anti-tumor immunity through translational adaptations. The aims of our project are to understand how metabolic reprogramming and translational adaptations coordinate ICI resistance. We identify new interactions between metabolic alterations and translational reprograming that participate to ICI resistance and could be used as new prognosis markers or new therapeutic targets to bypass resistance.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-4	*Biochemistry*	LAI Quynh-Huong	IRCAN

Biochemical Studies Reveal A Possible Correlation Between The Strength Of Apollo - TRF2 Complex And Longevity

Quynh-Huong Lai[1], Francesco Abagnale[1], Eric Gilson[1-4] and Marie-Josèphe Giraud-Panis[1]

[1]University Côte d'Azur, CNRS UMR7284/INSERM U1081, Institute for Research on Cancer and Aging, Nice (IRCAN), Faculty of Medicine, Nice, France. Giraud-panis@unice.fr

[2]Department of Geriatrics, Medical center on Aging of Shanghai Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

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Protection of telomeres is crucial for genome stability and cell survival. TRF2, a telomeric protein, allows formation of a lasso-like structure called the T-loop, therefore hiding the 5' single stranded overhang that ends telomeres. Reforming the T-loop after replication requires re-generating the 5' overhang. Contrary to classical double-strand breaks, this does not involve the MRN complex but necessitates the APOLLO protein (also named SNM1 and encoded by *DCLRE1B*). This protein is recruited to telomeres through an interaction between the TRFH domain of TRF2 and the terminal part of APOLLO.

Amazingly, two articles reporting genome comparison between long-lived and short-lived animals have observed adaptative signatures in *DCLRE1B* around the TRF2 binding domain. Further analysis of sequences of other short-lived species also revealed notable differences in this region suggesting a possible link between variations in the affinity of the TRF2-Apollo complex and longevity. To address this question, we analyzed the interaction between the TRFH domain of TRF2 and the C-terminal domain of Apollo in different species with different longevities: human, naked mole rat (the longest living rat, 30 years), killifish (the fish with the shortest longevity, 8 months), zebrafish (5 years), the Galapagos tortoise (200 years) and the painted turtle (40 years). Our results reveal an inverse correlation between affinity and longevity. Indeed, the shorter the longevity in giving species, the stronger the interaction. This suggests that the strength of the affinity of Apollo for TRF2 could constitute an important parameter in determining life span.

OC-5	*Cancer*	FRAISSARD Kéren	IPMC

Role Of Microtubules' Glutamylation In Resistance To Paclitaxel In Breast Cancer Model

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Context: Breast cancer is the most frequent cancer in women worldwide. Triple negative breast cancer represents 20% of breast cancers and is a sub-type in which cells do not have the hormonal receptors, preventing them from being sensitive to common treatments (Yin et al., Brest Cancer Res, 2021). The main mode of treatment for triple negative breast cancer is surgery coupled with chemotherapy. A common chemotherapy treatment is paclitaxel, it has been used for thirty years (Orr et all, Oncogene, 2003). Paclitaxel is efficient for short-term treatment, but in the long run cells become resistant (Łukasiewicz et al., Cancers, 2020). Paclitaxel stabilizes microtubules which prevent cells from dividing (Orr et all, Oncogene, 2003). It has been showed that microtubules' glutamylation stabilizes microtubules' network in breast cancer cells (Torrino et al., Cell metabolism, 2021). Because paclitaxel and microtubules' glutamylation both stabilize breast cancer cells' microtubules, we hypothesize that microtubules' glutamylation could be part of the paclitaxel resistance mechanism in breast cancer cells.

Objectives: Creating paclitaxel resistant cell lines and characterizing them to determine whether and how microtubules' glutamylation is involved in resistance to paclitaxel.

Results: Two breast cancer cell lines were used: MDA-MB-231 and MDA-MB-468. Cells were repeatedly treated with increasing exposure to paclitaxel until they became resistant. Their half maximal inhibitory concentration (IC50) to paclitaxel has been determined. IC50 231 R = 50nM whereas IC50 231 S= 2,5nM, and IC50 468 R = 50 nM whereas IC50 468 S = 1 nM. Tubulin glutamylation level was assessed by Western blot and immunofluorescence. Tubulin glutamylation is increased in both 231 and 468 resistant cells compared to sensitive cells. Proliferation was analysed by immunofluorescence with Ki67 antibody. Resistant cells seem to have a lower proliferation than sensitive cells in both cell lines.

Current and future work: Knock down of glutamylation in resistant cells, to quantify their level of resistance and characterize their phenotype, to see if it can be rescued.

OC-6	*Physiopathology*	STRAZZULLA Axelle	C3M

CD44 Could Aggravate Liver Fibrosis By Regulating Hepatic Stellate Cell Functions

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Keywords : MASLDs, fibrosis, CD44, hepatic stellate cell, TGFb

Background & aims: Liver fibrosis is the common response to chronic liver injury and leads to cirrhosis and its complications. Persistent inflammation is a driving force of liver fibrosis progression. In addition, liver collagen deposition associated with hepatic fibrosis is mainly dependent on proliferation, differentiation and activation of the hepatic stellate cells (HSCs). CD44, a glycoprotein mainly expressed in immune cells and HSCs, has been implicated in multiple inflammatory diseases but limited studies evaluated its role in liver fibrosis. We therefore explored its contribution to liver fibrosis in mice and patients and the regulation of HSCs functions.

Methods: Hepatic CD44 was evaluated in mouse models of fibrosis. Its role in liver fibrosis was evaluated in global CD44 knock out mice and human hepatic stellate cell line (LX2).

Results: Here, we report that hepatic CD44 expression correlated with liver injury and fibrosis in different mouse models of fibrosis. Interestingly, Cd44 deficiency mediated a protective effect on diet-induced fibrosis. In LX2 cell line, RNAseq analysis revealed that Cd44 silencing upregulates pathways involved in wound healing, matrix metalloproteinase and inflammatory responses. In addition, the silencing of Cd44 also enhanced the cell mobility and the secretion of inflammatory mediators including Il8, Ccl2 and Cxcl1. This secretory environment was strongly amplified after LPS stimulation and diminished the pro-fibrogenic polarization of human blood monocyte-derived macrophages induced by IL4 stimulation. The Cd44 silencing also strongly modified the TGFβ-mediated LX2 cell responses including a decreased expression of pro-fibrogenic markers like Acta2, Pdgfr and Col1a1.

Conclusion: Collectively, these data could suggest an important role of CD44 in the pathogenesis of liver fibrosis by regulating the migration, activation and secretory profile of hepatic stellate cells.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-7	*BioModelling*	COURTOIS Marine	ISA

Sterility On The Rocks: When Pest Love Life Challenges Sterile Insect Technique Success

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The Sterile Insect Technique (SIT) is more and more used in agriculture to manage crop pests. It entails the large-scale breeding, sterilization, and subsequent release of the targeted insects into crops. This approach lowers the population reproductive output and reduces associated damages. Despite its apparent simplicity in theory, each step of this technique poses practical hurdles to its effective implementation. Several challenges, such as residual fertility in sterile insect releases and the tendency of females to re-mate, can significantly impede SIT success.
To assess whether SIT efficiency is influenced by: (1) residual fertility and (2) multiple matings, we devise a population dynamics model using ordinary differential equations. This model is structured into larvae, wild males, sterile males, fertilized females (mated with wild males), and infertile females (mated with sterile males). Sterile males are released continuously into the population. Only fertilized females have the ability to lay eggs. We assume that fertility is determined by the last mating. Females can thus change status whether and when they re-mate.

(1) We determine the residual fertility threshold below which eradication can be achieved. This threshold depends on the offspring number of the targeted pest and fitness costs on released males. Moreover, pest control remains feasible even when this threshold is overshot. In this case, SIT allows to maintain pest population under an acceptable level.
(2) We compare scenarios where females undergo single mating with multiple matings separated by a refractory period. We investigate the impact of this refractory period, which can vary depending on whether it follows a mating with a fertile or sterile male.

Our study highlights the crucial role of reproductive mechanisms in shaping the efficiency of SIT control strategies, emphasizing the necessity of a thorough comprehension of the ecology and biology of the targeted pest. This understanding is essential not only for optimizing SIT but also for enhancing pest management practices overall.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-8	*Immunology*	BATISTIC Ludovic	C3M

Inflammasomes are important signaling platforms that play a crucial role in regulating inflammation. The activation of inflammasome is tightly controlled both transcriptionally and post-translationally, but little is known about the mechanism controlling their activation and the upstream signaling that regulates inflammasome assembly. My thesis project aims at providing evidence of the role of the RAC GTPases and its target protein p21-activated kinases 1 (PAK1) in activating inflammasomes during Psoriasis. My thesis results demonstrate that the inhibition of the RAC1-PAK1 axis effectively prevents the development of a psoriasis-like phenotype in a mice model of psoriasis. In addition, I also showed in human psoriatic lesional skin and in vitro using primary human cells that highly active RAC1 leads to specific cell type inflammasome activation, with NLRP3 in immune cells and NLRP1 in keratinocytes. These results provide important insights into the pathogenesis of psoriasis and highlight potential new avenues for therapeutic intervention. Understanding the role of the RAC-PAK-NLRs axis in psoriasis could lead to the development of targeted treatments aimed at modulating this pathway to effectively manage the disease.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-9	*Bioinformatics*	LABORY Justine	ISA

VIOLA: Variant PrIOritization using Latent spAce to improve mitochondrial diseases diagnosis

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Interpreting variants from whole-exome sequencing (WES) remains a major challenge, particularly for heterogeneous disorders like mitochondrial diseases. To address this, we developed VIOLA (Variant prIoritizatiOn using Latent spAce), a novel pipeline that combines unsupervised machine learning, transcriptomic data, and phenotype-driven filtering to prioritize likely pathogenic variants.

VIOLA first extracts functional annotations from VCF files and encodes them using a variational autoencoder (VAE) to capture complex patterns in a low-dimensional latent space. Outlier detection by DBSCAN identifies unusual variants likely to be disease- causing. This is followed by stringent filtering and phenotype integration using HPO terms. Then, VIOLA uses a customized ranking that combines statistical outlierness (Mahalanobis distance), transcriptomic co-expression data, and mitochondrial specific features into a unified score: the VIOLA score (Vscore). Based on this score, we defined two types of rankings: the VIOLA rank (all variants) and the ARrank (variants compatible with autosomal recessive inheritance). The Vscore is further aggregated with the Exomiser score, the state-of-the-art-tool for variant prioritization, to produce the VIOLA Aggregated score (VAscore).

Applied to a cohort of 20 suspected mitochondrial disease patients (including 4 diagnosed), VIOLA consistently ranked causal variants among the top candidates, outperforming standard tools. A robustness analysis with 100 randomized runs per patient confirmed the stability of the pipeline. VIOLA outputs HTML reports linked to major databases, making it accessible for clinicians and researchers. Overall, VIOLA is a new approach which is patient-specific for variant prioritization, addressing key limitations of existing methods and improving diagnostic yield in rare disease genomics.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-10	*Cancer*	PROTEAU Sarah	C3M

LKB1-SIK2 loss drives uveal melanoma proliferation and hypersensitivity to SLC8A1 and ROS inhibition

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INTRODUCTION: Uveal melanoma is the main primary intraocular malignancy in adults. Despite successful control of the primary tumor, up to 50% of the patients will develop metastasis, mainly in the liver. At this stage, the median survival is 12 months since metastatic uveal melanomas (mUM) are highly resistant to existing therapies. Therefore, there is an urgent need to find new targets and develop effective treatments for the patients.

METHODOLOGY: A kinome-wide CRISPR-Cas9 knockout screen was conducted in mUM to identify candidates involved in mUM cell survival and proliferation. Top candidates (LKB1, SIK2) were further validated, and clones were derived. To get insights into how these candidates function, RNA-seq analyses were performed, integrated and effect of top relevant effectors (SLC8A1) were assessed using gain (lentivirus) and loss (siRNA and mutant genes) of functions experiments. Alterations in metabolic activities (calcium, ROS) related to the LKB1-SIK2- SLC8A1 module were measured using fluorescent probes (Fura2, Rhod2, mtROS). The effect of targeting pharmacologically the metabolic alterations was studied using in vitro and in vivo experiments.

RESULTS: Following the genetic screen that identified the kinases LKB1 and one of its downstream effectors SIK2 as critical regulators of mUM cell proliferation and survival, LKB1 or SIK2 knock-out (KO) clones were derived. As expected, LKB1 or SIK2 deficient clones displayed strong increase in metastatic uveal melanoma cell proliferation and survival. In addition to genetic alteration, we found that the hepatocyte growth factor inhibits the LKB1- SIK2 axis and enhances mUM cells proliferation. Transcriptomic analysis revealed different gene sets associated with calcium metabolism in LKB1-KO and SIK2-KO cells, and accordingly Fura2 staining showed enhanced intracellular calcium level in the deficient cells compared to WT cells. RNA-seq datasets
revealed genes that were deregulated and related to calcium (Ca2+) metabolism such as the sodium (Na+)/(Ca2+) exchanger SLC8A1, also associated with reduced patient survival. SLC8A1 knockdown strongly reduced the proliferative capacity of LKB1-KO and SIK2-KO cells. Moreover, adding back SIK2 in LKB1-KO cells rescued the hyperproliferative phenotype of mUM cells demonstrating that SIK2 is a hub mediating the SLC8A1-dependent proliferation in LKB1-KO mUM cells. We also showed that mitochondrial Ca2+ and ROS level were increased in LKB1-KO and SIK2-KO cells and that their targeting induced cell death and impaired tumor growth.

CONCLUSION: Altogether, we show that LKB1/SIK2 module deficiency is critical to proliferation and survival of mUM cells. Finally, our study identifies the combination of SLC8A1 and mitochondrial ROS inhibitors as a promising therapeutic strategy for metastatic uveal melanoma patients.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-11	*Neurobiology*	RIBERA Aurore	IPMC

Hippocampus – nucleus accumbens at the basis of reward-driven memory deficits in aged male mice

Aurore Ribera, Manuel Dias-Silva, Emma Deneuville, Brenda Dias, Ingrid Bethus, Peter Vanhoutte, Jacques Barik, Paula Pousinha

The aging population experiences a loss of autonomy and motivation due to cognitive decline, which is associated with synaptic alterations in the CA1 region of the hippocampus (HPC). The volumes of the HPC and nucleus accumbens (NAc) decrease with age. However, brain aging alterations at the level of neuronal circuits remain largely understudied. While the HPC is involved in processing mnemonic and spatial information, the NAc is a key site for transforming hippocampal spatial codes into motivated actions. The NAc receives monosynaptic projections from both dorsal and ventral CA1. Inhibiting HPC⟶NAc projections reduces conditioned place preference (CPP)—a form of spatial reward memory—whereas optogenetic stimulation is sufficient to artificially induce CPP. The main goals of my project are to (1) investigate the impact of aging on the NAc microcircuit, (2) identify age-related specific alterations in HPC⟶NAc neurons, and (3) understand the cellular mechanisms underlying maladaptive behaviors involving this circuit during aging. The results show that 18-month-old female mice are preserved, exhibiting neither cellular nor behavioral alterations involving the HPCd-NAc circuit. In contrast, aged male mice exhibit glutamatergic hyperactivity in the HPCd-NAc projection, leading to dysregulation of the NAc microcircuit via D1 neurons. These mice show CPP deficits, which were restored by reducing the activity of HPC neurons projecting to the NAc through chemogenetics. Open questions remain, particularly regarding the identity of the CA1 fast-firing neuronal population projecting to the NAc and the impact of aging on PV neurons in the NAc. Addressing these questions will facilitate the identification of therapeutic targets to prevent or delay pathological aging.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

Plant Biology	GARCÍA RODRÍGUEZ Diego	Ulysseus

Identifying plant cellular targets of the Type III Secretion System Effector NopP from *Sinorhizobium fredii* HH103

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Abstract
Sinorhizobium fredii HH103 is a nitrogen fixing bacterium able to nodulate a broad range of legume plants, although its natural host is soybean (Glycine max). Nod factors, surface polysaccharides and secretion systems, like the Type III Secretion System (T3SS), are some of the bacterial mechanisms involved in the establishment of this symbiosis [1]. Like several other Gram-negative plant-pathogenic and symbiotic bacteria, S. fredii HH103 utilizes a T3SS to deliver proteins, called effectors (T3E), directly into their plant host cells. Pathogenic bacteria used the T3SS to evade the immune system and facilitate the infection. In rhizobia, the T3SS is involved in the suppression of plant defences, the host-range determination in the establishment of the symbiosis and the nodulation efficiency. Moreover, the T3SS genes and nodulation genes are co-regulated [2].
In this work we focus on the T3E NopP. NopP is specific to rhizobia and is involved in the blockade of nodulation in Rj2 soybean cultivars. An immunoprecipitation (IP) assay of NopP was performed and the cyclophilin CYP40 was showed to be a potential target of this effector. CYP40 is involved in the facilitation of the assembly of the RNA-induced silencing complex (RISC) [3]. In this work we show that NopP colocalizes with CYP40 by transient expression assays of nopP fused to RFP and Cyp40 fused to YFP in Nicotiana benthamiana leaves and confocal imaging. Bimolecular Fluorescence Complementation (BiFC) assays were also performed to determine the interaction of these two proteins in plant cells.

References
[1] López-Baena, F.J., Ruiz-Sainz, J.E., Rodríguez-Carvajal, M.A., Vinardell, J.M. Bacterial molecular signals in the Sinorhizobium fredii-soybean symbiosis. International Journal of Molecular Science, 2016, 17(5), 755.
[2] Jiménez-Guerrero, I., Medina, C., Vinardell, J.M., Ollero, F.J., López-Baena, F.J. The rhizobial type 3 secretion system: The Dr. Jekyll and Mr. Hyde in the rhizobium–legume symbiosis. International Journal of Molecular Sciences, 2022, 23(19), 11089.
[3] Taichiro, I., Yoshikawa, M., Meshi, T., Ishikawa, M. Cyclophilin 40 facilitates HSP90-mediated RISC assembly in plants. The EMBO Journal, 2012, 31, 267-278.

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ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

Cancer	**LUQUE PÉREZ Manuel**	Ulysseus

Targeting ARID1A as a therapeutic opportunity for Ovarian Clear Cell Carcinoma patients

ARID1A is a frequently mutated protein across a variety of different cancers. This protein belongs to the SWI-SNF complex, which is an ATP-dependent chromatin remodelling complex with different biochemically-distinct subunits. It mediates changes in chromatin accessibility, thus facilitating transcription of different genes. ARID1A is present in the BAF configuration of the SWI-SNF complex, being mutually exclusive with ARID1B. Moreover, ARID1A is the most commonly mutated subunit of this SWI-SNF complex, especially in a specific subtype of ovarian cancer, which is ovarian clear cell carcinoma (OCCC). OCCC accounts for 5 to 25% of all epithelial ovarian cancers, and it is an aggressive tumour due to its lack of targeted therapies. Normally, these patients do not respond favourably after a standard chemotherapy with carboplatin and paclitaxel. Importantly, ARID1A mutations are present in more than 50% of OCCC samples. This high prevalence makes ARID1A relevant factor to design future therapeutic options for OCCC patients. In order to study the functional role of ARID1A in OCCC, we overexpressed this protein endogenously by CRISPR activation system using different ovarian cancer cell lines. We checked for resistance of these ARID1A-overexpressing cells against certain replication stress (RS) inducing agents, which are drugs commonly used in ovarian cancer treatment for those patients not responding correctly to the conventional chemotherapy. These agents include Gemcitabine, PARPi or ATRi. We aim to see if ARID1A status in OCCC patients may be exploited as a prognosis factor for resistance to different RS-inducing drug. Furthermore, we aim to find some strategies to overcome this resistance and new therapeutic opportunities for OCCC.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-12	*Cancer*	KAHIL Mira	C3M

Combination therapy with YAP/TEAD and RAS inhibitors overcomes phenotypic cell plasticity-driven resistance in NRAS-mutated melanoma

Mira Kahil [1,2], Walaa Mohager [1,2], Frédéric Larbret [1,2], Nicolas Dumaz [3], Lionel Larue [4], Marcel Deckert [1,2], Sophie Tartare-Deckert [1,2]**

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Melanoma is the most aggressive skin cancer, characterized by remarkable cancer cell plasticity, contributing to intra-tumoral heterogeneity and therapeutic resistance. NRAS-mutant melanoma remains a clinical problem, particularly in patients who do not respond to immunotherapies. As a second-line option, MEK inhibitors as single agents fail to provide a significant overall survival benefit. Therefore, there is an unmet need for new therapeutic strategies to improve the management of NRAS-mutant melanoma. Here we assessed in vitro and in vivo the response of NRAS-mutant melanoma cells to RMC-6236, a novel non-covalent inhibitor of both oncogenic and wild type RAS isoforms currently undergoing clinical investigation in various cancers.

Our transcriptomic and proteomic analyses revealed that the anti-proliferative effect of RMC-6236 on NRAS-mutant melanoma cell lines is characterized by a phenotypic transition towards a less differentiated state, with increased expression of mesenchymal and extracellular matrix remodeling markers, along with the activation of a YAP-driven transcriptional signature and focal adhesion kinase (FAK) signaling. In vivo RMC-6236 slowed tumor growth and improved mouse survival. Melanoma cells treated with RMC-6236 in vivo exhibited reduced pigmentation and expressed mesenchymal and neural crest stem cell markers and YAP-target genes. The combination of RMC-6236 and IAG933 a YAP-TEAD inhibitor synergistically reduced proliferation prevented phenotypic transition, and induced apoptosis.

These findings suggest that YAP-TEAD pathway inhibition by IAG933 targets the adaptive response induced by RMC-6236 and enhances treatment efficacy.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-13	*Physiopathology*	CLARY Raphaëlle	C3M

Implication of REDD1 in the regulation of cGAS/STING pathway

Raphaëlle Clary, Karine Dumas, Jérôme Gilleron, Jennifer Jager, Inès Mucel, Brice Angot, Mireille Cormont, Jean-François Tanti and Sophie Giorgetti-Peraldi

Obesity is characterized by the expansion of adipose tissue (AT). It is a major public health issue due to its comorbidities, such as type 2 diabetes, liver diseases, cardiovascular diseases and cancer. Expansion of AT leads to its dysfunction with the development of inflammation, hypoxia, oxidative stress, and mitochondrial dysfunction.

Mitochondrial dysfunction within the AT participates in the development of insulin resistance by few mechanisms among others (i) the activation of Serine / Threonine Kinases that inhibit the insulin pathway and (ii) the generation of oxidative stress, for instance, through the phosphorylation of p38MAPK and the increase of NRF2 expression.
Mitochondrial dysfunction also leads to the activation of the inflammatory pathway cGAS/STING described to recognize cytosolic dsDNA. Moreover, literature has shown that the cGAS/STING pathway is upregulated in the AT of obese mice.

In our team, we investigate molecular mechanisms behind the AT dysfunction, and we identified the stress response protein REDD1 (Regulated in Development and DNA Damage responses-1), a mTORC1 inhibitor, as one of the possible actors of insulin resistance in the AT of obese mice.

In this work we investigate whether REDD1 is involved in the regulation of the cGAS/STING pathway.

Downregulation of REDD1 expression in 3T3-L1 adipocytes with siRNA (siREDD1 adipocytes) leads to (i) an upregulation of the expression of oxidative stress markers such as NRF2 and the phosphorylation of p38 MAPK and (ii) an increase of the expression of cGAS, STING and the phosphorylation of TBK1 (substrate of the cGAS/STING pathway).
To determine if the mechanisms behind the regulation of cGAS and STING by REDD1 are (i) dependent on mTORC1 signaling pathway and oxidative stress, we used rapamycin (known mTORC1 inhibitor) and N-Acetyl Cysteine (an antioxidant). Both those treatments showed a decrease in the expression of cGAS and STING compared to the untreated siREDD1 adipocytes suggesting that the regulation of the expression of cGAS and STING by REDD1 depends on both mTORC1 and oxidative stress.
We correlated those observations with an *In vivo* heterozygous mouse model for REDD1 (REDD1+/- mice). REDD1+/- mice were insulin resistant and displayed increased oxidative stress markers (NRF2 and P-p38MAPK) and cGAS and STING compared to wild-type mice.

This work suggests that REDD1 regulates the cGAS/STING pathway, and it appears that the mechanism is mTORC1 and ROS-dependent. The link between REDD1, mitochondrial dysfunction and cGAS/STING pathway is still under investigation.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-14	*Development*	VAYANKARA EDACHOLA Sreeparvathy	iBV

Plasticity, composition and function of stress-induced RNA condensates

Sreeparvathy Vayankara Edachola, Alia Bahri, Andrés Cardona, Hiba Laghrissi, Chloé Leray, Karine Jacquet, Sami Rouquet, Arnaud Hubstenberger.

The maintenance of cellular homeostasis requires precise spatiotemporal regulation of gene expression, often achieved through an interplay of RNA translation, repression and decay. Repressed mRNA-protein complexes, at high cytosolic concentrations, can cluster together to form membrane-less RNA granules capable of regulating mRNA storage, localization, translation and decay. This is particularly notable during environmental stress conditions, where large-scale translation inhibition leads to the formation of *de novo* stress granules and growth of constitutive P-body like condensates. Using the *C. Elegans* germline as a model system, we investigate the plasticity, composition and function of stress-induced RNA condensates to study RNA organization during physiological stress and determine if these granules are protective, pathological or just correlative in the cellular adaptation to stress.

By visualizing RNAs at single-molecule resolution in oocytes, we show that heat shock induces mRNA hyper-compaction in insoluble aggregates and promotes embryonic lethality. However, pre-organizing mRNA into quiescence-induced condensates before the heat shock reverses these phenotypes, suggesting the importance of condensate organization in cellular adaptability. Additionally, in order to determine the changes in condensate composition upon different kinds of stress and investigate their role in cellular adaptability, stress-induced RNA granules at 4°C and 32°C were purified through FAPS and sequenced. The data demonstrates how, through their composition and selectivity, these condensates regulate the cellular stress-induced transcriptomic changes. Overall, our study provides a comprehensive understanding of the regulation of mRNA transcriptome *in vivo* during physiological stress.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-15	*Biochem/Immunology*	ABDEL SATER Alice	IPMC

Mapping the immunodominant epitopes in PLA2R1, the major autoantigen in membranous nephropathy

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Membranous nephropathy (MN) is a rare but severe autoimmune kidney disease, with an annual incidence of about 1 case per 100,000 individuals. MN is characterized by the presence of immune complexes at the glomerular basement membrane, leading to podocyte injury and heavy proteinuria. The autoantigens associated with MN have remained elusive for 50 years. In 2009, our team and collaborators from Boston University identified PLA2R1 (phospholipase A2 receptor 1) as the major autoantigen, with circulating anti-PLA2R1 autoantibodies present in 55% of MN patients.

PLA2R1 is a 180-kDa transmembrane receptor with a large extracellular region comprising 10 domains: a cysteine-rich domain (CR), a fibronectin-like type II domain (FnII) and eight C-type lectin-like domains (C1-C8). We have shown that anti-PLA2R1 autoantibodies target conformational epitopes in up to 5 PLA2R1 domains, with immunodominant epitopes in CR and/or C1 domains. These findings classify patients into iCR (60%) and iC1 (40%) groups, with different clinical outcome and response to treatment.

A major objective of my thesis is to identify the exact conformational epitopes within the CR domain (129 amino acids and 3 disulfide bonds). To overcome the challenges of conformational epitope mapping, we generated 184 single-point mutants (including alanine scanning and other point mutations) and 69 domain chimeras covering the full CR domain. All mutants were validated for expression and proper folding in HEK293 cells by western blot and ELISA. The mutants were then tested for reactivity against 9 patients'sera (iCR/iC1), from France and Taiwan, and 6 recombinant monoclonal antibodies (mAbs) cloned from Taiwanese patients. We identified a single major epitope region targeted by all patients. This region consists of at least two discrete neighboring epitopes but is clearly distinct from the one previously proposed by others.

To definitively validate our findings, we want to determine the structure of CR-antibody complexes by X-ray crystallography and cryo-EM. Toward this goal, we have already produced recombinant CR domain and PLA2R1 soluble form in mg amount, and we are currently producing single-chain variable fragments (scFv) and Fragment antibodies (Fab) from patient's mAbs. Soluble PLA2R1 and CR domain will be assembled with scFv and Fab proteins to form complexes that will be used in X-ray crystallography and cryo-EM experiments. All this work will be expanded to C1, the second immunodominant epitope domain. The knowledge of the exact immunodominant epitopes will improve diagnosis and prognosis, and pave the way for specific therapies.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-16	*Immunology*	REZAPOVA Valeriia	LP2M

Dynamics in Osteoclasts: A Single-Cell Perspective on Fusion and Fission

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Osteoclasts (OCLs) are large, multinucleated cells responsible for bone resorption. They acquire their multinucleation through fusion of mononucleated precursors. OCLs can undergo fission forming osteomorphs - daughter cells that can migrate more efficiently and rapidly through bone marrow and bloodstream, and after form osteoclasts on a needed for resorption area by another cycle of fusion (McDonald et al., 2021). Despite this, the dynamic behavior of osteoclasts remains poorly understood.

In our study, we performed computational analysis of single-cell RNA sequencing (scRNA-seq) of cells with diYerent nuclear content (1N, 3–4N, and 5–6N), obtained after 4 days of bone marrow cell cultivation with M-CSF and RANKL. Osteoclast samples displayed varying number of RNA and genes per cell depending on multinucleation. Clusterization revealed 7 clusters, 2 of which were unique to multinucleated cells. All clusters expressed osteoclast markers, suggesting lineage commitment occurs at the precursor stage.

Velocity analysis showed the estimated initial and final clusters and this result was used for the trajectory inference (TI) analysis. TI analysis could split cells into 2 major lineages with endpoints of cluster with high bone resorption activity (cluster 6) and cluster with intermediate bone resorption and immunity function (cluster 5). Cluster 5 was associated with osteomorph markers.

To further investigate the developmental trajectory, our data were integrated with pre-osteoclast and osteoclast clusters from a published dataset (Tsukasaki et al., 2020). Cluster 5 did not correspond to any cluster in the reference dataset, suggesting that osteomorphs may arise specifically after 4 days of RANKL stimulation. Moreover, cluster 5 lacked expression of previously described markers of two OCL subpopulations, CD16/32 and CD200. Interestingly, CD16/32 expression peaked in 3–4N cells, whereas CD200 peaked in 5–6N cells. These findings were corroborated by flow cytometry (FACS) analysis.

Our study reveals novel insights into the transcriptional heterogeneity and dynamic behavior of osteoclasts during multinucleation. The differential expression of CD16/32 and CD200 across nuclear stages highlights previously unrecognized complexity in OCL subpopulations. Further validation of markers of cluster 5, enriched for osteomorph, is required.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-17	*Cancer*	PUJALTE MARTIN Marc	C3M

PEACH (ProstatE And Cancer Hypusination): Leveraging artificial intelligence (AI) to uncover the hidden role of eIF5A hypusination in prostate cancer

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INTRODUCTION : The oncogenesis of prostate cancer (PCa) involves the activation of the eukaryotic translation initiation factor 5A (eIF5A), whose function is critically dependent on hypusination—a unique post-translational modification involving the conjugation of the aminobutyl group of spermidine to a specific lysine residue. The PEACH study aims to investigate the expression of hypusinated eIF5A (eIF5Ahyp) in PCa.

METHOD : The PEACH study analyzed 70 prostate tissue slides collected from patients treated at the CHU of Nice and the Antoine Lacassagne Center. Slides were immunolabeled using AMACR, PanCK, DAPI, total eIF5A (eIF5Atot), and eIF5Ahyp. Since PCa is a multifocal disease, we delineated the tumoral and non-tumoral regions. Whole-slide imaging was performed using the Vectra Polaris scanner (Akoya, Villebon-sur-Yvette, France), and the HALO Image Analysis Platform (Indica Labs, Albuquerque, NM, USA) was used to train an AI-based classifier. The algorithm was trained to detect AMACR-positive cancer cells in tumoral regions and PanCK-positive glandular cells in non-tumoral regions and subsequently applied to quantify eIF5Atot and eIF5Ahyp expression. RNA-seq data related to eIF5A expression were retrieved from the and subsequently analyzed.

RESULTS : Seventy patients were included (2015–2020), with a median age of 67 years. Initial PSA was <10 in 34% of cases. The tumor stages were T2 (24%), T3 (75%), and T4 (1%), with 17% showing nodal involvement. Gleason scores were ≤7 in 61% and >7 in 39% of patients. At the time of analysis, 20% of patients were deceased. Out of the 70 slides, 38 have been analyzed so far. eIF5Ahyp expression was significantly higher in tumoral cells compared to non-tumoral prostate tissue, with a predominant nuclear localization (mean difference in labeled intensity: 28 (95% CI: 24 – 32; $p<0.0001$). No statistically significant correlation was found between eIF5Atot or eIF5Ahyp expression and nodal status (metastasis), Gleason score, or TNM classification.

CONCLUSION : The PEACH study demonstrates that eIF5Ahyp is overexpressed in prostate cancer cells, particularly within the nucleus, relative to non-tumoral tissue. Given its role in mRNA transport, this nuclear enrichment may suggest a functional contribution of eIF5Ahyp to PCa progression.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-18	*Developmental Bio*	NOGUÈRES Margot	iBV

Study of RNA regulation in axonal regrowth

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Axonal regeneration failure is a hallmark of neuronal circuit disruption in neurodegenerative diseases and traumatic injuries, highlighting the need to better understand the molecular mechanisms of axonal regrowth. To address the mechanisms underlying axonal regrowth, we use a robust and stereotyped developmental model characterized by the conservation of molecular players involved in post-traumatic axonal regrowth. Axonal regrowth is governed by a spatiotemporal control of gene expression regulated by RNA-Binding Proteins (RBPs), which control the transport and local translation of mRNAs in neurons. Our group has shown that the conserved RBP Imp/ZBP1 and its target mRNA, profilin, mediated the developmental axonal regrowth of *Drosophila* gamma neurons, which are essential for memory and sociability. Yet, how *imp* function is regulated in space and time in different neuronal contexts is still unclear.

The objective of my PhD is to characterize the general and conserved molecular mechanisms regulating mRNA transport during axonal regrowth. By combining genetic and cellular approaches, I have demonstrated that imp controls developmental axonal regrowth of CCAP/Bursicon neurons by regulating the expression of its target mRNA, profilin, which encodes an actin filament nucleator facilitator. To identify new regulators of imp function in axonal regrowth, the lab carried out an unbiased genetic screen using the CCAP/Bursicon neurons. From the 88% of Drosophila genome that have been covered, I recently identified twelve genes that regulate imp function in axonal regrowth. This study will provide new insights into the post-transcriptional mechanisms underlying developmental axonal regrowth that may also hold true in a post-traumatic context.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-19	*Cancer*	ECHAVIDRE William	CSM

β1-Integrin as a Key Regulator of Stemness and Radioresistance in Medulloblastoma

Medulloblastoma (MB) is a highly aggressive pediatric brain tumor, where a persistent stem-like phenotype drives recurrence and resistance to standard treatments, notably radiotherapy (RT). Identifying key regulators of MB stemness is essential to improve therapeutic outcomes. Among them, β1-integrin (ITGβ1), a known mediator of tumor progression in adult brain cancers, remains understudied in MB.

Through mRNA profiling of multiple MB cell lines, we observed a strong enrichment of ITGβ1 expression, particularly via the laminin-binding α6β1-integrin heterodimer, highlighting the tumor microenvironment's crucial role for sustaining MB stemness. To unravel ITGβ1's functional relevance, we generated ITGβ1-knockout (KO) D458 cells using CRISPR-Cas9. Loss of ITGβ1 impaired the expression of core stemness markers such as NESTIN and NOTCH-1, and markedly enhanced radiosensitivity as evidenced by sustained DNA damages post-RT, implicating ITGβ1 in radioresistance mechanisms. In vitro results were supported in vivo, where mice bearing ITGβ1 KO orthotopic tumors exhibited a twofold increase in survival post-RT. Importantly, high ITGβ1 expression strongly correlates with poor prognosis in the Cavalli MB patient cohort (R2 Genomics Platform), reinforcing its clinical and therapeutic relevance.

Pharmacological blockade of ITGβ1 with a monoclonal antibody in both D458 and CHLA-01-MED cells mirrored the effects of genetic depletion. Mechanistically, ITGβ1 targeting disrupted major signaling hubs, including FAK, AKT, and ERK, pathways known to orchestrate stemness maintenance and therapeutic evasion. Altogether, our findings establish ITGβ1 as a pivotal driver of MB stemness and resistance to radiotherapy. Therapeutic inhibition of ITGβ1 emerges as a promising strategy to sensitize MB cells to RT and improve patient outcomes.

Keywords: Medulloblastoma, β1-Integrin, Stemness, Radioresistance.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-20	*Physiopathology*	SCRIBE Célia	IPMC

A FGFR3 decoy receptor attenuates lung fibroblast-to-myofibroblast transition and pulmonary fibrosis

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Lung fibrosis, including idiopathic Pulmonary fibrosis (IPF), results from dysfunctional wound repair involving different cell types, fibroblasts, epithelial cells and macrophages, which respond to multiple soluble and matrix factors. Fibroblast growth factor (FGF) signaling has been implicated in the pathogenesis of lung fibrosis, in the regulation of fibroblast to myofibroblast transition (FMT), cell proliferation, and extracellular matrix (ECM) production. However, individual FGF family members may exert pro- and anti-fibrotic effects, depending on the responding cell, the expression levels of the different FGF receptors (FGFR1-4) and the context of other signaling molecules, such as Transforming growth factor β (TGF-β). In order to better understand the complex functions of FGFs on pulmonary fibrosis, we evaluated the effect of a modified version of a FGFR3 decoy receptor [1], that specifically sequesters FGFR3 ligands, including FGF1, FGF2 and FGF9 as a potential anti-fibrotic drug. The effect of several FGFs in the presence or the absence of the FGF ligand trap was evaluated in vitro on human lung fibroblasts from healthy donors or from IPF patients on various fibrotic parameters such as cell proliferation, cell contraction, ECM production and modulation of signaling pathways. The effect of the FGF ligands trap was also assessed in vivo on the bleomycin mouse model, by monitoring mice body weight, Ashcroft score, hydroxyproline and soluble collagen content. Our results revealed that FGFs (mainly FGF2) stimulate fibroblast proliferation, contraction, ECM production and expression of various fibrotic markers such as chemokine ligand 2 (CCL2), connective tissue growth factor (CTGF), interleukin 6 (IL6), interleukin receptor 4 (IL4R) or ECM-related genes like fibronectin (FN1). The FGF ligands trap was able to reduce this FGF mediated pro-fibrotic phenotype and to desensitize IPF cells to the TGF-β canonical pathway. In the bleomycin lung fibrosis mouse model, the FGF ligands trap partially reversed lung fibrosis, as evidenced by a reduced body weight loss as well as diminution of the aschcroft score, hydroxyproline and soluble collagen content in lung samples. In conclusion our data highlight the interplay between the TGF-β and the FGF signaling pathways in pulmonary fibrosis and demonstrate the potential of targeting FGFR3 signaling as a novel therapy for IPF.

[1] D. Gonçalves et al., « In vitro and in vivo characterization of Recifercept, a soluble fibroblast growth factor receptor 3, as treatment for achondroplasia », PLOS ONE, vol. 15, no 12, p. e0244368, déc. 2020, doi: 10.1371/journal.pone.0244368.

Keywords: Idiopathic Pulmonary Fibrosis, fibroblasts growth factors, myofibroblasts, soluble receptor, TGF-β pathways, cytokines..

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-21	*Plant Biology*	DUSSUTOUR Ange	ISA

Secretion of small non-coding RNA as new effectors in plant-nematode interaction

Ange Dussutour, Yara Noureddine, Martine da Rocha, Jérôme Zervudacki, Ann Po Cheng, Lionel Navarro, Arne Weiberg, Bruno Favery and Stéphanie Jaubert.

Root-knot nematodes (RKN) of the *Meloidogyne* genus are among the most destructive plant pathogens, causing significant agricultural losses amounting to billions of dollars each year. These plant-parasitic nematodes induce the formation of galls in root systems by inducing the dedifferentiation of few parenchyma cells into specialized giant, polynucleated, and hypermetabolic feeding cells that serve as nutrient sinks essential for their life cycle. This dramatic reprogramming of root cell identity is driven by *Meloidogyne* effectors secreted in root cells that manipulate host defense and gene expression. Since its discovery in the past decade, cross-kingdom RNA interference (RNAi) has emerged as a new mode of communication, based on the exchange of small non-coding RNAs (sncRNAs) that hijack RNA silencing pathways between interacting organisms. This raises the question of whether *Meloidogyne*-secreted sncRNAs play a role in the extensive gene expression reprogramming of root cells, facilitating the formation and maintenance of nematode-induced giant feeding cells. To investigate this, we performed immunoprecipitation of plant Argonaute 1 (AGO1) from infected roots followed by small RNA sequencing. Our analysis identified nine *Meloidogyne*-secreted microRNAs (miRNA) associated with *Solanum lycopersicum* AGO1. Similar experiments were also performed with *Medicago truncatula* and *Arabidopsis thaliana* infected roots to investigate if these secreted nematode miRNAs were specific of the host species. We identified two miRNAs secreted in all plant species which are known to be secreted by animal parasitic nematodes through vesicles. Using degradome sequencing, RNA sequencing, and computational target prediction algorithms, we identified the putative plant targets of these nematode secreted miRNAs whose cleavage activity of these target by min-miRNA was validated using dual-luciferase assay. Characterizing these secreted sncRNAs opens new perspectives on plant-RKN molecular dialogue and offers potential strategies for developing novel pest management approaches.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-22	*Biochemistry/Plant Bio*	MENUET Killian	ISA

Role of aphid MIF1 (Macrophage Migration Inhibitory Factor) protein on plant cell death

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Aphids are among the world's most common plant parasites, causing serious damage to agricultural crops. Green peach aphid populations have developed resistance to various regularly used pesticides, necessitating the development of new management techniques. Despite their significant impact on agriculture and food production, the molecular processes underpinning aphid–plant interactions remain largely unknown. Our recent work demonstrates that a macrophage migration inhibitory factor (MIF) is released in aphid saliva during feeding and suppresses host plant immunity by reducing cell death processes.

MIFs (Macrophage Migration Inhibitory Factors) are crucial pro-inflammatory cytokines conserved across kingdoms. In both vertebrates and invertebrates, MIFs play essential roles in regulating inflammatory responses, cell death, and cell proliferation. To better understand the role of aphid MIFs in the inhibition of plant cell death, we conducted morphological, cellular, molecular, and biochemical analyses to determine the type of cell death prevented by aphid MpMIF1 (Myzus persicae MIF1). Microscopic analysis revealed that MpMIF1 preserves cell and organelle morphology while protecting against endoplasmic reticulum and cytoskeletal stress.

Gene expression analysis showed that MpMIF1 significantly impacts key genes and proteins involved in cell death and regeneration. To investigate MpMIF1's effect on the DNA Damage Response (DDR), we performed γH2AX immunolocalization (a biomarker for DNA double-strand breaks (DSBs)) within plant cells. Our results revealed that MpMIF1 reduces H2AX phosphorylation, thereby decreasing DSB formation in the presence of a cell death inducer. These findings suggest that MpMIF1 may play a critical role in DDR in plants following biotic stress.

Moreover, in mammals, MIF proteins are known to negatively regulate p53 and Caspase-3 while activating MAPK signaling pathways. In our system, we found that MpMIF1 negatively affects SOG1 expression (the functional analog of p53) and Caspase-3-like activity (DEVDase) while increasing phosphorylation of MAPK Erk1/2 signaling in plants.

Interestingly, similar to the MIF-p53 interaction in mammals, our Spit-Luciferase and co-immunoprecipitation assays demonstrated that MpMIF1 physically interacts with the SOG1 protein. Since SOG1 and p53 do not share sequence similarity but perform analogous functions, this result suggests a remarkable conservation ofregulatory mechanisms between plants and mammals.

These findings provide valuable insights into the effects of aphid MIF on plant immune responses. Future biochemical analyses will further explore the molecular pathways affected by MpMIF1 to identify its molecular ligands inside the plant cell. These insights could facilitate the development of biocontrol techniques to mitigate the likelihood of resistance development.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-23	*Cancer*	LOPES GONÇALVES Rafael	IPMC

Highlighting the coding potential of the long non-coding RNA LUCAT1 associated with the aggressiveness of lung adenocarcinomas

Lung cancer is the most commonly diagnosed malignancy and the leading cause of cancer-related death worldwide. Adenocarcinoma (LUAD) is the most common subtype of non-small cell lung cancer (NSCLC), accounting for almost 40% of NSCLC cases, with a 5-year survival rate of around 20%. Many long non-coding RNAs (lncRNAs) are deregulated in cancer and are important regulators of gene expression. Their highly varied modes of action often involve their association with proteins (RBPs) that carry the enzymatic activity of ribonucleoprotein complexes (cRNPs). Our team is interested in a long non-coding RNA, LUCAT1, which is overexpressed in lung adenocarcinoma and correlates with the hypoxic status of tumours and a poor prognosis in patients. Having already shown a role in proliferation, invasion and the regulation of oxidative stress, this lncRNA is not found in all the cell types composing the respiratory epithelium. In this area, our aim is to identify the roles of LUCAT1 in a reconstituted respiratory epithelium and during its differentiation using CRISPR-Cas9 and in situ hybridisation approaches. One of our hypotheses is that LUCAT1 could mediate one of its roles by expressing a peptide via a smORF within its sequence. We have already been able to demonstrate the association of our RNA with polysomes using polysome profiling coupled to RT-qPCR. We have also demonstrated transient and stable expression of a peptide in several cell lines for which we have also generated CRISPR-dCas9 knockdowns. Our initial data suggest that this transcript may encode a peptide, but further work is required to demonstrate its endogenous existence and to clarify its involvement in the hypoxic response and in the different cell subtypes of the respiratory epithelium.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-24	*Cancer*	GERARD Alexandre	LP2M

Belatacept safety: insights from Pharmacoepidemiological and Pharmacovigilance data

Background:
Belatacept, a selective T-cell co-stimulation blocker, has emerged as a promising alternative to calcineurin inhibitors in kidney transplant recipients (KTR), avoiding their nephrotoxicity and cardiometabolic adverse drug reactions (ADRs). However, uncertainties remain regarding its safety profile, particularly outside controlled clinical trials. While real-world observational data have raised concerns about acute allograft rejection (AR) and infectious complications, especially during early post-transplant conversion, global pharmacovigilance data offer a complementary lens for detecting ADRs that may be underrepresented or mischaracterized in regulatory documents.

Methods:
We conducted two complementary studies. First, a retrospective cohort analysis was performed using the DIVAT multicenter French transplant database, including 392 adult KTRs treated with belatacept. Patients were stratified by timing of conversion (early ≤1 year vs. late >1 year post-transplant), and outcomes included AR incidence, infectious complications, and associated risk factors. Second, we analyzed post-marketing safety data from VigiBase®, the WHO global pharmacovigilance database, using disproportionality analyses (Information Component) to compare belatacept-related signals to the Summary of Product Characteristics (SmPC).

Results:
In the DIVAT cohort, AR occurred in 5.6% of KTRs (1.4 per 100 patient-years), with early conversion, prolonged warm ischemia, and positive hepatitis B surface antibodies as independent predictors. Infections, including CMV and pulmonary infections, were more frequent in early converters, though not always statistically significant. In VigiBase®, 2795 belatacept-related reports were identified, including 15.2% with fatal outcomes. Fifty-one potential safety signals, such as *Clostridium difficile* infection, hepatitis B reactivation, and hemophagocytic lymphohistiocytosis, were not listed in the SmPC. Conversely, one-third of labeled “common” or “very common”, ADRs such as Cushing’s syndrome or depression, had fewer than three reports, suggesting limited real-world relevance.

Conclusion:
These two complementary approaches highlight the evolving safety profile of belatacept. While real-world data confirm a relatively low AR rate, particularly with delayed conversion, early use may pose higher immunological and infectious risks. Pharmacovigilance analysis revealed potential unrecognized ADRs and questioned the relevance of some labeled reactions. Together, these findings underscore the need for periodic and multimodal reassessment of belatacept’s safety profile to inform practice and regulatory decisions.

OC-25	*Physiopathology*	HABBOUCHE Lama	C3M

Deciphering the role of IRE1α endoribonuclease activity in liver fibrosis

Background & aims : Liver fibrosis is the common response to chronic liver injury and leads to cirrhosis and its complications. Fibrosis is considered a poor prognostic predictor of liver disease progression and is becoming a major healthcare concern worldwide. However, there is still no effective, curative pharmacological treatment. Therefore, understanding the mechanisms underlying the onset of hepatic fibrosis is crucial to prevent its progression to terminal stages.
The onset of endoplasmic reticulum (ER) stress during the early stages of hepatic complications, along with persistent inflammation, are key driving forces in liver fibrosis progression. However, their exact roles in fibrosis progression remain to be fully explored. Additionally, liver collagen deposition associated with hepatic fibrosis is primarily dependent on the proliferation, differentiation, and activation of hepatic stellate cells (HSCs). The role of hepatocytes in this collagen deposition process, however, is not yet fully understood.
Thus, it is critical to identify a key regulator of these processes to prevent the development of fibrosis and its progression to terminal stages.
IRE1α, a transmembrane protein of the endoplasmic reticulum, has been implicated in various diseases, but limited studies have evaluated its role in liver fibrosis. Therefore, we explored the contribution of this crucial protein, particularly its endoribonuclease (RNase) activity, to liver fibrosis in patients and mice, as well as its regulation of hepatocyte and HSC functions.

Methods : Hepatic RNase IRE1a was evaluated in two mice models of fibrosis and in obese patients with metabolic dysfunction-associated steatotic liver disease (MASLD).
Its role in liver fibrosis was evaluated in a specific RNase IRE1a knock out mice (Ern1HepΔR) and human and murine hepatic stellate cell line (LX2 and GRX) and Hepatocytes (THLE2 and AML12).

Results : Here, we report that hepatic RNase IRE1α expression correlates with liver injury and fibrosis in various mouse models of fibrosis. Interestingly, RNase IRE1α deficiency conferred a protective effect against liver injury and fibrosis in a diet-induced fibrosis model. Its hepatic gene expression was also upregulated in liver fibrosis and correlates with liver injury in biopsy-proven MASLD patients.
In hepatocyte and hepatic stellate cell (HSC) lines, silencing of IRE1α, particularly its RNase activity, resulted in a reduction in the synthesis and secretion of collagen. The IRE1a silencing also strongly prevented the TGFß-mediated HSC and Hepatocyte cell activation as shown by decreased expression of pro-fibrogenic mediators (Acta2, Pdgfr and Tgfb). Overall, we were able to highlight the key role of IRE1α, especially its RNase activity, in the regulation of hepatocytes and stellate cells.

Our results highlight the fact that hepatocytes are the drivers of liver fibrosis. To investigate this, we generated mice deficient for the RNase activity of IRE1α specifically in hepatocytes (Ern1HepΔR) and fed them a diet that induces fibrosis. We observed the following: 1) decreased inflammation in Ern1HepΔR mice, 2) preserved resident macrophages (Kupffer cells) with reduced pro-fibrogenic polarization of monocyte-derived macrophages (MoMacs) in Ern1HepΔR, 3) attenuation of fibrosis in Ern1HepΔR mice, and 4) decreased cell death (apoptosis) in Ern1HepΔR mice.

Conclusion : Collectively, these data could suggest an important role of RNase IRE1a in the pathogenesis of liver fibrosis by regulating the activation, the synthesis and secretory profile of Hepatocyte and hepatic stellate cells.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

Neuro/Development	MORA ROMERO Bella	Ulysseus

Microglial electron transport chain sustains brain development with different roles for each complex

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Microglia are the brain innate immune cells with relevant functions during development, adult maintenance, and the progression of brain diseases. Microglial function is highly dependent on metabolic adaptations. Previous data suggest that similar to monocyte-derived cells, microglial activity depends on a metabolic switch from aerobic (dependent on the mitochondrial oxidative phosphorylation system –OXPHOS–) to anaerobic glycolysis. However, we and others have shown that microglial activity is correlated with the transcriptional upregulation of OXPHOS, suggesting their requirement for normal microglial activation during the critical developmental period or the activation associated with neurological disorders. To further investigate the role of the electron transport chain in microglial function during development, we generated mouse models deficient for either Complex I or Complex III activity in microglia (MGcCI or MGcCIII) from the embryonic stage. Previously (Mora-Romero et al., 2024)[1], we characterized the MGcCI mouse model and demonstrated that the lack of CI in microglia strongly reduces ATP levels and increases NADH, suggesting reductive stress. Remarkably, MGcCI microglia is highly active at the transcriptional level, passing from a functional and morphological active state at juvenile age (1 month old) to a dysfunctional state at adult age (3 months old). Moreover, MGcCI mice develop behavioral deficits and early lethality at three months old. To better understand the mechanisms underlying these phenotypes, we generated the MGcCIII mouse model. As expected, MGcCIII microglia show a stronger ATP reduction than MGcCI microglia but a milder decrease of the NADH levels. However, MGcCIII microglia do not show signs of dysfunctionality until 10 months of age, when animals start to develop behavioural problems and start to die prematurely. Therefore, we propose that there might be additional mechanisms beyond the lack of ATP that explain the stronger/earlier phenotype observed in MGcCI animals compared to the MGcCIII model. To decipher these mechanisms, we are currently conducting a battery of experiments including metabolomics and epigenomics assays.

References

[1] Mora-Romero, B. et al. Microglia mitochondrial complex I deficiency during development induces glial dysfunction and early lethality. Nat. Metab. https://doi.org/10.1038/s42255-024-01081-0 (2024).

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

Host/Patho Interactions	GONZALEZ ROVIRA Maria	Ulysseus

Microbial signatures in the womb as determinant in the foetal exposome

Introduction / Objectives
The prenatal exposome plays a critical role in shaping foetal immune development, influencing both immune tolerance and postnatal immune programming. Among the various factors that make up this exposome, prenatal microbial colonization - particularly within the amniotic fluid (AF)- may be a key contributor. This study aims to investigate the presence of microorganisms in the AF of healthy pregnant women by employing both culture-based techniques and advanced sequencing technologies.

Methodology
A total of 148 pregnant women from three hospitals in Seville, Spain, were aseptically recruited, with 154 AF samples collected at two distinct gestational stages: amniocentesis (n=127, between weeks 13 and 33) and elective caesarean sections (n=27, at ≥37 weeks). The inclusion criteria for sample analysis in our laboratory were based on rigorous quality control standards, including the absence of blood and a minimum sample volume requirement. Consequently, 12 AF samples were excluded from the study. The presence of viable microorganisms was assessed using culture methods, followed by identification via 16S rRNA gene sequencing. Additionally, two complementary metagenomic approaches were employed for genomic DNA analysis: 16S rRNA gene sequencing with PacBio technology and shotgun metagenomic sequencing on the Illumina platform.

Results
Cultivable microorganisms were detected in 33.1% of the analyzed samples. 96.7% of the amniocentesis plate yielded a single colony, whereas the caesarean section samples exhibited a more diverse pattern. 16S rRNA sequencing revealed bacterial taxa from the phyla Firmicutes, Actinobacteria, Proteobacteria, Bacteroidetes, and Fusobacteria. The most common genera detected by both culture and sequencing were Bacillus, Cutibacterium, and Staphylococcus. In contrast, shotgun sequencing facilitated the identification of the complete genome of Phyllobacterium. Beta diversity analysis revealed no significant differences across gestational stages, collection centres, or foetal diagnoses. The negative controls indicated the minimal background of the process.

Conclusions
These findings suggest that viable bacteria and/or their DNA can access the prenatal environment prior to birth. However, their presence may be transient and regulated by maternal and foetal immune mechanisms. The use of complementary techniques emphasizes the importance of an integrated methodological approach to achieve a deeper understanding of the potential role of microorganisms in foetal development.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-26	*Neurobiology*	DEBORD Juliane	IPMC

The PINK1 – alpha-synuclein interplay in Parkinson's disease

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Parkinson's disease (PD) is a movement disorder characterized by dopaminergic neurons degeneration. The main histological hallmarks are intracytoplasmic inclusions of protein aggregates, called Lewy bodies, the major component of which is aggregated alpha-synuclein (asyn). Thus, PD is classified as a proteinopathy like other age-related neurodegenerative diseases.

The complete set of pathological dysfunctions in PD is not yet fully understood. In neurodegenerative diseases, the protein degradation paths, the proteasome pathway and autophagic pathways, are defective. Several genes deregulated in PD (SNCA, PINK1, PRKN, etc.) are linked to these pathways. Indeed, the kinase PINK1, the encoding gene of which is associated, when mutated,to a subset of early autosomal recessive forms of PD, is a major actor in mitochondrial autophagy. Moreover, loss of function of PINK1 is associated with alterations in protein clearance paths and an increase in asyn aggregation. Interestingly, asyn controls its own degradation by modulating an autophagic pathway.

Our project aims at investigating the possible involvement of PINK1 in asyn control by autophagic intermediates.

Data obtained so far provide evidence that PINK1 controls asyn levels in vitro and mice brain. Interestingly we have identified a key lysosomal function modulator as a substrate of PINK1 and we are actually determining its implication in asyn regulation by PINK1. Depletion of PINK1 in vitro corroborates the implication of lysosomal intermediates in asyn regulation by PINK1. The next steps are to validate the PINK1 role in the control of asyn inmouseprimary culture neurons and post-mortem samples of sporadic PD brains.

Overall, our data unravel the existence of a novel signaling cascade by which PINK1 could modulate asyn expression and as corollary a new therapeutic pipeline based on PINK1 ability to control of asyn protein levels.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-27	*Immunology*	VU-TO Giang	IRCAN

Lack of MDA5 delays HSC aging partly by retaining proteostasis.

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Hallmarks of hematopoietic aging include dysfunction of hematopoietic stem cells (HSCs), characterized by reduced regenerative capacity, decreased differentiation potential, and a skewed bias toward the myeloid lineage. These aging-induced changes in HSCs result from the accumulation of dysregulated inflammatory signaling, DNA damage throughout their lifetime. In this study, we found the innate immune RNA sensor, melanoma differentiation-associated protein 5 (MDA5), as a critical regulator of HSC aging. Several hallmarks of aging were alleviated in the hematopoietic system of *Mda5*$^{-/-}$. *Mda5*$^{-/-}$ HSCs displayed reduced inflammation, both intrinsically and within their bone marrow (BM) microenvironment, alongside diminished accumulation of myeloid-biased and aged HSCs. Moreover, aged *Mda5*$^{-/-}$ HSCs maintained enhanced quiescence and superior repopulation capacity compared to wild-type (WT) HSCs during transplantation assays. Mechanistically, integrated genome-wide and single-cell transcriptomic analyses revealed that Heat Shock Factor 1 (HSF1), a master regulator of protein homeostasis (or proteostasis), acts as a key upstream modulator of aging-associated gene dysregulation in *Mda5*$^{-/-}$ HSCs. Consistent with this, aged *Mda5*$^{-/-}$ HSCs exhibited improved proteostasis, and inhibition of HSF1 reversed their youthful phenotypic traits in in vitro. Conversely, activating HSF1 in aged WT HSCs ameliorated age-related dysfunction, confirming HSF1's central role in mediating these effects.

Collectively, our findings demonstrate that MDA5 deletion mitigates HSC aging by tempering inflammatory signaling and sustaining proteostatic resilience through HSF1 activation. This highlights MDA5 as a potential therapeutic target to counteract the decline of hematopoietic function during aging.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-28	*System Biology*	OUAHMI Hajar	LP2M

eIF5A inhibition enhances hypoxia tolerance and improves islet transplantation outcomes

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Background. Pancreatic islet transplantation is an alternative for patients with Type 1 diabetes (T1D) but is limited by the number of islets available. Indeed, many islets are lost during the procedure from preparation to transplantation, mainly due to ischemia/reperfusion injury. In addition, a recipient requires three successive islet transplants, thus necessitating several donors. We have shown that GC7 (N1-guanyl-1,7-diaminoheptane), an inhibitor of eIF5A hypusination, improves the resistance of various cells and tissues to ischemia/reperfusion, including a pancreatic beta cell line. We therefore investigated the effect of GC7 on the quality and quantity of mouse pancreatic islets when used during the isolation procedure, and then on the functional recovery of these islets when transplanted into mouse models of T1D.

Methods. Pancreatic islets were obtained by digesting mouse pancreases with a collagenase/GC7
mixture. We then analyzed their short- and long-term survival, morphology, function and resistance to ischemia/reperfusion. Finally, a suboptimal number of these islets (~150) were transplanted under the renal capsule of T1D mice with severe hyperglycemia.

Results. Islets conditioned with GC7 showed improved survival at 24h and 72h and better protection against ischemia/reperfusion injury. T1D mice transplanted with a sub-optimal number of these islets showed better glycemic control with a -35% variation in blood glucose at D20 (vs. +6% for control islets) demonstrating better functionality and survival than control islets.

Conclusion. GC7-conditioned islets showed improved survival at 24 and 72 h and better protection against ischemia/reperfusion injury.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-29	*Biochemistry/Plant Bio*	SALADINI DI ROVETINO Marlen	ISA

Monitoring resistance of *Spodoptera frugiperda* populations from Thailand

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Spodoptera frugiperda is a lepidopteran pest, also known as the fall armyworm (FAW). This polyphagous insect feeds on more than 350 plant species, including maize and rice, and is causing significant yield losses. Moreover, it is an invasive species, native to America, but since 2016, it has gradually invaded other continents and reached Thailand for the first time in 2018. As a major pest, this species has been massively exposed to insecticides and *Bacillus thuringiensis* toxins and is currently resistant to 47 molecules, according to the Arthropod Pesticide Resistance Database. We wanted to investigate the insecticide resistance status of FAW populations present in Thailand. These populations were collected from maize fields in several locations. The two main insecticide resistance mechanisms were analyzed in these populations. The presence of target site mutations, which are known to confer resistance to insecticides, was monitored. Additionally, the expression level of the detoxification gene cytochrome P450 and the transcriptional factor that regulates these genes were followed. These data provide essential information for appropriate management in the field.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-30	*Neurobiology*	MANGEL Anthony	iBV

Postoperative shoulder surgery : study of the contribution of neurological cross-effects during the rehabilitation period

MANGEL Anthony, BRONSARD Nicolas, CHOPLIN Arnaud

Introduction : Epidemiological studies are projecting a rise of rotator cuff surgery in the coming decades. Patients are expected to go back to their professionnal activities within 8 months after surgery, which represents a substancial societal cost. Rehabilitation is recommended to help the patients recover, but to this day no rehabilitation method has proven its efficacy to reduce this delay.
Based on translational research in neurosciences, new methods are being tested. Cross education is a rehabilitation approach based on the observation that, during unilateral strengthening, adaptation of the central nervous system allows partial sharing of gains in motor skills, strength and mobility with the contralateral limb.
The addition of a strength cross education protocol to standard rehabilitation has been proven to be effective in the early recovery of strength, but not functionality, in unilateral orthopaedic patients populations.
We therefore propose to study the effectiveness of the addition of a cross education protocol based on motor skills to standard rehabilitation on the early functional recovery of patients who underwent rotator cuff repair.

Methodology : To this end, we plan to carry out a comparative clinical trial of superiority to a rehabilitation protocol based on international recommendations.
In order to investigate the existence of any barriers that patients in the experimental arm could express, we conducted non-structured interviews with patients who recently underwent a rotator cuff surgery.

Results : The results of the preliminary qualitative study showed that patients expressed only marginal resistance to the protocol.
Experimental protocol is in validation period with the clinical partners and will be then sent to the ethics comitee.

Discussion : Patients were motivated to stay active and to have a chance to accelerate their recovery, as long as the protocol was clearly explained and not too time-consuming. These elements enable us to design a patient leaflet to increase adherence and compliance with the experimental protocol.
The analysis of our results should allow us to study the efficacy of motricity-based cross education on the return to work delay and rate. It should also enable us to deepen our understanding about its clinical effects and its safetyness of use.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-31	*Cancer*	SIRERA Jessy	IRCAN

Targeting PSMD14 in metastatic renal cell carcinomas. A promising therapy?

Kidney cancer accounts for 3% of all adult cancers. 15 000 new cases are diagnosed annually in France and an associated mortality of nearly 4 000 cases. Clear cell Renal Cell Carcinoma (ccRCC) is the most widespread kidney cancer subtype, constituting 75% of kidney cancers with 315 000 new cases worldwide every year. Current standart of care include surgery (for early stage) and immunotherapy (immune checkpoint inhibitor) coupled with anti-angiogenics. However, therapeutic resistance occurs in 1/3 of patients, leading to relapse and poor prognosis. Identifying novel therapeutic targets is crucial to enhance treatment efficacy and maintain quality of life.

Déubiquitinases (DUBs) have recently gained attention in cancer research due to their role in regulating protein stability through the ubiquitin-proteasome system. Dysregulation of this system have been implicated in the aberrant stabilization of oncogenes proteins, contributing to tumorigenesis and poor clinical outcomes. In the context of RCC, the functional significance of DUBs remains poorly characterized.

Using a loss of function screening approach based on DUB siRNA library, we identified PSMD14 enzyme (26S proteasome non-ATPase regulatory subunit 14) as an essential gene required for the survival and proliferation of ccRCC cell lines.

Elevated expression of PSMD14 was correlated with reduced overall survival in mRCC patients. Immunohistochemical analyses confirmed increase expression of PMSD14 protein in tumor tissue, particularly during disease progression.

For the functional characterization, silencing of PSMD14 with specific siRNA induces ccRCC cell death and decreasing their proliferation, invasion, and migration. Pharmacological inhibition with Capzimin, a selective inhibitor of PSMD14, yielded similar anti-tumor effects and demonstrated preferential cytotoxicity in cancer cells compared to normal cells. Overexpression studies using lentiviral particles revealed that ectopic expression of PSMD14 enhances the aggressiveness of ccRCC cells, supporting its role as a tumor-promoting factor.

Our results highlight PSMD14 as a potential therapeutic target for ccRCC. To validate and expand investigations, further studies will focus on:

1. Identifying downstream substrates of PSMD14 that contribute to the aggressive phenotype of tumor cells.
2. Performing “In vivo” experiments:

- Microinjection of control or PSMD14 silenced ccRCC cells into the zebrafish larvae to measure the inhibition of the local and distal migratory capacities.

- Xenograft experiments in immunodeficient mice to address the anti-tumoral efficacy of Capzimin “in vivo”.

This study aims to elucidate the oncogenic potential of PSMD14 in ccRCC and to validate Capzmin-mediated pharmacological inhibition as a novel therapeutic strategy.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-32	*Structural Biology*	FYTILI Eirini Maria	IPMC

Investigating the role of UBTD1 in gland formation and maintenance

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Glands are organs that produce and secrete substances that have an important role in our body. Mammary glands are responsible for milk secretion for breastfeeding of the offspring and prostate is important for the secretion of seminal liquid .The epithelium of both glands is formed by a bilayer of cells, luminal cells that have secretory properties, surrounded by basal cells that provide a structural support for the epithelium and maintain the ductal integrity .The architecture of glands is crucial for their function and maintenance , which relies on the fine balance of proliferation and differentiation controlled by adult stem cells. Stem cells behavior is controlled by chemical and mechanical signals coming from their surrounding environment. We previously identified UBTD1 as a mechanoregulator that controls a major mechanotransduction pathway YAP. In addition, we demonstrated that UBTD1 is crucial to regulating EGF signaling. This signaling pathway is important for epithelial maintenance, stem cells and cancer. Since UBTD1 is expressed in basal stem cells in gland, our objective is to decipher the role of UBTD1 in gland formation and maintenance.

Towards this goal we followed a structural approach and studied the localization of the protein and by in silico structural analysis we identified two potential acylation sites on the N-terminal of the protein. We showed that UBTD1 is palmitoylated and myristoylated and that because of this dual acylation UBTD1 is located at the plasma membrane and because of this dual acylation UBTD1 is located at the plasma membrane. By studying the half-life and the trafficking of the protein in the cell, we proved that palmitoylation is responsible for UBTD1 localization and stability at the membrane. We used a proteomic approach to identify potential partners.

Finally, at a cellular level, preliminary data of the team showed that when we overexpress UBTD1 there is a defect in cell matrix adhesion. We studied adhesion upon knock down of UBTD1 and quantified intracellular and extracellular fibronectin secretion. We showed that UBTD1 controls fibronectin secretion and that TGFbeta regulates UBTD1. In perspective we are planning to study some aspects of the glands such as secretion and proliferation in 3D models of organoids.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-33	*Bioinformatics/Omics*	BELLOUTI Ouafaa	IRCAN

Characterization of Pathways Involved in the Silencing Activity of the Repressor REST.

O. Bellouti, D. Van-Essen, S. Saccani

Accurate gene regulation is essential for all developmental processes, and breakdown in gene regulatory processes underly all cancers and multiple other diseases.

Gene regulation is governed by activating & repressing genomic elements. However, whereas the functions of activating elements at promoters and enhancers have been well-studied (Chepelev et al., 2012. Arnold et al., 2013), the mechanisms of gene repression by silencers are poorly understood.Identification in our lab of silencer elements across the mammalian genome has revealed a significant enrichment for binding by the repressor protein REST / NRSF at a subset of silencers (Hussain et all.,2023, Lopez in prep). REST misexpression or mutation associated with multiple cancers, and it has been proposed that gene repression by REST can exert both oncogenic and tumor-suppressor functions, depending on the cancer type (Arizmendi-Izazaga et all., 2023, Jin et all.,2023). However, the pathways utilized by silencers to mediate repression, including those bound by REST, are still not well characterized.

In this project we have set up unbiased knockout screens to identify the factors required for silencer-driven repression, here focusing on REST-associated silencers; and we are using loss-of-function, transcriptomic, and ChIP-seq analyses to characterize the targets and pathways that are regulated by these factors throughout the genome.

Knowledge of the factors and pathways required for silencing will provide new insights into normal gene regulation, as well as novel targets and diagnostic markers for cancer and other diseases linked to gene misregulation.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-34	*Cancer/Immunology*	LAMGHARI Noura	IPMC

The role of CLEC2A/ NKp65 interaction in the immune surveillance in the skin

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The C-type lectin receptor CLEC2A has been described to be expressed in keratinocytes and fibroblasts in human skin [1,2]. Indeed CLEC2A binds to the NK/ILC3 cell-activating receptor NKp65, increasing their cytotoxic activity upon engagement [1,3]. This interaction appears to be largely restricted to the skin[1]. Previous work from the laboratory showed that CLEC2A expression is lost in patients with xeroderma pigmentosum and squamous cell carcinoma, thus facilitating tumor development [2]. These results suggest that CLEC2A/NKp65 interaction plays a major role in immune surveillance of the skin. In my current study, I aim to further investigate the mechanisms regulating CLEC2A expression in fibroblasts and keratinocytes, as well as the expression of NKp65 in human NK cells. Indeed, we could confirm by qPCR, WB and IF that CLEC2A is expressed in human skin, in primary fibroblasts and we identified a specific expression in differentiated but not in undifferentiated primary keratinocytes. Moreover, functional assays demonstrated that blocking CLEC2A/NKp65 interaction with antibodies reduces the cytotoxicity of NK92 cells against CLEC2A-expressing U937 targets. In parallel, to gain an understanding of the expression profile of CLEC2A in pathological contexts, we analyzed publicly available single-cell RNA sequencing data from normal skin and skin from patients with psoriasis, atopic dermatitis and squamous cell carcinoma. We found a downregulation of CLEC2A associated with inflammation and skin cancer. This is consistent with the decreased expression of CLEC2A on fibroblasts stimulated in vitro with IL-1 and TNF-α. Further work is ongoing to unravel the immune regulations orchestrated by CLEC2A/NKp65 at homeostasis and in inflammatory skin diseases up to the onset of skin cancer.

1. Spreu J, Kuttruff S, Stejfova V, Dennehy KM, Schittek B, Steinle A. Interaction of C-type lectin-like receptors NKp65 and KACL facilitates dedicated immune recognition of human keratinocytes. *Proc Natl Acad Sci*. 2010;107(11):5100-5105. doi:10.1073/pnas.0913108107
2. Gonçalves-Maia M, Gache Y, Basante M, et al. NK Cell and Fibroblast-Mediated Regulation of Skin Squamous Cell Carcinoma Invasion by CLEC2A Is Compromised in Xeroderma Pigmentosum. *J Invest Dermatol*. 2020;140(9):1723-1732. doi:10.1016/j.jid.2020.01.021
3. Kühnel I, Vogler I, Spreu J, Bonig H, Döring C, Steinle A. The activating receptor NKp65 is selectively expressed by human ILC3 and demarcates ILC3 from mature NK cells. *Eur J Immunol*. 2024;54(4):2250318. doi:10.1002/eji.202250318

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-35	*Physiopathology*	GARNIER Mathilde	RETINES

Physiotherapists clinical practice for mental health in France : optimize the student trainning to promote their future professional practice

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Introduction : Mental disorders are considered as public health issues that implies psychic, physical and social consequences. Health and social authorities must manage the patients' vulnerabilities linked to the illness. This study focuses on understanding the physiotherapist's input to help this purpose.
In other countries, physiotherapists offer body-centered therapies for patients' somatic disorders. In France, however, this practice is underdeveloped. The aim of this thesis project is to respond to a request from French health policies to develop the practice of physiotherapy for patients suffering from mental disorders.

Methods : Several qualitiative methodologies (expert interviews) and reviews are carried out to confirm the findings and build the theoretical context of this thesis.

Results : The initial results highlight the need to optimize the physiotherapists' trainning. We propose to address this issue by optimizing the French physiotherapists' trainning in the management of mental disorders.

Discussion : This result should enable us to construct an educational device concerning the physiotherapy's practice for mental disorders. We will then implement and analyse this system within physiotherapy trainning institutes. By optimizing the trainning of professionals and adapting pedagogical tools, we hope to promote the clinical practice of physiotherapy for mental disorders.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

Neurobiology	PARADELA LEAL Carmen	Ulysseus

SPα/DNAJC5 deficiency leads to axon terminals degeneration in Purkinje Cells

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Cysteine String Protein α (CSPα/DNAJC5) is a co-chaperone located at the synaptic vesicle that prevents presynaptic degeneration. Mutations in the human DNAJC5 gene lead to Kufs disease (CLN4), a rare neurodegenerative disorder that primarily affects young adults. Mice lacking CSPα develop severe neurological phenotypes and early death, with inhibitory parvalbumin-positive (PV+) interneurons being particularly affected. Despite its importance, the role and mechanisms of CSPα/DNAJC5 in cerebellar synapses have not been thoroughly investigated. We have generated conditional knockout mice that specifically are devoid of CSPα/DNAJC5 in PV+ neurons. These mice exhibit a remarkable motor phenotype that might have cerebellar component. We have investigated mechanisms of synaptic and neuronal dysfunction in Purkinje cells (PCs), crucial neurons in the cerebellar network. We employed confocal microscopy and Imaris analysis software to reconstruct the axo-somatic synapses of PCs onto the large glutamatergic neurons (LGN) at the deep cerebellar nuclei (DCN). Our analysis revealed a remarkable morphological phenotype that is compatible with a cell-autonomous degenerative mechanism associated with CSPα/DNAJC5 deficiency. Moreover, our ultrastructural analysis using transmission electron microscopy uncovered the loss and demyelination of PC axons. In addition, we observed increased number and activation of astrocytes and microglia at the DCN, which accompanies presynaptic degeneration. Besides, we have also detected pathological alterations in the cerebellum of a Kufs disease mouse model recently generated in our laboratory (https://www.biorxiv.org/content/10.1101/2023.05.10.540177v1 and Science Advances, in press) . Our findings provide a foundation for a deeper understanding of the mechanisms by which CSPα/DNAJC5 maintains PC synapses and for investigating the synaptic dependence of neuronal survival.

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ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

Microbiology	DE LA PENA NOYA Javier	Ulysseus

Pseudomonas putida membrane vesicles: a potential biocontrol tool?

Pseudomonas putida is a gram-negative bacterium inhabiting the rhizosphere of plants. Due to its successful antagonism towards phytopathogens, it can be used as a biocontrol agent to protect crops. Beyond well-known mechanisms of cell-to- cell interactions i.e. siderophores, T6SS or quorum sensing, membrane vesicles (MVs) have arisen as a novel communication system operating across species and kingdoms. MVs are small membranous spheric vessels conveying biomolecules like DNA or metabolites between cells. Among the functions conducted by MVs are the elimination of waste, nutrient acquisition, or the secretion of bioactive molecules. Analysing the mechanisms underlying MV biogenesis and cargo packaging is instrumental to develop novel technologies based on MV for biocontrol purposes. To this end, we tested a range of conditions to assess MV yields and morphologies in the model organism P. putida. These include extraction of MVs at different physiological phases, grown on different carbon sources, and at different temperatures and iron availability. We analysed the size and concentration of P. putida MVs employing Nanosight technology. Complementarily, we used a dye that intercalates in the lipid bilayer of the MVs emitting fluorescence. Subsequently, we visualised the morphology and integrity of the MVs by transmission electron microscopy. Finally, we analysed the proteomic profile of these samples by quantitative proteomics (LC-MS/MS) to identify proteins consistently present across all conditions. This will allow us to deduce which ones are involved in MV biogenesis. Our observations indicate that the size of the MVs ranges between 20– 600 nm depending on the analysed condition, being 100 nm the most frequent size. We observed that while high temperature leads to the formation of smaller MVs (~80 nm), benzoate generates larger ones (~125 nm). Additionally, glycerol increases P. putida vesiculation by 5-fold compared with the LB control.

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ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-36	*Cancer*	PENG Siyong	C3M

HIF-2α Drives Neuroendocrine Transdifferentiation in Castration-Resistant Prostate Cancer via Autophagy Regulation

Background
Prostate cancer (PCa), the second most prevalent cancer in men, exhibits poor prognosis when associated with neuroendocrine (NE) differentiation. Hypoxia-inducible factor-1 (HIF-1), the master regulator of hypoxia, has been reported to play a key role in prostate carcinogenesis and progression. However, the role of HIF-2, especially in therapy-reduced neuroendocrine differentiation, remains elusive.

Methods
We established a multi-level experimental framework to investigate prostate cancer progression and HIF-2 functionality. This included: (1) In vitro PCa cell line models (LNCaP, DU145, PC3, NCI-H660) representing an ascending gradient of metastatic potential; (2) An enzalutamide-induced NE differentiation model based on long-term androgen-deprived in LNCaP cells; (3) Patient-derived tumoroids generated from clinical prostate cancer specimens and (4) rare tissue samples obtained directly from patients. HIF-2α function, a subunit of the HIF-2 complex that is stabilized only under hypoxic conditions, was systematically investigated in model (2) using CRISPR/Cas9-mediated knockout/overexpression approaches, followed by analysis via Western blotting, qPCR, migration assays, and autophagic flux monitoring.

Results
Our findings revealed that, in model (1) HIF-2α is stabilized and activated in the NCI-H660 neuroendocrine cell line in normoxia, while it remains undetectable in androgen-dependent LNCaP cells—even under hypoxic conditions. Forced overexpression of HIF-2α significantly enhanced the migratory capacity of LNCaP cells. In model (2), Enzalutamide treatment induced an increase expression of HIF-2α at both mRNA level (marked increase) and protein level (modest increase) as alongside upregulation of neuroendocrine markers. Autophagy flux was also increased following enzalutmaide treatment. Modulation of HIF-2α expression revealed that overexpression further enhanced autophagy and accelerated neuroendocrine transdifferentiation while the knockout of HIF-2a reduced autophagic activitylevel and slowed down NE differentiation. Finally, in model (3), the application of HIF-2α inhibitor in patient-derived neuroendocrine tumoroids appeared to decrease the expression of NE markers.

Conclusion
These results identify HIF-2 as a novel driver of prostate cancer progression. By regulating autophagy, HIF-2 also contributes to NE transdifferentiation induced by anti-androgen treatment. This discovery highlights HIF-2 as a promising therapeutic target in prostate cancer.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-37	*Neurobiology*	AZOULAY Benjamin	IPMC

APP-derived AETA peptide modulates brain network activity

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The amyloid-β precursor protein (APP) is a transmembrane protein constitutively expressed in the brain and highly implicated in Alzheimer's disease aetiology. We previously identified a novel cleavage site of APP, the η-secretase site *(Willem et al. Nature 2015, PMID:26322584)*. Peptides resulting from this cleavage and α- or β-secretase-dependent proteolysis are the extracellular soluble AETA peptides (Aη-α or Aη-β, respectively). Our previous work also demonstrated that AETA modulates synaptic plasticity and significantly reduces calcium activity in the hippocampus (HPC) *in vivo*. These results suggest that AETA may serves as an interesting modulator of hippocampal network activity, potentially influencing the dynamics of the neuronal network. To study the involvement of AETA in the regulation of neuronal networks, two new mouse lines were used: The APPdelETA line, where η-secretase processing is abolished (no more AETA); and the AETA-m line, where human AETA is produced and secreted in the brain. *In vivo* electrophysiological studies using Local Field Potential (LFP) provide initial insights into how variations in AETA levels impact brain network activity in HPC and a long-range cortical connection, the Medial Prefrontal Cortex (mPFC). These initial results confirm that AETA modulates network activity, and in particular, the coupled activity between Theta and Gamma rhythms in both regions during REM sleep, a coupling already reported to be involved in memory processing *(Bott et al. Cerebral Cortex 2016, PMID:26250776)*. To further understand the impact of AETA on neural network activity, we plan to record this neural network during memory tasks and sleep phases following these tasks.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-38	*BioModelling*	MAMJOUD Iman	C3M

P19ARF expression in adipocytes lowers obesity and insulin resistance risk via adipocyte differentiation control

Iman Mamjoud, Nathalie Boulet, Cindy Méziat, Inès Mucel, Jennifer Jager, Jean-François Tanti, Mireille Cormont.

The transcription factor p53 is activated in adipocytes during obesity and promotes systemic insulin resistance. Among its regulators, the tumor suppressor p19ARF stabilizes p53 and is induced in adipocytes of obese mice. However, the metabolic impact of its overexpression remains unknown.
To investigate the role of p19ARF in obesity-related dysfunction, we generated mouse models: p19ARF knockout in white and beige/brown adipocytes (p19ARF AdKO), p19ARF knockout exclusively in beige/brown adipocytes (p19ARF BadKO), and p53 knockout in both (p53 AdKO). Mice expressing AdipoQ-cre or UCP1-cre were used to generate white and beige/brown adipocyte-specific and only beige/brown adipocyte-specific invalidation, respectively, by crossing them with floxed p19ARF or floxed p53 mice.

p19ARF AdKO mice exhibit no phenotype on a standard diet. However, after 10 weeks on a high-fat diet, they develop glucose intolerance and insulin resistance compared to control littermates. This phenotype is driven by increased weight gain, fat mass accumulation, and a pathological expansion of epididymal adipose tissue via adipocyte hypertrophy. Body weight gain is independent of food intake or activity. Instead, the underlying cause is a significant reduction in energy expenditure. When housed at thermoneutral conditions, no metabolic differences between p19ARF AdKO and their controls are observed. Thus, impaired thermogenesis in brown/beige adipocytes contributes to the pronounced weight gain in p19ARF AdKO mice. However, no metabolic differences were observed in p19ARF BadKO mice, indicating that p19ARF in brown/beige adipocytes does not play a significant role. The thermogenic dysfunction in p19ARF AdKO mice likely arises from inter-organ crosstalk. Additionally, p53 AdKO mice do not develop metabolic disorders, indicating that p19ARF 's effects are p53-independent.
To explore underlying mechanisms, we studied early events after 3 weeks on a high-fat diet, when weight and metabolic parameters in p19ARF AdKO mice remain comparable to controls. Transcriptomic analysis of epididymal adipocytes reveals upregulation of lipid metabolism genes and downregulation of inflammation-related genes. Additionally, p53 target genes are reduced, supporting p19ARF's role in stabilizing p53. At this stage, p19ARF invalidation appears to protect adipocyte function. We also observed lower epididymal adipose tissue mass in p19ARF mice, altered progenitor subpopulations, and reduced gene expression of markers for mature pre-adipocytes, suggesting a defect in adipogenesis.
These findings suggest that p19ARF upregulation in adipocytes during obesity development plays a sequential role. In early obesity, p19ARF exerts deleterious effects via p53 stabilization, while promoting hyperplasic adipose tissue expansion through a p53-independent mechanism, later conferring beneficial effects. p19ARF ’s dual function may act as a protective mechanism, limiting obesity-related metabolic complications.

OC-39	*Immunology/Microbio*	DUBOIS Margaux	MICORALIS

Investigating Salivary Cytokines as Potential Biomarkers for Dental Caries: A Preliminary Analysis

Margaux Dubois, Morgane Ortis, Alain Doglio, Marie-France Bertrand

Identifying salivary cytokine biomarkers predictive of dental caries holds significant potential for personalized clinical practice. Early detection via salivary diagnostics would enable tailored interventions based on individual pathophysiological mechanisms. Salivary cytokines detection could enhance diagnosis, predict caries progression risk, and guide therapy. The aim of this cross-sectional study is to analyze the oral and immune changes depending on the presence of dental caries. A preliminary analysis was conducted to assess variations in cytokine profiles among different participant groups.

The study was a cross-sectional, non-randomised, single-centre RIPH 3 study involving 80 participants aged 18-30 years. Oral examination and unstimulated saliva sampling were carried out among the participants, grouped into caries (n=31) and healthy (n=49) groups. General (age, sex, BMI, physical activity, smoking, stress) and oral clinical indicators (plaque index, gingival index, decay-missing-filled index [DMF]) were recorded. Nine cytokines (IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-17A, IL-1β, TNF-α, IFN-γ) saliva levels were quantified by a sensitive multiplex ELISA assay MSD technology. Statistical tests employed included Shapiro-Wilk test for normality, Mann-Whitney U test and Kruskal-Wallis test for non-normal quantitative data. ROUT method was employed to exclude outliers. Graphpad Prism software was used to perform statistical analysis.

Statistical analysis showed no significant inter-group differences in age, BMI, physical activity, or tobacco use. However, the caries group presented with a significantly higher DMF index and plaque index ($p<0.05$).Following outlier removal, salivary IL-17A levels were significantly higher in the caries group compared with the healthy group ($p=0.0219$). Besides, after data cleaning and exclusion of the patients with gingival inflammation from both groups, IL-17A concentration remained significantly higher in the caries group ($p=0.0490$). No other significant differences in salivary cytokine levels were detected between the groups.

IL-17A plays a key role in mucosal immunity by strongly inducing the production of inflammatory cytokines and chemokines. This study revealed a potential significant association between elevated salivary IL-17A levels and the presence of dental caries, suggesting that active defense mechanisms may be triggered in response to cavity formation." While these findings suggest the potential for cytokine-based caries detection, further research with a larger sample size is warranted. In parallel, the implementation of a high-throughput microbiological detection platform is under development to quantify 40 oral bacteria belonging to the commensal and pathogenic microbiota and 8 viruses from the Herpesviridae family. The combination of these two detection techniques will provide a global view of oral microbiological and immunological profiles to identify oral signatures associated with oral health and disease.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-40	*Physiopathology*	ANGOT Brice	C3M

Role of the mechanosensitive ion channel Piezo1 in the regulation of the thermogenic functions of brown adipocytes

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Thermogenic brown adipocytes dissipate excess energy as heat. During this process called non-shivering thermogenesis, lipids and glucose are used as fuel to support the uncoupled respiration of these adipocytes due to the unique UCP1 protein expressed in their mitochondria. Activation of thermogenic brown adipocytes by cold or beta-adrenergic receptor agonists such as CL316,243 (CL) increases energy expenditure, reduces body weight, improves carbohydrate-lipid metabolism and insulin sensitivity. A better understanding of their activation could lead to the identification of new targets against obesity.

Brown adipocytes are mechanosensitive, suggesting that mechanosensors regulate their functions. As mechanosensitive ion channels are early and fast players in mechanotransduction, we investigated their expression levels and roles in brown adipocytes. We show that Piezo1 is highly expressed and functional in brown adipose tissue. Its expression is increased by CL in a brown adipocyte cell line as well as in the brown adipose tissue of cold-adapted mice. This effect depends on the activation of lipolysis.

We generated mice with a specific invalidation of Piezo1 in brown adipocytes (Piezo1BAd.KO mice). These mice, on standard diet, have less fat mass than Piezo1flox/flox control mice. This reduction was also observed during the first 4 weeks of a high fat diet (HFD).
After 13 weeks of HFD, Piezo1BAd.KO and control mice have similar body fat, but glucose tolerance in Piezo1BAd.KO mice is improved. We also show that CL induction of de novo lipogenesis genes in the brown adipose tissue of Piezo1BAd.KO mice is higher to that of control mice.

Our results demonstrate that activation of lipolysis is required for induction of Piezo1 in brown adipocytes, which negatively regulates de novo lipogenesis, potentially affecting the coupling between lipid metabolism and thermogenesis.

ABSTRACTS
ORAL COMMUNICATIONS
3rd YEAR PhD STUDENTS

OC-41	*Biochem/Structure*	ABOU-ALI Mélanie	IRCAN

Understand mitochondrial defects leading to cardiac damage associated with CHCHD10 variants

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Key words: CHCHD10, mitochondria, rare disease, knock-in mice, OMA1, cardiomyopathy

In 2014, my team identified a variant in the CHCHD10 gene encoding for a mitochondrial protein. Patients develop a mitochondrial myopathy and a complex neurological phenotype. Since then, several CHCHD10 variants were identified in a large clinical spectrum such as cardiomyopathies.

My team generated the first Chchd10S59L/+ mice model that recapitulate patients' symptoms. These animals develop a fatal cardiomyopathy leading to their death between 11 to 13 months. In the heart of the mice, the S59L variant triggers a molecular cascade that leads to OMA1 activity, a mitochondrial protein that regulates several processes in the mitochondrion. My project aims to understand the role of OMA1 in cardiomyocytes degeneration. For this, I obtained a Chchd10S59L/+ mice model were OMA1 is inactive. In the crossings, I observed a partial rescue of mitochondrial functions in the heart at 6 months. In a new model of cardiomyocytes derived from patients' cells, I observed morphological and calcium flow anomalies, both important for contraction. I also observed impaired mitochondrial functions. My results suggest that OMA1 has a deleterious role in the molecular cascade triggered by the S59L variant. This variant leads to mitochondrial dysfunctions in both the mice and a new model of cardiomyocytes derived from patients' cells. My work opens up new therapeutic avenues for these severe and incurable pathologies.

ABSTRACTS
POSTERS
2nd YEAR PhD STUDENTS

P-1	*Immunology*	FAKIH Ibrahim	C3M

The transcriptional role of Ro60 in the Anti-in5lammatory response in macrophages and monocytes

I. Fakih, M. Trabucchi

Ro60, a protein of the ribonucleoprotein complex RoRNP, associates with YRNAs, a class of non-coding RNAS, to ensure RNA surveillance and maturation within cells. This complex plays a role in RNA stability, preventing premature degradation and assisting in the management of misfolded RNAs, particularly under cellular stress.

In systemic autoimmune diseases, such as Sjögren syndrome (SS), the function of Ro60 is compromised by the production of speci5ic autoantibodies that penetrate the cell nucleus and inactivates Ro60, thereby disrupting these regulatory functions (Wolin and Reinisch, 2006).

The inactivation of Ro60 promotes the development of an immune response in SS patients, suggesting a link between Ro60 dysfunction and the pathogenesis of this disease.

Clinical data indicate that patients with SS have an increased risk of cardiovascular events, largely due to an accelerated atherosclerotic process (Cost et al., 2021). Monocytes and macrophages are altered in SS, contributing to an immune imbalance that promotes chronic inflammation and cardiovascular complications (Ma et al., 2019).

However, the precise mechanisms by which Ro60 influences these immune cells, as well as its potential role in modulating the inflammatory response, remain largely unknown.

Based on robust preliminary data, we hypothesize that the alteration of Ro60, via nuclear penetration of anti-Ro60 autoantibodies, disrupts the regulation of key genes involved in the anti-inflammatory response, particularly when monocytes/macrophages are exposed to atherogenic lipids such as palmitic acid.
The originality of this project lies in the exploration of a novel role for Ro60 in transcriptional regulation via its association with chromatin. This regulation is particularly important in monocytes and macrophages stimulated by atherogenic lipids, such as palmitic acid.

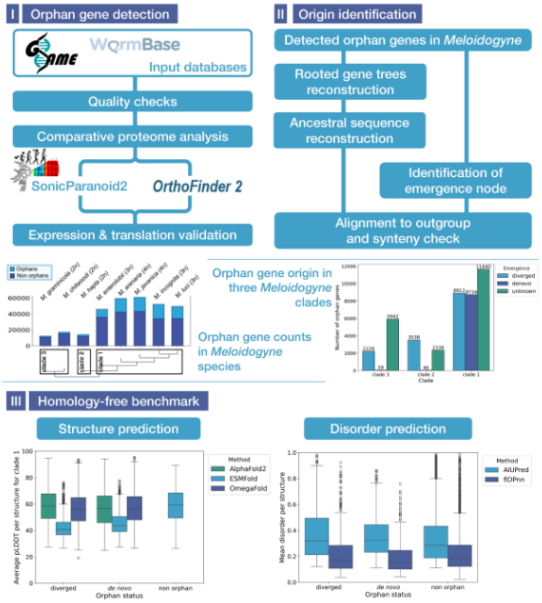
We propose that the loss of Ro60 function, induced by autoantibodies in the context of SS, leads to transcriptional dysregulation that exacerbates the inflammatory response, thereby promoting disease progression and the development of cardiovascular comorbidities.

P-2	*Bioinformatics*	SEÇKIN Ercan	ISA

Whole-genome detection and origin identification of orphan genes in plant-parasitic nematodes

Context - Genes lacking homology in other species are systematically found in genomes and have various important functions [1]. The presence of the majority of these so-called orphan genes can be explained by extensive divergence from pre-existing genes up to the point where no homologs can be identified. Another possibility is de novo gene birth, which consists in the emergence of genes from non-genic regions. Due to the limited accuracy of homology searches and the challenges posed by fragmented genome assemblies, establishing reliable correspondences between genomes can be difficult. Distinguishing between de novo genes and highly diverged homologs is particularly challenging, and relies on the comparison with a phylogenetically close outgroup species genome, that helps identifying homology with rapidly changing coding and non-coding regions. Root-knot nematodes (Meloidogyne) represent an interesting model for studying the origin of orphan genes: indeed, (i) the majority of their genes known to be involved in plant parasitism have no recognizable homologs outside the genus [2], and (ii) several of these species have undergone whole genome duplications with the potential for high divergence between gene copies [3].

Orphan detection and origin identification - We present a bioinformatics pipeline designed to identify orphan genes and to investigate their evolutionary history, emergence dynamics and possible de novo origin. Firstly, the pipeline conducts a comparative homology search for identifying putative groups of orphan orthologs (orthogroups). Secondly, their expression is verified with transcriptomic and proteomic data. Once the orphan orthogroups are identified, their ancestral sequences are reconstructed by gap-aware phylogenetic methods. The pipeline then reconciles gene trees with the species tree and reconstructs ancestral sequences at each branch. The distinction between divergent and de novo genes is then established by aligning these ancestral sequences to a closely related species, coupled with syntenic approaches. In this study, we apply this pipeline on recently acquired genomes of Meloidogyne, divided in three clades of respectively 5, 1, 2 closely related species. We find that among all detected orphan genes, 19% are most likely the result of de novo gene birth (predominantly found in clade 1), and at least 30% are the result of high divergence. For the remaining 51% the pipeline does not give conclusive results, mostly due to missing alignment on the outgroup species and fragmented synteny.



A challenging, homology-free benchmark for structure, disorder, and emergence predictors

Data concerning the five most recent Meloidogyne species (clade 1) constitutes a well-equilibrated, unbiased benchmark for de novo gene predictors, as well as for disorder and structure predictions. We used this homology-free benchmark to test AlphaFold2, ESMFold and OmegaFold: all predictors produced a majority of protein structures with “low” (pLDDT<70) or “very low” (pLDDT<50) average self-confidence score. This result does not seem linked to an abundance of intrinsically disordered regions: neither general-use nor homology-agnostic disorder predictors (resp. AIUPred and fIDPnn) detect an increased disorder. Similar conclusions were reached in a recent study on Drosophila [4].

References

1. Tautz D, Domazet-Lošo T. The evolutionary origin of orphan genes. Nat Rev Genet. 2011 Oct;12(10):692–702.
2. Mitchum MG, Hussey RS, Baum TJ, Wang X, Elling AA, Wubben M, et al. Nematode effector proteins: an emerging paradigm of parasitism. New Phytol. 2013 Sep;199(4):879–94.
3. Castagnone-Sereno P, Danchin EGJ, Perfus-Barbeoch L, Abad P. Diversity and Evolution of Root-Knot Nematodes, Genus Meloidogyne : New Insights from the Genomic Era. Annu Rev Phytopathol. 2013 Aug 4;51(1):203–20.
4. Middendorf L, Eicholt LA. Random, de novo, and conserved proteins: How structure and disorder predictors perform differently. Proteins Struct Funct Bioinforma. 2024 Jun;92(6):757–67.

ABSTRACTS
POSTERS
2nd YEAR PhD STUDENTS

P-3	*Cancer*	DELLA CROCE Laetitia	IPMC

NUMB inhibits cell invasion by stimulating EFA6B-mediating Arf6 Activation

Breast cancer is the most common cancer in women globally, but also the best described. We have observed that decreased expression of the EFA6B protein in breast tumors is associated with a poor prognostic factor. EFA6B is involved in membrane transport, actin cytoskeleton reorganization and the establishment of epithelial polarity. Part of its action derives from its ability to activate the small G protein Arf6. Previous work carried out by the laboratory has demonstrated that a reduction in EFA6B expression levels in normal mammary cells results in the acquisition of a partially mesenchymal phenotype and collective invasion properties through the activation of the small G protein Cdc42, a protein known to be involved in filopodia and invadopodia formation.

Furthermore, another study carried out by the laboratory shows that the NUMB, a protein described as tumor suppressor but also to be involved in endocytosis processes, is a direct partner of EFA6B capable of powerfully stimulating Arf6 activation. Here, we investigate the molecular mechanisms implicating these proteins in the negative control of the invasive processes. We show that overexpression of NUMB in heterozygous EFA6B KO mammary cells inhibits the invasive process by both strongly activating Arf6 and inhibiting Cdc42. These results suggest that the over-activation of the residual EFA6B pool is necessary and sufficient to restore a non-invasive phenotype.

ABSTRACTS
POSTERS
2nd YEAR PhD STUDENTS

P-4	*Developmental Biology*	LERAY Chloé	iBV

Alteration of RNA condensates during aging

RNA condensat is a hallmark of degenerative cells, but can also be non-pathological and indicative of a healthy cellular response to stress or quiescence (Cardona et al., 2023). The debate persists on whether condensation, initially a protective mechanism, becomes pathological during aging. While the time-dependent maturation of RNA condensates is well-documented in vitro, the aging of RNA condensates in animal models remains unexplored. Understanding the evolution of RNA condensates in the broader context of aging and its associated signaling pathways is crucial.

To investigate the impact of aging on RNA condensates, we employ grP-Bodies in arrested oocytes in *C. elegans* as a model. In *C. elegans*, aging is linked to modifications in oocyte structure and reduced fertility, characterized by lower ovulation rates and decreased embryonic viability. Additionally, the absence of a crucial protein for grP-Bodies formation results in decreased embryonic viability. Our objective is to comprehend the alterations in grP-Bodies during the aging process in C. elegans and their consequent effects on embryonic viability.

To achieve this goal, I aim to characterize grP-Bodies remodeling during aging by investigating (1) changes in the composition of grP-Bodies, (2) alterations in the structure of grP-Bodies during aging, and (3) changes in translation. The focus is on establishing a potential link between the maintenance of grP-Bodies and embryonic viability during aging. A FAPS purification of grP-Bodies during aging has been performed, and the obtained samples will undergo RNA sequencing to identify compositional changes in RNA condensates during aging. Simultaneously, structural alterations in grP-Bodies during aging are being observed using imaging approaches. Finally, translation alterations during aging will be studied through polysome profiling. Using an animal model, my research will provide a better understanding of the impact of physiological aging on RNA condensates.

P-5	*Biochemistry/Neuro*	LEBEL Quentin	IPMC

Investigating the neuronal consequences of the small G-protein Arf6 SUMOylation

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#Equal contribution
* Equal contribution

SUMOylation is a post-translational modification involving the covalent enzymatic conjugation of the Small Ubiquitin-like MOdifier (SUMO) polypeptide to specific lysine residues of substrate proteins. SUMOylation regulates the dynamics of multi-protein complexes by preventing protein-protein interactions or by providing new binding sites for novel protein interactors. The ADP ribosylation factor (Arf6) is a small GTP-binding protein that switches between an active GTP-bound and an inactive GDP-bound state. Arf6 is mainly localized at the plasma membrane and participates in the reorganization of the actin cytoskeleton and the regulation of lipid membrane flows including endocytosis, recycling and exocytosis. Interestingly, we demonstrated for the first time, that Arf6 is SUMOylated in vivo. To assess the functional consequences of this Arf6 modification, we first identified the lysine residues targeted by the SUMO system. We then used various SUMO-defective Arf6 mutants and molecular replacement strategy in neurons to characterize the impact of Arf6 SUMOylation on its subcellular localization, on axonal growth, on the dendritic arborization complexity as well as on the density and morphology of dendritic spines. We next investigated the role of Arf6 SUMOylation on the localization of surface-expressed AMPA receptors to start assessing the physiological impact of this post-translational modification in neurons.

P-6	*BioModelling*	GAO Yuan	ISA

Using multi-object tracking and subject reidentification to elucidate group dynamics and interactions among insects

Yuan Gao, Dr. Vincent Calcagno (INRAe, team M2P2) and Dr. François Brémond (Inria, team STARS)

Minute insects of the genus Trichogramma are widely used as biocontrol agents for pest suppression, like against the European corn borer (Ostrinia nubilalis) with mass releases of individuals in agricultural fields (Smith, 1996 : ~200k/ha/week). At such high-density groups, it is expected that Trichogramma individuals display agonistic behaviors such as fights or superparasitism (i.e laying of eggs inside a host egg already parasitized) leading to reduced biocontrol efficiency. Observations of intra-specific aggressive behavior between T.brassicae females at low-density groups (Elisa Venturini, M1 internship : ~20 individuals/experiment). In link to that, previous work in the institute established the existence in Trichogrammas of consistent behavioral differences (“personalities” , Lartigue et al, 2021) that opens the potential of strain selection for biocontrol based on it. Therefore, it is crucial to study the interactions between individuals in the context of groups to understand and quantify these inter-individual variations.

Biological question : Does the group context have an impact on inter-individual differences and what are the dynamics of the resulting group ? Automated video-tracking methods are increasingly developed and used in behavioral studies as it allows high-throughput quantitative data acquisition (Dell et al, 2014). Currently, studies in groups of individuals are limited by the impossibility to maintain individual’s identities throughout time, especially in cases without visual discrimination. Fortunately, recent advances in Artificial Intelligence (AI) techniques, such as Multi-Object Tracking (MOT) and subject ReIdentification (ReID), enables the tracking of unmarked individuals in groups which is vital for insects that are most of the time visually indistinguishable. Right now, AI techniques are being implemented in biology (Gómez-Vargas et al, 2023) but their usage largely remains a challenge by biologists that are unfamiliar with informatics. The ambition to build a bridge between ecology and informatics led to the creation of a tracking pipeline called “TrichTrack” (Pani et al, 2021) with the goal to make it easy to use by biologists and quickly adaptable to many other animal species.

Objectives : My PhD project general objective is understanding the influence of group context on the behavior of individuals. In particular, demonstrate the ability of the pipeline to identify individuals for the informatic part and to elucidate the relationship between individual and group phenotype, with major interest on the interactions involved, for the biological part.

P-7	*Immuno/Microbiology*	SAÏSSI Margot	C3M

Molecular and functional study of inflammasomes in the detection of toxins secreted by *Bacillus cereus* bacteria during sepsis in preterm neonates

Bacillus cereus (B. cereus) is a ubiquitous Gram-positive bacteria found in the environment, involved in foodborne infections but also responsible for bacteraemia and sepsis in preterm neonates. The pathogenicity of *B. cereus* strains is due to toxins expression, however, the role and impact of toxins on the immune system of neonates are still poorly understood. Some enterotoxins secreted by *B. cereus* have recently been identified as NLRP3 inflammasome activators. Inflammasomes are important signalling platforms activated during innate immune response and play a crucial role in regulating inflammation. Therefore, we hypothesise that the pathogenicity of *B. cereus* is due to the overactivation of the innate immune system and my project aims to study the molecular mechanisms of inflammasome activation by toxins secreted by *B. cereus* during systemic infection and sepsis in premature neonates. This study is conducted with clinical *B. cereus* strains that caused bacteraemia in preterm neonates isolated in a national clinical trial organized by our team. Mass spectrometry analysis of bacterial secretomes highlighted that virulent strains secrete the cytolysin, a virulence factor not yet described in *B. cereus* bacteraemia. Cytolysin treatment on murine bone marrow derived macrophages primed with LPS induced inflammasome activation and cytotoxicity. Transfection in cells highlighted its co-localisation with lysosomes and phago-lysosomes. A single amino acid mutation in the transmembrane domain of the cytolysin or a pre-treatment with cholesterol can inhibit its activity since it targets cholesterol on cell membrane via the transmembrane domain. To study the innate immune response in vivo, we set up a model of newborn mice bacteraemia via intraperitoneal injection. The immunophenotyping of the spleen of the mice treated with cytolysin showed a decrease of monocytes and macrophages and an increase of neutrophiles. These results provide important insights into the pathogenesis of *B. cereus* and understanding the cytolysin action on inflammasomes during sepsis could lead to the development of targeted treatments to effectively manage the infection.

P-8	*Physiopathology*	CRUSSET Floricia	iBV

Development of a physiopathological human visceral adipose tissue model of obesity

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Keywords : Adipose tissue, Obesity, inflammation, fibrosis, 3D modeL

Development of obesity leads to the accumulation of visceral adipose tissue (VAT), a metabolically active tissue characterized by inflammation, fibrosis, and dysregulated metabolic processes [1][2]. VAT is strongly associated with an increased risk of developing metabolic disorders such as type 2 diabetes, insulin resistance, Metabolic Associated Steatohepatitis (MASH) and cardiovascular diseases [3][4].

Current non-animal models, such as 2D cell cultures, organoids, and microfluidic chip systems, have limited physiological relevance and do not fully mimic the physiopathology of obese visceral adipose tissue [5]. Furthermore, acquiring VAT is difficult due to the requirement for specialized and regulated clinical studies. The development of new clinically relevant models is therefore essential to screen therapeutic compounds in order to identify novel treatments for obesity-related metabolic diseases. However, the expression levels of inflammatory, fibrotic and metabolic markers in visceral obese human adipose tissue are not well defined in the literature.

To overcome this limitation, we analyzed visceral and subcutaneous adipose tissue samples from 10 obese patients, obtained through a clinical study, to establish a molecular, phenotypic, and functional profile of VAT in obesity. Using a medium-throughput microfluidic qPCR and multiplex cytokine assays, we characterized and quantified markers of inflammation, fibrosis, and metabolism. Our analysis revealed a distinct pathological signature of obese VAT compared to obese subcutaneous adipose tissue, characterized by an increased inflammation, a potential impairment in ECM degradation leading to pathological fibrosis, and a metabolic dysregulation.

In order to develop a model mimicking obese visceral adipose tissue, lean subcutaneous adipose tissues from surgical waste were cultured for several weeks thanks to ExAdEx patented process and exposed to various stimuli to reproduce the expression profiles of markers found in obese VAT. Preliminary results show that a specific TNFα stimulation kinetic can reproduce an inflammatory phenotype similar to that observed in obese VAT in lean AT. Furthermore, the gene expression profile linked to VAT pathology can be modulated using different stimuli such as TGF-β1. This approach enables the development of fibrotic and metabolic AT models that faithfully mimics the physiopathological features of human VAT. These models represent promising preclinical tools for the screening and development of novel therapies against obesity-related metabolic diseases.

[1] Khanna, Deepesh et al. "Obesity: A Chronic Low-Grade Inflammation and Its Markers." Cureus vol. 14,2 e22711. 28 Feb. 2022, doi:10.7759/cureus.22711
[2] Gliniak, Christy M et al. "Adipose tissue fibrosis: the unwanted houseguest invited by obesity." The Journal of endocrinology vol. 259,3 e230180. 19 Oct. 2023, doi:10.1530/JOE-23-0180
[3] Gutiérrez-Cuevas, Jorge et al. "Molecular Mechanisms of Obesity-Linked Cardiac Dysfunction: An Up-Date on Current Knowledge." Cells vol. 10,3 629. 12 Mar. 2021, doi:10.3390/cells10030629
[4] Lopez-Yus, Marta et al. "Unraveling Adipose Tissue Dysfunction: Molecular Mechanisms, Novel Biomarkers, and Therapeutic Targets for Liver Fat Deposition." Cells vol. 13,5 380. 22 Feb. 2024, doi:10.3390/cells13050380
[5] Loewa A, Feng JJ, Hedtrich S. Human disease models in drug development. Nat Rev Bioeng. 2023 May 11:1-15. doi: 10.1038/s44222-023-00063-3. Epub ahead of print. PMID: 37359774; PMCID: PMC10173243.

ABSTRACTS
POSTERS
2nd YEAR PhD STUDENTS

P-9	*Bioinformatics/Omics*	FIERVILLE Morgane	IPMC

Early COPD single-cell and spatial transcriptomics

Chronic obstructive pulmonary disease (COPD) is one of the main causes of death in world (WHO), either alone or through an increased disposition to lung cancer. We built COPD dataset based on human biopsies collected in patients at early stages of the disease. Single cell and spatial transcriptomics approaches were used in order to better delineate the molecular drivers of the bifurcation toward the disease. Spatial transcriptomics (ST) analyzed large tissue sections (up to 3cm2), representing a total of about one million cells on which the expression of 5000 genes was assessed at a single-cellular resolution. By measuring cell-cell interactions and subcellular RNA expression in each cell type, we were able to define several hallmarks of the disease, such as the imbalance of secretory versus multiciliated cells in the airways. Individual cells were annotated using scMusketeers, a modular deep learning model that was keen at the identifying rare cell types and reducing batch effect, based on a reference annotation from the Human Lung Cell Atlas (HLCA). We analyze more particularly airway zones, after developing a method to unfold curved local structures. We derived from this approach a quantification of the spatial distribution of the cells and transcripts along or perpendicular to the two principal axes of the bronchi.

ABSTRACTS
POSTERS
2nd YEAR PhD STUDENTS

P-10	*Cancer*	ARTIERES Lydia	IRCAN

Molecular crosstalk between IL-1α and TGF-β drives Carcinoma Associated Fibroblasts heterogeneity in cutaneous squamous cell carcinomas.

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Cutaneous squamous cell carcinoma (cSCC) is the second most prevalent type of skin cancer, marked by the oncogenic proliferation of squamous keratinocytes within the epidermis. Its progression and invasive capacity are influenced by the tumor microenvironment (TME), where carcinoma-associated fibroblasts (CAFs) play crucial roles in promoting metastasis, angiogenesis, and resistance to therapy. Therefore, CAFs have emerged as compelling therapeutic targets in the treatment of skin carcinomas.

Within the TME of skin carcinomas, at least two distinct CAF subtypes have been identified: myofibroblastic CAFs (myCAFs) and inflammatory CAFs (iCAFs), which coexist but perform divergent functions. Our findings suggest that the secretome of cSCC cells preferentially induces the emergence of iCAFs during early tumor development, while simultaneously suppressing myCAF phenotype differentiation.

Mechanistically, this CAF subtype imbalance appears to involve distinct signaling pathways, with MEK/ERK activation playing a central role in inhibiting myCAF differentiation.

Through this study, we aim to unravel the mechanisms governing CAF heterogeneity and their respective contributions to cSCC progression. Ultimately, these insights may pave the way for novel anti-cancer and anti-metastatic therapies targeting the differentiation and functions of specific CAF subpopulations.

ABSTRACTS
POSTERS
2nd YEAR PhD STUDENTS

P-11	*Development/Neuro*	CASADO Doïna	ISA

Gravity sensory perception in drosophila larvae

D. Casado, E. Simon, R. Bonche, MP Esposito, J. Berni, N.M. Romero

Gravity is the main environmental cue animals use to initiate movement and orient themselves in space. Insect larvae, following a period of rapid growth and just before metamorphosis, engage in exploratory behavior to find an ideal pupation site. But how do larvae sense gravity to orient themselves? Despite its fundamental role, gravity perception's molecular and neural mechanisms remain poorly understood. While Newtonian physics describes gravity as a constant force, its direction changes with movement, adding complexity to its perception. Drosophila adults employ two main strategies to detect gravity: integrating forces across the entire body or sensing acceleration at a specific point. This perception relies on the integration of multiple sensory inputs.

Using the Drosophila larva as a model organism, we have made significant progress in understanding larval gravity perception. We have identified a pre-pupal orientation larval behavior, which has been instrumental in identifying the gravity sensory organ. To do this, we carried out a gravitational assay using larval orientation, combined with systematic inactivation of mechanosensory neurons, enabling us to identify the larvae's gravitational sensory organs. We acutely blocked neurotransmission in Gal4-positive neurons using a mechano-Gal4 collection (the regulatory region of each identified mechanoreceptor, like piezo or trps, controls the Gal4 expression) and a temperature-sensitive effector line UAS-ShiTS. Among the Gal4 lines tested, we pinpointed five lines, all located within the sensory chordotonal organs (Cho). This suggests that Cho organs likely sense gravity by integrating directional forces across the body. We expect this work will establish the basis for understanding the molecular basis of gravity perception.

P-12	*Physiopathology*	BROGUET Clarisse	C3M

Development and validation of autologous melanocyte suspension amplified by cell culture for surgical treatment of vitiligo

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Vitiligo is a depigmentation disorder characterized by the selective loss of melanocytes, the cells responsible for producing skin pigment. This autoimmune condition results in depigmented skin areas. Vitiligo is the most prevalent cause of depigmentation, with a global prevalence ranging from 0.5% to 2%. Although vitiligo is not life-threatening, it can profoundly affect patients' lives. Indeed, individuals with vitiligo often experience a significant reduction in quality of life, impacting daily activities, employment, social and sexual relationships, and psychosocial health.

Various treatment options are available, selected on the type of vitiligo, the extent and the body location of the lesions, as well as the patient's age, phototype, impact on quality of life, and patient expectations. However, several challenges exist, such as difficult-to-treat areas, treatment failure in some patients, and a high risk of relapse (40-50% within the first year), rendering the management of vitiligo a significant dermatological challenge. Notably, surgical treatment has room for improvement. It is the gold standard for segmental vitiligo, but also for non-segmental vitiligo after a prolonged period of stability (6 to 12 months) when medical treatment has failed. It is based on a simple principle: the transfer of an epidermal suspension containing melanocytes from the patient's non-lesional skin to the vitiligo patches. However, current techniques involve neither the selection of melanocytes from epidermal suspension, nor their expansion, which limits their number, surface treated, and hence their use.

The innovative technique developed during this thesis aims to overcome these limitations. It involves extraction of melanocytes from the patient's pigmented skin in a minimally invasive manner, followed by amplification through cell culture. Once a sufficiently large cell bank is established, a suspension of autologous melanocytes can be grafted back to the patient, allowing for the treatment of large surface areas. This study was aimed to optimize the melanocytes extraction and the culture conditions to ensure that the amplified melanocytes retain identical phenotypic and genotypic characteristics to the original cells. For this, morphology and key melanocyte markers were monitored during passages. Additionally, nucleic acids were extracted throughout the culture process to ensure genomic integrity and the absence of oncogenic pathway alterations at both transcriptional and genomic levels.

P-13	*Microbiology*	CARLEA Federica	IRCAN

Endosymbiotic populations in Saccharomyces genus.

Federica Carlea, Gianni Liti

Team: Population genomics & complex traits

Symbiosis, the co-existence of two or more organisms, is a key driver of ecological and evolutionary processes. Prokaryotic cells frequently form symbiotic relationships across kingdoms, profoundly influencing host physiology and adaptation. While bacterial symbioses with animals, such as in the human gut microbiome, are well-studied, interactions between bacteria and fungi, particularly yeasts, remain underexplored. Yeasts, ubiquitous unicellular fungi acting as saprophytes on plant or animal matter, possess diverse enzymatic capabilities enabling them to thrive in varied environments. In yeasts, endosymbionts are typically localized within the vacuole, a key compartment involved in storage, biosynthesis, and endocytosis. Stressful environments can drive bacteria to become temporary or permanent residents within yeast vacuoles. Current literature highlights associations of *Candida* yeast species with bacteria such as *Microbacterium sp.*, *Helicobacter sp.*, and *Staphylococcus sp.* Our research focuses on the symbiotic relationships between *Saccharomyces* yeasts and their endosymbionts, examining how the symbionts influence the yeast life cycle, physiological traits, and stress responses. We also aim to determine the evolutionary origins of yeast endosymbiosis and its prevalence across the *Saccharomyces* genus. Leveraging extensive yeast collections and phylogenetic approaches, we aim to explore the ecological and evolutionary dynamics of these interactions, providing new insights into the complexity of eukaryotes and prokaryotes interac

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P-14	*Biochemistry*	MADY Ahmed	IRCAN

The role of a high-fat diet in hematopoietic stem cells-Funded by LABEX Chair of excellence

HSCs accumulate in the bone marrow during aging, while they simultaneously lose their regeneration and self-renewal capacity. Additionally, the hematopoietic stem cell niche, whose main role is to support HSCs and safeguard their functionality, also exhibits distinct phenotypes upon aging. Increased adipogenesis, inflammatory signaling and senescence are common features of the aged HSC niche with vast consequences on HSCs. Various challenges faced by the body throughout life contribute to the deterioration of the hematopoietic system during aging, but the mechanistic basis of this process is not yet elucidated. For example, it is known that a high-fat diet renders hematopoietic stem cells (HSCs) less potent and leads to the loss of their stemness (Hermetet, et al., 2019), but it is not known whether the transcriptional and epigenetic changes induced by high fat diet contribute to the aging of HSCs. We will also check whether high fat diet establishes an epigenetic memory of events simulating aging. Our aim is to examine whether a high-fat diet induces stable epigenetic changes and transcriptional priming in hematopoietic stem cells that are like what occurs during physiological aging and thus contribute to aging phenotypes. For this reason, we will follow a high-fat diet for four or eight weeks to examine, after eight weeks, whether memory has formed in HSCs following the first four-week challenge. We assume that inflammation is a crucial factor in regulating the memory of a high-fat diet and are therefore using wild-type and knock-out mice for the innate immune sensor MDA5 which, when activated, gives rise to a type 1 interferon response and pro-inflammatory cytokines.

P-15	*Plant Biology*	ROSENTHAL PEREIRA LIMA Marina	ISA

Side effects of botanical pesticides: A case study on essential oils

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Research Institute: UMR INRAE 1355 – UniCA - ISA

Synthetic pesticides have been widely used to protect crops from insect pests. While effective, their overuse poses serious risks, including toxicity to humans and non-target organisms, chemical residues in food, environmental pollution, and the emergence of resistant pest populations. Consequently, alternative solutions such as biopesticides are being explored to reduce reliance on synthetic chemicals. Among these, botanical pesticides, particularly essential oils (EOs), have gained attention due to their rich composition of bioactive aromatic compounds, which serve as natural defenses through toxic, repellent, and deterrent effects against pests and pathogens.

Essential oils are generally considered safe, as evidenced by their use in food and cosmetic products and are expected to degrade rapidly in the environment due to their chemical instability. However, to anticipate and mitigate potential risks before widespread adoption, as learned from the history of synthetic pesticides, it is essential to thoroughly assess potential side effects in agricultural settings.

Within the context of Integrated Pest Management (IPM), it is crucial to evaluate the effects of botanical pesticides on beneficial organisms, particularly natural enemies of pests. Although often perceived as safer alternatives, EOs can still adversely affect these non-target species. Understanding and mitigating these effects is essential to preserving biological control agents and ensuring the overall success of IPM strategies.

This study aims to the sublethal effects of anise and fennel essential oils on non-target organisms, focusing on the aphid predator *Chrysoperla affinis*. The study aims to assess their impact on survival and predation rates, thereby contributing to a more comprehensive understanding of the potential of these botanical pesticides as sustainable tools in pest management. Ultimately, the goal is to support the development of IPM strategies that incorporate natural products to reduce dependence on synthetic insecticides and promote environmentally sustainable agriculture.

P-16	*Cancer/Immuno*	CHAPEAU Mélissa	C3M

Reprogrammed fibroblasts promote melanoma progression and immune evasion in the lymph node niche

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Melanoma is an aggressive skin cancer that, if not detected early, can metastasize beginning with lymph node invasion. This step is critical as it allows cancer cells to enter the bloodstream and spread to distant organs. Understanding lymph node invasion mechanisms could enable earlier and more effective interventions. During the pre-metastatic phase, melanoma cells secrete factors that reprogram lymph nodes, creating a niche favorable to tumor spread. While cancer-associated fibroblasts are known to promote cancer progression, little is known about the role of lymph node fibroblasts (Fibroblastic Reticular Cells, FRCs). FRCs play a key role in lymph node structure, as well as in T cell homeostasis. To mimic FRC pre-metastatic reprogramming, healthy human FRCs are incubated with melanoma secreted factors. We identified by RNAseq that these factors induce FRCs transcriptional reprogramming. Control and melanoma-reprogrammed FRCs are then cocultured with T cells or tumor cells to assess dysregulated interactions using flow cytometry and real-time microscopy. My results reveal that melanoma-reprogrammed FRCs enhance tumor cell proliferation, motility and resistance to targeted therapies. Additionally, they disrupt the anti-tumor immune response by altering T cell motility and upregulating immune checkpoint such as PD1 on T cells. These findings highlight the critical role of FRCs in creating a tumor-permissive microenvironment in early melanoma progression, and suggest new therapeutic approaches based on targeting the interactions between FRCs, tumor cells, and T cells.

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P-17	*Neuro/Immunology*	GARCIA GARCIA Raquel	Ulysseus

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Role of MOK signaling in inflammation-induced microglial activation in vivo

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Exacerbated microglial activation and sustained neuroinflammation are pathological hallmarks of Parkinson's disease (PD) and other neurodegenerative disorders. Indeed, accumulated data support the view that dysregulated microglial responses could be drivers in disease onset and progression. We have recently unleashed MAPK/MAK/MRK overlapping kinase (MOK) as a mediator of inflammatory and type-I IFN responses in microglia (Pérez-Cabello, PNAS 2023) – both of which have emerged as key immune settings in PD and other neurodegenerative diseases. Moreover, we identified BRD4 as a transcriptional regulator whose phosphorylation state and binding to several proinflammatory gene promoters are controlled by MOK (Pérez-Cabello, PNAS 2023). Our newly obtained results demonstrate that MOK controls microglial activation and neuroinflammation in a mouse model in vivo. In addition, our data from experiments using MOK-KO cells and ex-vivo samples from our MOK-KO mice demonstrate that certain signaling kinases linked to neurodegenerative diseases are downstream of MOK in inflammatory microglia, and also indicate that MOK plays a role in mitochondrial respiration performance. Overall, we provide new evidence on the role of MOK signaling kinase in microglial responses and its potential relevance in the context of PD and other neurodegenerative diseases.

P-18	*Plant Biology*	HERRERO GOMEZ Irene	Ulysseus

IalB, a rhizobial protein present in extracellular vesicles: a putative player in legume colonization and nodulation

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The symbiotic relationship between rhizobia and leguminous plants results in the formation of nitrogen-fixing nodules on the plant roots. Within these nodules, rhizobia convert atmospheric nitrogen into a form usable by the plant, enhancing soil fertility and reducing reliance on synthetic fertilizers. The symbiotic partners establish a complex molecular dialogue exchanging Nod factors, flavonoids, secreted proteins, and extracellular membrane vesicles (EVs), among others. This dialogue precedes the invasion of root hairs through the formation of infection threads and subsequent nodule organogenesis. EVs are lipid bilayer vesicles detached from the bacterial and eukaryotic surfaces. They are attracting attention in the field of plant-microbe interactions as they carry to distant sites bioactive molecules, including proteins between symbiotic partners.

We aim to dissect the EV-mediated crosstalk between *Rhizobium tropici* CIAT 899 and its legume hosts, *Phaseolus vulgaris* and *Lotus burttii*. To this end, we performed proteomic analyses of the CIAT 899 secretome and EVs, identifying proteins of potential interest in the symbiotic dialogue. Among them, the Invasion-Associated Locus B (IalB) protein was selected for further study due to its potential role in enhancing root colonization and infection by rhizobia. Bioinformatic analyses revealed that IalB is a periplasmic protein, and its sequence presents an intrinsically disordered region, suggesting a potential interaction site with other proteins. The fact that IalB is present in EVs and the secretome, coupled with its predicted interaction capability, implies a possible role in host plant communication.

Current experiments involve interactomic studies to identify *Phaseolus vulgaris* proteins interacting with IalB. Bacterial colonization assays indicate that the strain overexpressing *ialB* produces more infection threads and nodules in *L. burttii* roots compared to the wild-type strain, while the *ialB* mutant phenotype is under evaluation. Preliminary results suggest that IalB may play an important role in rhizobial legume symbiosis.

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P-19	*Biochemistry/Cancer*	BENACEUR Oumayma	C3M

Identification of new pharmacological eIF5A inhibitors against prostate cancer using a new enzymatic assay – the Hyp'Assay

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The latest epidemiological studies predict that by 2040 the incidence and mortality associated with prostate cancer (PCa) will double. The development of new pharmacological strategies appears to be the only way to curb the PCa mortality curve. Our laboratory has demonstrated that eIF5A plays an important role in PCa. eIF5A is a translation factor that must be hypusinated to be active. Hypusination is a unique post-translational modification, affecting only eIF5A. It is dependent on two enzymes: DHPS and DOHH and their substrates respectively the spermidine (a polyamine) and oxygen and iron.
Only a few pharmacological inhibitors of hypusination have been described and none of them are used in the clinic. The most described DHPS inhibitor is GC7. It is a competitive spermidine analogue. Because of the spermidine concentration in cells (millimolar range), competitive inhibitors cannot be used. No specific inhibitor has been described for DOHH. The only available inhibitors are iron chelators.

The paucity of new inhibitors is probably due to the hurdle of testing DHPS and DOHH activities. Classical assays require radioactive molecules coupled with HPLC.

We set up the Hyp'Assay, a non-radioactive cell-free assay to measure eIF5A hypusination. Hypusination is performed in 96 or 384 wells using recombinant human eIF5A, DHPS, and DOHH and is revealed by a specific hypusinated eIF5A antibody. The Hyp'Assay can be used to find DHPS and DOHH inhibitors. The Hyp'Assay has been published in PLOS One early this year.

The Hyp'Assay has been used to do a screening of 10 314 molecules from a chemical library specializing in protein-protein interaction inhibitors in collaboration with Dr. Morelli's team at the CRCM. This chemical library could enable us to find non-competitive inhibitors of DHPS and the first inhibitors of DOHH. We have already found 85 potential inhibitors of the hypusination.

Together, the Hyp'Assay is a very convenient and sensitive assay used for the first large-scale screening of DHPS/DOHH inhibitors. 85 potential inhibitors have been found that could be used for the treatment of cancer and other pathologies associated with increased activity of eIF5A.

P-20	*Physiopathology/Neuro*	LUBRANO DI SCAMPAMORTE Hélène	IPMC

Modulation of ASICs by endogenous lipids

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ASICs (Acid-Sensing Ion Channels) are excitatory cationic channels known to be activated by extracellular protons. They are widely expressed in the entire pathway of pain, where they appear as emerging actors in the signalling processes of nociception and pain. Moreover, besides protons, we identified endogenous lipids – such as lyso-phosphatidylcholine (LPC) – as new modulators of ASICs. These lipids are therefore potentially able to alter nociceptive signalling with pathophysiological consequences, and we recently demonstrated a role of LPC in the development of rheumatic pain both in rodents and humans.

Here, we investigated the effects of LPC analogues on ASIC3, identifying some of them as potentiators and/or activators of the channel, and other being inactive. These effects were similar to that of LPC and dependent on extracellular pH. Interestingly, it was found that one of these analogues could be more particularly relevant for skeletal muscle tissue thanks to lipidomic analyses made on different human samples from healthy controls. The in vivo effect of this analogue was next tested by carrying out pain behavioural experiments on mice, showing that intramuscular injections of this analogue could induce an ASIC3-dependant long lasting secondary mechanical allodynia.

Altogether, these results indicate that endogenous lipids such as LPC and analogues are positive modulators or ASICs, and especially ASIC3, which could be important in the pathophysiology of chronic pain arising from deep tissues such as muscle or joint. For the next steps, this investigation aims to better characterise the molecular mechanisms by which lipids act on ASIC3, with perspectives towards a better understanding of nociception signalling through this particular ion channel which behave as a coincident detector, as well as of rheumatic pain pathophysiology.

Keywords: ASIC, lipids, chronic pain, electrophysiology

P-21	*Immunology*	TRAN Nghia	IRCAN

Investigate the role of RIG-I-like receptors and Transposable element (TE) families in hematopoietic and progenitor stem cell (HSPC) development

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Keywords: *Hematopoietic stem and progenitor cells, transposable elements, RIG-I-like receptors, hematopoiesis*

Hematopoietic stem and progenitor cells (HSPCs) are essential for lifelong hematopoiesis, possessing the dual capacity for self-renewal and multilineage differentiation. During embryogenesis, definitive HSPCs emerge through a tightly regulated endothelial-to-hematopoietic transition (EHT), a process influenced by both intrinsic and extrinsic inflammatory pathways. Recent studies indicated that nucleic acid sensing pathways, particularly RNA sensing pathways mediated by RIG-I-like receptors (RLRs), which traditionally characterized for antiviral defense, are critical modulators of HSPC development and are activated by transposable elements (TEs) expressed in different EHT cell types. However, the precise mechanisms, especially the relative contributions of intrinsic and extrinsic RLR activity, remains poorly understood. In this study, we investigate the role of TEs and the mechanistic underpinnings of RLRs in developmental hematopoiesis. Using zebrafish model, we performed RNA sequencing on sorted cell populations (GATA1+ erythroid cells, CD41+ HSPCs, and MPEG+ macrophages) to uncover cell-type-specific differences in gene and TE expression profiles at different time points during EHT (36- and 48-hours post fertilization). The results suggested TE-driven signaling and its potential to shape inflammatory tone in a lineage-restricted manner. Indeed, major differences between expressed TEs were found among the different lineages but not in the same lineage at different time points. Additionally, mTORC1 signaling was found deregulated in RLR mutants and we are now exploring how TE driven RLR activation regulates mTORC1 pathway.

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P-22	*Bioinformatics/Omics*	OUALI Safae	TIRO/MATOs

Search for metabolomic signatures to determine the exposome of honey bees (Apis mellifera), a colony health indicator.

Safae Ouali, Serena Giuliano, Anne Claire Martel, Sabine Lindenthal, Thierry Pourcher, Véronique Duquesne, Sonia Dagnino.

Bees play a fundamental role in the balance of ecosystems, contributing to biodiversity and serving as bioindicators of environmental quality. However, in recent years, a worrying decline in bee populations has been observed worldwide. This phenomenon is attributed to various stress factors likely to weaken colonies and increase their mortality, including pesticides and pathogens. The links between these factors and the deterioration in bee health have been established, but the underlying molecular effects remain poorly understood. To better characterise these effects, controlled exposures with pesticides and experiments in natural conditions have been carried out. The aim of these studies is to identify biomarkers of bee metabolome capable of specifically signaling the cause of mortality, thereby adding to the targeted analyses. To achieve this, an analytical approach based on high-resolution mass spectrometry (HRMS) is being developed. The first results of this method will be presented here. Univariate and multivariate statistical analyses revealed distinct metabolomic profiles in bees exposed topesticides. The results of this study highlight the potential of this approach, not only to monitor and protect bee populations, but also to take advantage of their role as sentinel species, providing valuable information on the health of the ecosystem.

Keywords: exposome, metabolomics, bioinformatics, biomarkers, HRMS.

References:

Broadrup et al., 2019. Honey bee (Apis mellifera) exposomes and dysregulated metabolic pathways associated with Nosema ceranae infection. PLoS ONE 14, e0213249. https://doi.org/10.1371/journal.pone.0213249

Chen, H. et al., 2021. Metabolomic analysis of honey bees (Apis mellifera) response to carbendazim based on UPLC-MS. Pesticide Biochemistry and Physiology 179, 104975. https://doi.org/10.1016/j.pestbp.2021.104975

Shi et al., 2018. Metabolomic analysis of honey bee, Apis mellifera L. response to thiacloprid. Pesticide Biochemistry and Physiology 152, 17–23. https://doi.org/10.1016/j.pestbp.2018.08.003

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P-23	*Cancer*	MARTIN James	C3M

Melanoma is a cancer arising from the malignant transformation of melanocytes. The global incidence of melanoma is rising, especially in young age cohorts, underscoring its importance as a public health issue. The introduction of immune checkpoint therapy has revolutionised the treatment of metastatic melanoma, however a significant number of patients display innate resistance, and 20-30% of patients develop acquired resistance.

Due to the consumption of resources by cancer cells and vascularization impairments, the tumour microenvironment (TME) is frequently poor in nutrients and oxygen, establishing competition for nutriment access between cancer and stromal cells. Interestingly, several studies have demonstrated that arginine is one of the most depleted nutrient in the TME. In addition, prior research has demonstrated that arginine depletion drives epigenetic rewriting in cancer involving repressive chromatin remodelling.

In this context, my objective is investigating the role in arginine depletion in driving epigenetic rewiring in melanoma as well as resistance to targeted therapies and immune checkpoint inhibitors (ICI).

My preliminary experiments have demonstrated that arginine deprivation drives a decrease in the expression of DNA methyltransferases 1 and 3A (DNMTs). Furthermore, our results indicates that arginine deprivation drives resistance to BRAFi and MEKi in melanoma cell lines as well as resistance to anti-PD-1 therapy in murine melanoma models.

Thus, our goal with this project is to understand what are the mechanisms linking arginine deprivation , epigenetic rewiring and melanoma resistance in order to propose innovative strategy to fight against melanoma resistance.

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P-24	*Microbiology*	FINKELSTEIN Jade	ISA

Impact of chronic dietary intake of Bacillus thuringiensis insecticides on the gut environment and susceptibility to chronic inflammatory bowel diseases.

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Bacillus thuringiensis (Bt) spore-based bioinsecticides are widely used in agriculture for targeting specific insect pests. However, due to the resilient and persistent nature of Bt spores, they are now widespread in the environment and food chain. Bt belongs to the Bacillus cereus (Bc) group, which includes opportunistic pathogens. This group is linked to food poisoning and is the leading cause of foodborne outbreaks in France and Europe. The presence of opportunistic pathogens in the gut is known to promote inflammation, and when this inflammation becomes chronic, it can contribute to the development of chronic inflammatory bowel diseases (IBD). In addition, these pathogens can disrupt the balance of the intestinal microbiota, which can also contribute to the development of intestinal pathologies in the long term. Although short-term studies suggest that Bt spores may not harm non-target organisms, their long-term effects on the digestive system and gut microbiota - especially the potential risk of chronic inflammation in genetically predisposed individuals - remain unclear. Therefore, investigating the long-term impact of Bt spores on gut health is crucial.

My research uses adult Drosophila melanogaster as a model to explore the effects of chronic ingestion of Bt spores on gut physiology. Our results revealed reduced lifespan in exposed flies associated with altered gut structure, intestinal inflammation and oxidative stress. During the first year of my PhD, I focused on assessing fly longevity, gut permeability and bacterial load quantification. Complementary analyses, including a dysbiosis assay and experiments on axenic and immunocompromised flies, are ongoing to deepen our understanding of the Bt-induced mechanisms affecting gut physiology. These findings highlight potential health risks associated with chronic Bt exposure and underscore the importance of re-evaluating the long-term safety of Bt insecticides and their potential impact on public health

ABSTRACTS
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P-25	*Omics/System Bio*	MCANDREW Eamon	IPMC

A single-cell RNA isoform atlas of the human lung during early development and early COPD

The human airways, which deliver properly hydrated, microbe-free air to the distal lung, are the target of diseases such as chronic obstructive pulmonary disease (COPD), the fourth leading cause of death worldwide, lung cancer, the leading cause of cancer mortality, and asthma, the most common chronic childhood disease. Respiratory function depends on precise coordination between over a hundred specialised respiratory cell types.

Recent advances in single-cell RNA sequencing and spatial transcriptomics have already improved our understanding of respiratory cell identity and function. However, existing atlases focus on global gene expression data, without considering the diversity of RNA isoforms that result from alternative splicing. Given that 90% of human genes can undergo alternative splicing, a much greater diversity of transcriptional diversity is expected than that measured using current technologies. Aberrant splicing is often a feature of many diseases, particularly cancer and early developmental disorders. From this point of view, the characterisation of isoforms in different physiological and pathological contexts can provide key information on the transcriptional alterations at work in health and disease.

To address this gap, our group developed specialised techniques. ScNaUmi-seq is a wet-lab protocol combining droplet barcoding from 10x Genomics and long-read sequencing from Oxford Nanopore, incorporating UMI-guided error correction. It enables large-scale capture of full-length isoform sequences. SiCeLoRe is a computational framework that assigns cell barcodes and UMIs to Nanopore reads. Together, these tools generate cell-by-isoform count arrays, enabling detailed analysis of isoform specificity across cell types and contexts.

Using these methods, we generated single-cell long-read transcriptomes from 76,397 human airway cells across 14 adult and 5 fetal samples. The adult cohort includes 63,625 cells from healthy individuals and COPD patients, both smokers and non-smokers, sampled from four nasal and ten tracheobronchial regions, covering 49 distinct cell types. The fetal cohort comprises 12,772 cells from the lungs at gestational weeks 11, 15, and 20, spanning over 50 distinct cell types. Together, these datasets enable comprehensive mapping of isoform-level regulation across developmental stages, anatomical compartments, and disease states, offering new insights into the role of transcript diversity in respiratory biology.

P-26	*Dev. Bio/Neuro*	RAVEL Nils	iBV

Brain laterality : genes, circuits and behaviours in drosophila model

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Left/Right (LR) asymmetries are widespread in animals, and play a central role in the organisation and function of many organs (heart, brain, ...). In the nervous system, multiple levels of LR asymmetries coexist: anatomical, connective, and functional (hand preference, language, memory, ...). Illustrating their functional importance in humans, several cognitive disorders (autism, schizophrenia, dyslexia, ...) are strongly correlated with defects in the laterality of the nervous system. However, very little is known about the genetic basis and function of brain laterality. The laboratory recently identified the first genes/signalling pathways controlling adult brain asymmetry in Drosophila (Lapraz et al., Nat Com 2023). In this organism, H neurons represent a group of 20 neurons (10 in each hemisphere) projecting their axons into a synaptic zone “the asymmetric body” (AB) only on the right side of the brain. The laboratory has identified the conserved Netrin axon guidance pathway, which shows asymmetric activity of its ligand (NetrinB), active only on the right side and allowing the projection of H neurons in the right AB. Mutations in the Netrin pathway produce symmetrical animals, with H neurons projecting to both the left and right AB. Interestingly, loss of asymmetry in H neurons causes long-term memory defects. In this work we carried out a sensitive non-biased pan-genomic “Modifier” screen aiming at the identification of new genes and signalling pathways affecting brain laterality in Drosophila. This screen allowed us to identify more than 10 new regulators of the nervous system asymmetry, with the loss of function of some of them leading to a novel “inversion” phenotype (H neurons projecting on the left AB). As a result of our unbiased approach, identified genes belongs to various families (transcription factor, nuclear receptor, enzyme, ...) and have various known functions (cell differentiation, cytoskeletal, metabolism, ...). Characterisation of the candidate genes indicates that they act in different group of neurons before the first manifestations of cerebral symmetries. Future experiments will focus on the identification of the precise mechanisms to which these genes participate, as well as behavioural tests on flies with different “asymmetric status” (control/lost/inverted). This project will allow to establish a first genetic network controlling asymmetry in Drosophila and direct evidence of the functional relevance of asymmetry variation in individuals.

ABSTRACTS
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2nd YEAR PhD STUDENTS

P-27	*Cancer*	GONÇALVES Diogo	C3M

PINK1-dependent mitophagy is protumoral during lung cancer progression

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Mitophagy, a selective form of autophagy implicated in the elimination of damaged mitochondria, has emerged as a major process enabling cancer cells to resist both environmental stress and chemotherapeutic agents. Furthermore, it was recently established that mitophagy holds an essential role in the regulation of inflammatory responses, a key aspect of tumorigenesis. Lung cancer is a leading cause of death worldwide. While recent major advances were made in the treatment of this disease, the overall 5-year survival rate is only 15%, reinforcing the need for innovative and more efficient therapeutic strategies. Given the reliance of lung cancer on autophagy and mitochondrial metabolism, we focused on the PINK1-dependent mitophagy pathway, which plays a pivotal role in mitochondrial homeostasis.

Immunohistochemistry analysis revealed enhanced PINK1 expression and activity in lung cancer patients, findings confirmed by in silico analysis of published phosphoproteomic datasets. To elucidate the role of PINK1-mediated mitophagy in lung tumorigenesis, we analyzed the level of mitophagy in a genetically engineered mouse models of lung adenocarcinoma. To investigate mitophagy in vivo, we breed KrasLSL-G12D deficient for p53 (KP model) with Mito-QC mice, that are expressing a pH-sensitive fluorescent mitochondrial tandem allowing the assessment of mitophagy. Using this unique model, we observed that mitophagy was increased in both pre-neoplastic lesions and adenocarcinoma, a finding consistent with increased PINK1 expression and activity, compared to non-lesional areas. To interrogate the functional significance of PINK1 expression in lung cancer development, we used cutting-edge intratracheal injection of Cre recombinase-expressing lentivirus with a specific sgRNA to ablate PINK1 expression in vivo. Remarkably, deletion of PINK1 led to a significant reduction in tumor burden and a concomitant decrease in mitophagy. Those results were further validated using an allograft model, where PINK1-deficient KP cells generated smaller tumors in vivo.

Complementary in vitro studies demonstrated that PINK1 deficient cells have impaired mitochondrial respiration and enhanced antioxidant defenses underscoring the critical role of PINK1-mediated mitophagy in maintaining mitochondrial function and redox homeostasis in lung cancer cells. Overall, our study highlights the pivotal role of PINK1-mediated mitophagy in cancer development and its potential as a therapeutic target.

Keywords: mitophagy, Pink1, mito-QC, oncogenesis, Lung Cancer, intratracheal in vivo invalidation.

P-28	*Marine Biology*	WURTZ Mickael	IRCAN

Successive amputations induce morphological rejuvenation in Nematostella vectensis

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Aging is a complex, multifactorial process resulting in a progressive loss of physiological integrity, characterized by an increased susceptibility to death. Interestingly, not all living beings are equally susceptible to aging. Indeed, several marine organisms including some cnidarians (e.g., sea anemones, corals) appear to exhibit extreme longevity. Among them, the sea anemone N. vectensis, shows no apparent signs of aging over time and offers a wealth of resources, techniques and tools for functional genomics and molecular and cellular analysis. To gain insight into N. vectensis' aging biology, its longevity and the underlying cellular and molecular mechanisms are being investigated.

The project is articulated around two specific aims: 1) systematically characterizing longevity at the morphological, physiological, cellular and molecular levels over time; 2) perturb this longevity by genetic approaches or by applying chronic stress. For the latter we performed successive amputation-regeneration cycles combined with starvation, both affecting stem cells and therefore potentially accelerating the exhaustion of the stem cells, one of the hallmarks of aging. Animals were assessed for their survival and reproduction rates to determine its longevity, as well survival rates and morphological features following chronic stress.

Our preliminary results indicate stable reproduction and mortality rates in N. vectensis polyps allowing us to predict a minimal lifespan of several decades. Concerning the application of chronic stress, N. vectensis appears to be resilient to successive amputations as animals regenerate for several cycles without any notable increase of mortality. Interestingly though, successive amputations induce several morphological changes in the animals resulting in a juvenile-like morphology. Combined with starvation, although a notable increase of mortality has been characterized, the apparition of the juvenile-like morphology is accelerated. These intriguing observations lay the foundations for ongoing work, aiming at characterizing the underlying molecular and cellular of this morphological rejuvenation.

P-29	*Immuno/Microbiology*	GUILLEBON Claire	C3M

Characterization of the systemic innate immune response upon infection with Bacillus cereus spores

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Keywords : Bacillus, Spore, Systemic infection, Innate immune response, Drosophila

The Bacillus thuringiensis (Bt) spore-forming bacteria are used as bioinsecticides specifically targeting lepidopteran crop pests.. Their wide use in agriculture favors encounters with non- target organisms.

The Bacillus cereus (Bc) spore-forming bacteria are ubiquitous in the environment and many strains of which are opportunistic pathogens. Spores are a highly resistant form of the bacteria. This group is implicated in food poisoning (1st cause in France and Europe) and in systemic nosocomial infections (fatal in 30% of cases in newborns). In the hospital environment, infections occur likely via spores that are present on medical equipment. Due to their resistance properties, spores are very difficult to eliminate and their presence in medical facilities is problematic. It is therefore important to better understand the defense mechanisms implemented by the host following infection with these bacteria to set up therapeutic measures to avoid the fatal issue of these infections.

The well conserved innate immune response being the first barrier against infections, I'm studying the response mounted after systemic infection with different strains of the Bc group: agricultural strains, reference strains, probiotics and hospital strains which have caused septicemia in newborns. I am particularly investigating the immune response triggered by the spore form of the bacteria. I draw a parallel between this response and the activation of immune pathways caused by vegetative bacteria, which is well documented. My first results show that systemic infection with the vegetative form of Bt is more virulent than with the spore form of the bacteria.

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P-30	*Physiopathology*	ALEXOPOULOU Zampeta-Sofia	CoBteK

Validation of Speech-based Digital Cognitive Assessment Composite Scores for the Detection of Mild Cognitive Impairment Over Paper-based Clinical Assessments

Background: Subtle alterations in speech patterns may precede clinical dementia onset. Clinical trials increasingly focus on the identification of patients with Mild Cognitive Impairment (MCI) for disease-modifying treatments. Increasingly, digital speech-based assessments have gained importance for scalable and objective MCI screening.

Objective: This study aimed to validate a fully remote, automated speech-based digital cognitive assessment for the detection of MCI compared to gold-standard paper-based clinical assessments.

Methods: Within the PROSPECT-AD project, we collected speech and clinical data from the German DELCODE and DESCRIBE cohorts, specifically from 21 healthy controls (HC), 110 patients with Subjective Cognitive Decline (SCD), and 59 with MCI. Partial correlation analysis was employed to examine associations between speech- based scores and clinical measures. Kruskal-Wallis tests were used to explore group differences. Intraclass correlation coefficient was calculated to examine the agreement between clinical and speech-based assessments. We compared the classification performance of gold-standard clinical scores and a composite speech-based digital cognitive assessment score (SB-C) for differentiating MCI from HC/SCD.

Results: There was a significant difference in global cognition as measured by SB-C between groups based on the Clinical Dementia Rating score (0 vs 0.5) ($H(1) = 23.98$, $p < 0.001$). SB-C and its domain-specific composite scores of memory, executive function and processing speed were significantly correlated with global and domain- specific gold-standard paper-based assessments. There was a high agreement between the automated and the paper-based assessment of the semantic verbal fluency task. Finally, in logistic regression classification, the model combining SB-C and clinical tests yielded an excellent discriminatory power in identifying MCI cases (Area Under the Curve = 0.86).

Conclusion: We conclude that fully automated speech-based cognitive assessments can be effective and sensitive in capturing cognitive abilities. More importantly they hold promise toward remote and scalable MCI screening compared to conventional paper-based assessments, with implications in both clinical practice and trials

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P-31	*Bioinformatics/Omics*	MUKESHA Kabandana Dany	CoBteK

Metabolomic Signatures and Machine Learning Models for Distinguishing Alzheimer's Disease and Dementia with Lewy Bodies

Objectives:
Alzheimer's Disease (AD) and Dementia with Lewy Bodies (DLB) are difficult to distinguish clinically due to overlapping symptoms, resulting in delayed or incorrect diagnoses. This study uses metabolomic profiles from serum samples and machine learning models to identify key biomarkers that distinguish these conditions.

Methods:
Serum samples from 55 AD, 14 DLB, and 52 healthy control (HC) individuals from the ADDIA cohort were analyzed using a targeted metabolomics approach. Metabolites were quantified with the AbsoluteIDQ® p400 HR kit (Biocrates Life Sciences AG) and analyzed via high-resolution liquid chromatography-mass spectrometry (LC-HR-MS). Machine learning models, including Lasso, Random Forest, and XGBoost, were trained for classification. *APOE* genotyping was performed using the CE-IVDR APOEasy® kit and incorporated into the models.

Results:
AD patients exhibited a significantly higher prevalence of *APOE* e3/e4 and e4/e4 genotypes compared to DLB and HC ($p<0.001$). Lipid dysregulations, particularly in phosphatidylcholines, lysophosphatidylcholines, triglycerides, and sphingomyelins, were observed across all groups. Lasso identified 63 key metabolites, improving the AUC for distinguishing AD from DLB from 0.78 to 0.81 with *APOE* inclusion. Similarly, the AUC for AD vs HC increased from 0.78 to 0.83 with *APOE*, while no improvement was seen for DLB vs HC (AUC=0.78).

Conclusions:
This study demonstrates the potential of metabolomic biomarkers in differentiating AD from DLB, with *APOE* genotyping enhancing classification accuracy. Future efforts will focus on validating findings in larger cohorts and translating these findings into non-invasive, cost-effective tool set to reduce AD and DLB misdiagnosis.

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P-32	*Biochem/Microbiol*	BANCILHON Déborah	IPMC

Mosquito-borne Zika virus (ZIKV) has become a serious health threat due to its rapid global spread and associated pathologies. Faced with the risk of emergence of ZIKV strains recently isolated in Africa, it is vital to define the important molecular, cellular and structural mechanisms linked to infection and viral persistence in certain tissues, as well as to contribute to the development of therapeutic countermeasures. During infection, ZIKV manipulates the host's lipid membranes and intracellular proteins to create a microenvironment favorable to its replication and propagation, notably through the formation of replication organelles (ROs). These ROs establish close contacts with endoplasmic reticulum (ER)-derived membrane bundles and appear to be enriched in sphingolipids and cholesterol. However, the host proteins involved in this membrane remodeling are poorly described. Our preliminary data suggest that the OSBP/VAP-A protein complex, controlling non-vesicular lipid fluxes between organelles at membrane contact sites (MCS), contributes to ZIKV infection. Our hypothesis is that these proteins, through their predominant roles in lipid exchange and MCS architecture, modulate the composition of the membranes from which ZIKV benefits for its replication. Hence, our prior aim is to assess ZIKV's dependence on host lipid pathways, in particular those controlled by OSBP/VAP-A for the formation of ROs during infection. In a second phase, the project will be devoted to studying the mechanism of action of new analogues of natural molecules with antiviral properties that target OSBP/VAP-A. These data will provide a better understanding of the pathophysiology of ZIKV, and weapons to combat this virus for which there is currently no treatment or vaccine available.

P-33	*Cancer*	SEGUI Fabien	CSM

Ferritin as a Therapeutic Target for Iron-Dependent Cell Death in Medulloblastoma

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Iron is one of the most abundant metals in the brain and plays a pivotal role in numerous biological processes. Iron is also essential for brain development due to its involvement in neural stem cell proliferation and differentiation. This highlightsthe importance of tightly regulated iron homeostasis in the brain, from early development through adulthood. Dysregulated iron metabolism is also a key hallmark of embryonal brain tumors, such as medulloblastoma (MB). These tumors rely on increased content of ferritin, the only known iron storage protein complex. Iron chelators effectively deprive cancer cells of iron in vitro but are ineffective in vivo due to unspecific iron deprivation which causes side effects. Given ferritin's central role in iron homeostasis, we hypothesize that targeting ferritin could enhance the specificity of cancer cell targeting.
Genetic deletion of the ferritin heavy chain (FTH) significantly hindered the proliferative capacity of MB cells. Intracranial implantation of FTH knock-out (FTH-/-) cells resulted in delayed tumour growth and extended survival of mice compared to their WT counterparts. Besides, FTH-/- cells exhibited increased sensitivity to iron overload, characterized by elevated content of lipid hydroperoxide and cell death, which was prevented by a ferroptosis inhibitor. Interestingly, reduction of ferric (Fe3+) to ferrous (Fe2+) ions by high doses of vitamin C (Vit C, 10mM) also induced cell death in WT cells. However, it did not show characteristic lipid hydroperoxide and was not rescued by any cell death inhibitor, suggesting the occurrence of an iron-dependent non-ferroptotic cell death. Interestingly, the major molecular event observed was degradation of FTH, most likely due to overwhelming Fe2+ content in the cell. Conversely, lower concentrations of Vit C (1 mM) led to an upregulation of FTH expression in WT cells, allowing them to survive. Instead, FTH KO cells, not being able to upregulate FTH, show massive cell death upon the same treatment.

Our data clearly indicate that ferritin plays a pivotal role both as an iron-buffering complex, providing adequate iron for proliferation, and as an antioxidant defense system, allowing cancer cells to survive oxidative stress. Thus, targeting ferritin for anti-cancer treatment appears promising, as it could be cancer-specific, increasing the efficiency of cancer eradication and improving patient lifespan.

P-34	*Structural Biology*	JABAUD Laure	ISA

Timing of chitin/chitosan matrix assembly in insects

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Chitin is a key component for the cuticle that serves as an exoskeleton in insects. It is a polymer of the monosaccharide N-acetyl-glucosamine (GlcNAc) produced by the membrane-bound glycotransferase chitin synthase. Chitin and its deacetylated form, chitosan, associated with chitin/chitosan-binding proteins adopt a tri-dimensional organization, a matrix, in the extracellular space.

With current data, the hypothesis is that variabilities of properties of the chitin matrix in different body parts and stages of insects are due to the deacetylation fraction and pattern and the association with chitin/chitosan-binding proteins. The project aims at understanding how the chitin/chitosan matrix is developing in time and space and to know how the chitin/chitosan-binding proteins are incorporated into the matrix.

For this purpose, I focus on the leg system of the fruit fly Drosophila melanogaster. Before actually studying the underlying molecular aspects, to us, it is important to understand the variability of the matrix structure. Therefore, results for other Drosophila species will be used to compare and to understand the diversity of this system. In the leg, I study a specific structure called the trochanter, this structure is poorly described but is probably required for locomotion and flight. Currently, I am characterizing all leg segments with respect to the trochanter and compare the different pairs of legs for males and females for the same D. melanogaster strain, between strains and different species. Based on this data, I expect to better understand the formation of the trochanter chitin/chitosan and proteins matrix.

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P-35	*Cancer/Immunol*	DJEBBOUR Hyame	IPMC

The extracellular matrix of oral squamous cell carcinoma modulates the spatial distribution and phenotypes of tumor-associated macrophages in OSCC mouse model

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Oral squamous cell carcinomas (OSCC) are cancers of the oral cavity and the sixth most common cancer worldwide. Only 50% of the OSCC patients survive up to years after diagnosis due to relapse and loco-regional spread following treatment failure. Recent studies have shown that Tenascin-C (TNC) is a major ECM component upregulated in OSCC with immunosuppressive functions and promotes tumor progression. However, its role in the regulation of the phagocytic immune cells, especially tumor-associated macrophages (TAMs), main actors of the OSCC tumor immune microenvironment has not been thoroughly investigated. TAMs, by secreting pro-inflammatory cytokines and promoting angiogenesis, contribute to the immunosuppressive tumor microenvironment, enhancing tumor growth and metastasis.

Recent studies from the laboratory revealed the phenotypic heterogeneity of macrophage subsets in human OSCC using spectral flow cytometry combined with multiparametric imaging, and identified a subset of macrophages expressing the CD206 mannose receptor and the CD11c integrin predominantly localized within tenascin-C (TNC)-rich regions. In that context, the aim of my PhD project is to comprehensively characterize macrophage subsets including the $CD206^{+}CD11c^{+}$ macrophage subset in murine models of OSCC. I will focus on in-depth phenotypic, functional, and spatial profiling, as well as elucidating the role of tenascin-C (TNC) in modulating the function and behavior of these macrophages within the tumor microenvironment. To address these objectives, I use two complementary murine models of OSCC: a 4-nitroquinoline-1-oxide (4-NQO)-induced carcinogenesis model that recapitulates the multistep progression of OSCC, and an orthotopic OSCC model based on the intra-lingual implantation of mEERL95 tumor cell line generated in TNC wild-type and knock-out mice.

Spectral flow cytometry analysis revealed macrophage heterogeneity in both 4-NQO-induced OSCC and mEERL95 models with the presence of a $CD206^{+}CD11c^{+}$ macrophage subset, similarly to our findings in human OSCC. Interestingly, the $CD206^{+}CD11c^{+}$ macrophage subset is significantly enriched in 4-NQO-induced OSCC expressing tenascin-C (TNC). In addition, spatial analysis by multiparametric immunofluorescence revealed the accumulation of $CD206^{+}CD11c^{+}$ macrophages within TNC-enriched regions. This macrophage subset has increased expression of maturation markers and phagocytic activity, suggesting a potential role in tumor antigen presentation within the tumor microenvironment. Moreover, a notable sex-specific difference in macrophage phenotype and function was observed, highlighting the need for further investigation into gender-related variations in macrophage behavior in OSCC.

P-36	*Cancer*	REVERTE PAGOLA Gonzalo	Ulysseus

Functional Evaluation and Treatment of Sarcopenia in Patients with Non-Metastatic Castration-Resistant Prostate Cancer

Prostate cancer remains one of the most prevalent cancers worldwide, with non-metastatic castration-resistant prostate cancer (nmCRPC) posing a significant clinical challenge. Recent advancements in treatment have focused on delaying metastasis; however, sarcopenia—characterized by muscle mass loss and functional decline—has emerged as a critical factor influencing patient prognosis, treatment toxicity, and overall quality of life.

This project aims to detect and intervene in sarcopenia among nmCRPC patients, incorporating a two-phase approach: (1) Detection, through morphological and functional assessments using computed tomography (CT), bioimpedance, handgrip dynamometry, gait analysis, and mobility tests; and (2) Intervention, involving a tailored lifestyle modification program that integrates supervised exercise and nutritional strategies. A multidisciplinary team—including oncologists, a sports medicine expert, and a specialized nurse—will lead the initiative, ensuring a patient-centered approach.

The primary objectives are to enhance prognosis and quality of life by reducing sarcopenia prevalence, assessing the impact of exercise and nutrition on treatment tolerance, and conducting early interventions in at-risk patients. Cost-effectiveness analysis will also be performed, evaluating economic implications for healthcare systems.

Potential limitations include sample selection biases, adherence to the training program, technological access, follow-up duration, and individual response variability. Addressing these challenges will be crucial for validating the project's feasibility.

By integrating sarcopenia assessment into routine clinical practice, this project seeks to establish a standardized protocol that optimizes patient care, ultimately contributing to improved health outcomes for nmCRPC patients

P-37	*Biochem/Cell Cycle*	GARCIA BERNARDO Lorena	Ulysseus

The cohesin complex associated protein PRR12 is involved in the DNA damage response

Lorena García-Bernardo, María Ceballos-Chávez, Patricia Navarro-Cansino, Lucía González-López, Román Gonalez-Prieto, Pablo Huertas, Sonia Jimeno, Mario García-Domínguez and Jose C. Reyes

The maintenance of genomic stability is essential for cellular homeostasis, and dysregulation of the DNA damage response (DDR) is a hallmark of cancer and age-associated diseases. While several key DDR regulators have been well characterized, the role of many nuclear proteins remains unexplored. PRR12 (Proline-Rich Protein 12) is a cohesin interactor whose mutation causes a severe neurological and visual syndrome. Structurally, PRR12 contains two AT-hook domains and two globular domains at its C-terminal end. Although the precise function of the globular domains was previously unknown, our findings demonstrate that they mediate protein-protein interactions. The protein is also largely composed of low-complexity regions, typical of proteins undergoing liquid-liquid phase separation (LLPS)— a phenomenon involved in DNA damage repair, among other processes, by facilitating the spatiotemporal concentration of repair factors at DNA double-strand break sites. Here, we identify PRR12 as a novel participant in the cellular response to DNA damage. Using CRISPR-mediated knockout and RNAi approaches, we show that PRR12 depletion sensitizes cells to ionizing radiation. Mechanistically, we find that PRR12 is recruited to sites of DNA damage and physically interacts with established DDR factors. These findings suggest that PRR12 is a key mediator of the early DNA damage response and may represent a novel therapeutic target in tumors with compromised genome integrity.

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P-38	*Biochem/Cancer*	KARAULIC Arthur	IRCAN

Lymphatic and Vascular Resistance Factor: Study of a new form of VEGFA with unique properties in pediatric medulloblastoma.

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Affilations : Université Côte d'Azur ; Institute for Research on Cancer and Aging (IRCAN) UMR CNRS 7204 / U INSERM 1081 ; Fondation ARC ; Cancéropôle PACA.

Medulloblastoma (MB), the second most prevalent solid brain tumor in pediatric patients, is composed of four molecular subgroups (Wingless (Wnt), Sonic Hedgehog (SHH), Group 3, and Group 4), each characterized by increasing aggressiveness. Despite multimodal treatments, 30% of patients experience relapse with the fatal onset of metastases within five years.

The intricate network of blood and lymphatic vessels plays a key role in the metastatic spread of MB. Vascular endothelial growth factor (VEGF) is a central player in angiogenesis, the process of forming new blood vessels. It binds to receptors with tyrosine kinase activity (VEGFR1 and VEGFR2) and coreceptors known as neuropilins 1 and 2 (NRP1/2).

Recently, my host team uncovered a novel form of VEGF resulting from alternative splicing, altering the open reading frame, and introducing a unique C-terminal part comprising an additional 60 amino acids (Montemagno, C et al Mol Oncol 2023). This newly identified variant, named "Lymphatic and Vascular Resistance Factor (LVRF)," demonstrates distinctive pro-angiogenic and pro-lymphangiogenic characteristics. LVRF promotes the aggressiveness of highly vascularized kidney cancer, conferring resistance to anti-angiogenic therapies.

My investigation revealed elevated LVRF expression in treatment-resistant cells, prompting inquiries into its role as a stress response factor. Comparative analysis demonstrated heightened LVRF expression compared to healthy neuronal cells. Its expression increases following metabolic or hypoxic stress commonly encountered in rapidly growing tumors. Silencing LVRF expression using siRNA resulted in reduced MB cell proliferation and subsequent cell death. This "down-regulation" also impeded the migration of tumor cells, a crucial parameter reflecting intrinsic aggressiveness.

In conclusion, LVRF plays a pivotal role in key parameters governing MB cell aggressiveness. These findings lay the foundation for more in-depth studies on the genetic and pharmacological inhibition of LVRF, as well as the consequences of in vivo LVRF inhibition.

P-39	*Physiopathology*	DA CUNHA Eloise	CoBteK

Differentiating underlying pathologies in early Alzheimer's clinical phenotypes: interest of acoustic markers for predicting CSF biomarkers and clinical evolution

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Background:
Accurate early detection and specific classification of Alzheimer's disease (AD) is a critical challenge in neurogeriatrics. Diagnosing this condition often requires invasive procedures to analyze cerebrospinal fluid (CSF) biomarkers such as B-amyloid and tau proteins. Logopenic primary progressive aphasia (lvPPA), a syndrome primarily affecting language with an AD-like phenotype, frequently progresses to AD (1). However, the current diagnostic process is insufficient to differentiate lvPPA from AD and predict the clinical course of lvPPA patients. Recent research indicates that automated acoustic analysis of sentence repetition task can discriminate lvPPA and AD at onset time (2). Therefore, this study explores the potential of acoustic markers to predict CSF biomarkers in lvPPA and their clinical evolution.
Methods:
This longitudinal study included 26 patients: 14 with an initial diagnosis of lvPPA and 12 with AD. All patients underwent CSF analysis. AD biomarkers were present in all AD patients and in 7 lvPPA patients (lvPPA+), while the remaining 7 lvPPA patients (lvPPA-) did not exhibit AD biomarkers. Patients performed a sentence span task, targeting the phonological loop, at the time of diagnosis (3). A total of 67 prosodic and temporal features were extracted from these speech recordings. Subsequently, their clinical evolution was assessed over 12 to 18 months. Following this, a multinomial logistic regression was performed to predict the final diagnostic classification, considering both CSF results and clinical diagnostic evolution. This classification resulted in three groups: AD patients with a CSF-confirmed diagnosis, lvPPA patients with AD biomarkers who progressed to AD, and lvPPA patients without AD biomarkers who retained an lvPPA diagnosis. To refine the model, 39 parameters with adapted variance inflation factors (VIF) were selected. Cross-validation with a 70/30 train-test split was used to evaluate model performance.
Results:
The first multinomial logistic regression model with 67 acoustic covariates demonstrated strong predictive performance, with an overall accuracy of 80%, an AUC of 0.89 and a R^2 of 0.53. Precision scores were 0.71 (AUC=0.88) for predicting progression to lvPPA+, 0.77 (AUC = 0.86) for lvPPA-, and 0.88 (AUC = 0.89) for AD. In a refined model using 39 significant predictors, 16 variables significantly improved prediction accuracy, leading to an increased R^2 of 0.73 and a highly significant Likelihood Ratio Test (p-value = 3.5e-51). Although the general predictive accuracy of the test set decreased to 76%, these results highlight a significant predictive model for CSF biomarkers and clinical evolution in the context of Alzheimer's-like phenotype. Therefore, this exploratory analysis suggests that acoustic speech markers could serve as valuable predictors of both CSF biomarkers and the pathological progression of neurodegenerative diseases.
Conclusion:
This study suggests that acoustic markers could serve as accessible predictive indicators for the pathological evolution of Alzheimer-like clinical phenotypes at the onset of neurodegeneration. These findings highlight the potential of acoustic classification as a non-invasive tool to enhance early diagnosis and improve patient's care orientation. To confirm these results, further research with larger datasets and advanced classification techniques is warranted to validate these promising results.

Keywords: Alzheimer Disease, Primary Progressive Aphasia, Acoustic markers, Cerebrospinal Fluid

Clinical Trial Registry: This study was registered and approved by CPP Ile de France X (N° IDRCB: 2019-A00342-55 accepted on 11 September 2019).
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References:
Gorno-Tempini, & al. *Neurology*. 2011 76, 1006–1014. https://doi.org/10.1212/WNL.0b013e31821103e6
Da Cunha E, & al. *Life*. 2022; 12(7):933. https://doi.org/10.3390/life12070933
Arslan, S., & al. *Alzheimers Dement.* 2020, *16*, e042842. https://doi.org/10.1002/alz.042842

Eloïse Da Cunha is a speech and language pathologist (MSc) and a Ph.D. candidate in neurogeriatrics at the CoBTeK laboratory, University Côte d'Azur. She also presents courses in the Department of Speech-Language Pathology at the Faculty of Medicine in Nice. Her doctoral research, funded by the Interdisciplinary Institute of Artificial Intelligence Côte d'Azur, focuses on developing innovative, non-invasive diagnostic tools for neurodegenerative diseases, particularly Alzheimer's disease, frontotemporal lobar degeneration, and primary progressive aphasia. By integrating artificial intelligence with acoustic and vocal markers, her work aims to enhance early diagnosis and accurately predict the clinical progression of these diseases. This research involves creating automated classification models to identify specific neurodegenerative patterns, with the goal of improving patient care through timely and precise interventions tailored to the unique progression of each disease.

P-40	*Bioinformatics*	GOSSET Clément	LP2M

Maximum Cold Ischemia Duration for a Kidney Allograft: A Prediction Model for Allograft Failure at the Time of Organ Allocation.

Clement Gosset

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Background: Many determinants of kidney allograft failure are established at the time of allocation by organ distribution agencies. At this point, the main modifiable factor is the du- ration of cold ischemia (CIT). Currently, no practical tool exists to determine the maximum permissible cold ischemia time for a specific recipient at allocation.

Methods: We analyzed two prospective cohorts including kidney transplant recipients from European medical centers: a derivation cohort of 7040 recipients and a validation cohort of 6131 recipients. The main outcome was allograft failure (return to dialysis or pre-emptive retransplantation). We assessed 26 determinants of allograft failure available at the time of allograft allocation including cold ischemia time as a modifiable factor. Prediction models were developed using a classical survival analysis and a competing risk framework.

Findings: Allograft failure occurred in 16% (1113) of the derivation cohort and 14% (832) of the validation cohort. Independent determinants of allograft failure were donor age (HR 2.2 for donors above 65 years old), previous allografts (HR 1.48), dialysis history (HR 1.65 for Hemodialysis), diabetes (HR 1.42), vascular disease (HR 1.28), HLA-DR incompatibility (HR 1.16), donor serum creatinine (HR 1), and cold ischemia time (HR 1). Donor age was the strongest contributor, while cold ischemia was the only modifiable factor. These factors were combined into two predictive models of kidney allograft failure (Cox regression and Fine Gray) showing accurate calibration, and discrimination with a C-Index of 0·66 (95% CI: 0·63 to 0·70 at year one) on the validation cohort for the Fine Gray model. The Fine-Gray model, which accounts for the competing risks between allograft failure and patient death, was used to develop a practical tool for predicting allograft failure based on cold ischemia.

Interpretation: Prediction model at the time of allocation provides a simple and practical tool 2 which may guide organ distribution agencies and medico-surgical teams by customizing cold ischemia time for a kidney allograft transplantation.

P-41	*Cancer*	RIVAULT Adèle	C3M

Adressing oncoproteins to the lysosome using synthetic chimeric molecules

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Inhibition of oncogenic proteins has long been a cornerstone in the treatment of leukemia. However, the emergence of treatment resistance due to mutations in these targets has spurred the development and rapid advancement of targeted protein degraders, such as PROTAC technology.

Our objective is to develop an innovative approach using ADOLYS compounds to directly address oncogenes to lysosomal degradation through the Chaperone Mediated Autophagy (CMA) process. These ADOLYS compounds are precisely designed chimeric molecules that intricately connect two proteins, the chaperone protein HSC70 necessary for lysosomal delivery and the oncogenic target protein.

Acute Myeloid Leukemia (AML) frequently involves mutations in the FMS-like tyrosine kinase 3 (FLT3) gene, found in about 30% of AML cases. The most prevalent mutation is the internal tandem duplication (FLT3-ITD), present in approximately 25% of AML cases. This mutation drives the disease, leading to a high leukemic burden and poor prognosis. Effective treatment has been characterized by inhibiting the BTK protein kinase, which acts downstream of FLT3-ITD, using Ibrutinib. Our approach aims to degrade BTK, a critical oncogenic target in this condition.

To achieve this, we propose synthesizing a chimeric compound that merges an anchoring motif for the chaperone protein HSC70 – the KEFRQ-like motif – with a BTK protein inhibitor. The goal is to use the chaperone-mediated autophagy (CMA) process to specifically degrade the BTK protein kinase. Development of this heterobivalent construct involves 4 main stages: firstly, preliminary work on Ibrutinib efficacy conservation, screening of KFERQ-like motif for HSC70 binding, management of the oncogene and its degradation by CMA, and finally optimization of the degrader scaffold.

P-42	*Dev. Bio/Marine Bio*	HOFMÄNNER Kai	IRCAN

Initiating regeneration: Insights from genes with regeneration-specific expression dynamics

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To what extent regeneration redeploys the molecular mechanisms underlying embryogenesis is a historical question in the field of regeneration biology. Using the sea anemone Nematostella vectensis (Cnidaria, Anthozoa),, a recent study performed a comparative transcriptome analysis and revealed a set of genes with a regeneration-specific expression dynamics .

To decipher the role these genes may play during regeneration in N. vectensis, the current project is articulated around three specific axes: 1) Selection and characterization of the spatio- temporal expression dynamics of the "regeneration-specific" genes of interest (rsGOIs) using temporal expression data and whole mount in situ hybridization; 2) Identification of regulatory elements initiating injury-induced "regeneration-specific" gene expression using ATAC-seq and cis-regulatory assays; 3) Investigation of the role (requirement / sufficiency) of the rsGOIs using functional genomic approaches (KO/KI).

We have determined a list of 23 rsGOIs whose expression is activated shortly after injury (2- 4hpa) and at the onset of regeneration (18-24hpa). Their expression is restricted at the amputation-site and /or in the mesenteries, an internal structure that is crucially required for the initiation of the process of regeneration. The development of constitutive KO lines, as well as a conditional overexpression system to test the sufficiency of the rsGOIs have been initiated. To develop relevant "sufficiency" assays, we have performed an in-depth analysis of the capacity of cWnt activation to initiate ectopic head formation following injury. This allowed us to understand the duration during which the injury is permissive for a pro-regenerative response. In sum, this works sets the foundation to assess and understand the roles of rsGOIs at the onset of regeneration and their potential sufficiency to induce a regenerative response.

ABSTRACTS
POSTERS
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P-43	*Neurobiology*	BALDUZZI Jonathan	IPMC

Preclinical study of Neurosense: a European project to fight against SUDEP

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Sudden Unexpected Death in Epilepsy (SUDEP) is characterized for the most part by a generalized tonic-clonic seizure followed by an apnea and a cardiac arrest. SUDEP is a major issue for for epileptic patients in general and their families (1/1000 patient die each year) and for Dravet syndrome in particular, which shows a particular high SUDEP risk. There are no methods yet for predicting and preventing SUDEP. The European project Neurosense (NEUROendocrine SENSor for SUDEP prediction and prevention; https://neurosense-project.eu/project/) has the final goal to develop the first SUDEP Medical Device (SMD) prototype to anticipate life-threatening seizures and trigger automatic emergency drug administration to prevent SUDEP. The basic hypothesis of the project is that dysfunctions in arousal mechanisms are involved in SUDEP. The first step of this project, the preclinical study, is to find and quantify arousal biomarkers in Dravet syndrome mouse models carrying mutations of the Scn1a gene (NaV1.1 sodium channel) and correlate their dysfunctions to SUDEP occurrence in mice. For this, using microdialysis, we quantify biomarkers implicated in arousal mechanisms during seizures (spontaneous or induced with the convulsant flurothyl) and correlate their dynamics with SUDEP events.

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ABSTRACTS
POSTERS
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P-44	*Immunol/Microbiol*	MARION Valentine	C3M

The immune memory is not only restricted to the adaptive immunity. The innate immune system is also able to memorize an event and mount an increased response. This is called trained immunity. Among the innate immune cells, monocytes/macrophages have been the most described ones with an enhanced inflammatory response, along with an increased expression of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1β. It has also been shown that NLRP3 inflammasome plays a key role in macrophage trained immunity in response to a pro-inflammatory occidental diet. Inflammasomes are cytosolic molecular complexes that, once activated, maturate the proinflammatory cytokines IL-1β and IL-18. However, little is known concerning the role of NLRP3 inflammasome in the induction of trained immunity in response to bacterial virulence factors, and the molecular actors involved in an infectious model remain to be elucidated. We demonstrated that NLRP3 inflammasome pathway is required for both CNF1 and nigericin toxins induced trained immunity, two known bacterial toxins triggering NLRP3 activation and IL-1β secretion. Epigenetic and transcriptional modifications induced by CNF1 toxin were characterized by RNA-seq/ATAC-seq, which allowed the identification of the set of genes involved in the establishment of this phenotype. *Bcl2a1* was found to be overexpressed in the context of trained immunity and its invalidation specifically reduced TNF-α, IL-6 and IL-1β cytokine expression. It seems to be a key factor in the establishment of NLRP3-induced trained immunity. BCL2A1 is a pro-apoptotique protein known for its role in the regulation of apoptosis, but nothing is described concerning its potential role in trained immunity. Co-immunoprecipitation as well as immunofluorescence imaging suggested a potential direct interaction between BCL2A1 and NLRP3. These results provide both an important missing insight in the molecular events critical for trained immunity induction and a potential novel drug target to modulate trained immunity.

P-45	*Cancer*	AUSSEL Anaïs	C3M

Role of serine metabolism in the adaptation of B cell lymphomas to L-Asparaginase treatment

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Diffuse B Large Cell Lymphoma (DLBCL) is the most common and aggressive type of Non-Hodgkin's B-cell lymphomas. Since more than two decades, patients with DLBCL are treated with an immuno-chemotherapy (R-CHOP), which significantly improved their overall survival. However, 40% of patients still experience therapeutic failure. We recently established the proof of concept of L-asparaginase (ASNase) anti-tumor efficacy in patients with R-CHOP-refractory DLBCL. ASNase is an enzyme catalyzing the hydrolysis of L-asparagine in the bloodstream and is clinically used to treat patients with acute lymphoblastic leukemia. Patients with R- CHOP refractory-DLBCL treated with ASNase had a regression of their tumor burden, but all patients eventually relapsed, suggesting the presence of remaining cancer cells capable of adaptation to ASNase treatment. Mechanisms involved in tumor cells' adaptation to ASNase treatment are unexplored. Using a preclinical model of murine B-cell lymphomas, we set up in vitro and in vivo models to address this issue. By metabolomic analysis, we identified metabolic deregulations in malignant B cells treated with ASNase in vitro and in vivo. The metabolic flexibility of malignant B cells surviving ASNase treatment is characterized by an increased intracellular L-serine levels, a feature described to favor tumor progression. Increased total intracellular L-serine levels is independent of serine uptake but it is associated with an increased expression of enzymes involved in its de novo biosynthesis (PHGDH, PSAT1 and PSPH). Using ^{13}C6-Glucose and ^{15}N(amine)-L-Glutamine, we demonstrated an increased levels of newly synthetized serine by malignant B cells surviving ASNase treatment in vitro and in vivo. Moreover, combining ASNase with a PHGDH inhibitor (BI4916) increased cell death and delayed tumor cell's adaptation to ASNase treatment in vitro. Our results together suggest the role of serine metabolism in escape mechanism of asparagine-restricted cancer cells.

ABSTRACTS
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P-46	*Bioinformatics/Omics*	KHATIR Wassila	IPMC

Fragile X Syndrome (FXS) is the most common inherited intellectual disability and the first monogenic cause of Autism Spectrum Disorders. This neurodevelopmental disorder is associated with a wide array of phenotypic manifestations, including intellectual deficiency, attention deficit, hyperactivity, social anxiety, and epilepsy. FXS primarily arises from the deletion of Fragile X Mental Retardation Protein (FMRP), encoded by the Fmr1 gene. Despite significant progress in understanding the molecular mechanisms of FXS, no effective therapeutic options currently exist, necessitating further investigation into the cellular processes disrupted by the disease.

FMRP plays a critical role in neuronal physiology by regulating various cellular processes and mRNA targets, which in turn influence multiple biological pathways. Although numerous omics studies have investigated the cellular dysregulations associated with FXS, these analyses have primarily focused on individual molecular layers, such as transcriptomics, translatomics, and proteomics. However, the inherent complexity of biological systems—where proteins are synthesized from mRNA, which is transcribed from DNA, and feedback regulation controls these processes—suggests that molecular disruptions in diseases like FXS are likely to be coordinated across multiple omic layers.

To address this gap, emerging multi-omics integration technologies, underpinned by artificial intelligence, provide powerful tools to reduce the complexity of biological phenotypes and enhance our understanding of intricate diseases. These technologies enable the identification of patterns across molecular layers, uncovering coordinated disruptions that govern disease processes.

The objective of this project is to conduct an integrative multi-omics analysis of FXS pathology. By comparing wild-type and Fmr1 knockout models, this study aims to identify key neurodevelopmental pathways, elucidate the interactions between molecular mechanisms, and propose potential biomarkers and therapeutic targets for FXS, with the ultimate goal of informing the development of novel therapeutic strategies.

ABSTRACTS
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P-47	*Cancer/Immunology*	MARTINELLO Chiara	C3M

In vivo CAR T cell therapy against angioimmunoblastic T cell lymphoma

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Angioimmunoblastic T cell lymphoma (AITL), one of the most prominent mature T cell lymphomas subtypes, represents a rare complex malignancy affecting mostly elderly, with no specific treatment available and a poor survival outcome.

We have previously generated a unique preclinical mouse model for AITL by overexpressing glyceraldehyde-3-phosphate dehydrogenase (GAPDH) exclusively in T cells, resulting in a T cell lymphoma closely mimicking the clinical and pathological features of human AITL disease (mAITL mouse), with the CD4+ follicular helper T cells being the drivers of the malignancy. By targeted lentiviral (LV) transduction, we generated CD8+ T cells expressing a chimeric antigen receptor (CAR) against the CD4 epitope present on the malignant T cells. To allow the vector's exclusive entry into CD8+ T cells, the anti-CD4CAR LV has been pseudotyped with a CD8 receptor-targeted measles virus envelope (anti-CD4CAR CD8-LV).

Anti-CD4CAR CD8-LV transduced murine AITL biopsies resulted in CAR expression on CD8+ T cells and in their expansion, accompanied by an almost complete elimination of the neoplastic CD4+ T cells, as compared to the control transduced with GPF-encoding CD8-LV. We then evaluated the anti-CD4CAR CD8-LV functionality and specificity in vivo by direct injection into the bloodstream of our preclinical mAITL model. This resulted as well in the generation of functional anti-CD4CAR CD8+ effector T cells in vivo and in a significant reduction of the CD4+ neoplastic T cells from the tumor, which correlated with an increased survival of the mAITL mice.

This study might offer a new therapeutic perspective for patients suffering from a CD4-driven T cell lymphoma, which could surmount the main problems of current ex vivo CAR T cell therapy.

ABSTRACTS
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P-48	*Microbiology*	LAUGIER Simon	IRCAN

Local Adaptation and Genotype-Phenotype Variation Across Continental Scales

Simon Laugier, 2ème année,
Équipe « Population Genomics and Complex Traits » (Dr Liti), IRCAN, CNRS, INSERM

Yeasts, as unicellular fungi, have been widely utilized in food production and biotechnology, with *Saccharomyces cerevisiae* serving as a key model for genomics, cell biology, and biochemistry. While the evolutionary history of *S. cerevisiae* is closely linked to human activities, its sister species, *S. paradoxus*, is considered a fully wild counterpart, making it an ideal candidate for population genomics studies. Since the first Saccharomyces Genome Resequencing Project (SGRP) in 2009, extensive genomic comparisons have provided insights into population structure, geographic distribution, introgression, and natural outcrossing in these species.
In the framework of the fifth iteration of the SGRP, we aim to expand this genomic resource by sequencing thousands of yeast isolates from diverse environments, encompassing both wild and domesticated strains. Through multiple phenotypic assays on over 2500 individuals, we will investigate the genetic basis of key traits such as chronological lifespan, growth under varying nutrient conditions, and sporulation capacity.

This project provides a preliminary analysis of the high-throughput phenotyping of *Saccharomyces spp.* isolated during the natural sampling campaign (SGRP5), offering an initial insight into local adaptation and species history

ABSTRACTS
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P-49	*Immuno/Physiopatho*	GIROLET Camille	LP2M

INTEGRATED TRANSCRIPTOMIC AND FUNCTIONAL ANALYSIS REVEALED SEXUAL DYSMORPHISM IN MATURE OSTEOCLASTS

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Sexual dysmorphism in bone mass and in susceptibility to osteoporosis is well known and is attributed to multiple hormonal, genetic and environmental factors influencing the differentiation and function of bone cells. Among them, the bone-resorbing osteoclasts (OCLs) are crucial for maintaining bone homeostasis. OCLs are myeloid cells, a lineage characterized by its diversity and sexual dysmorphism. We previously reported the existence of different OCL subpopulations having distinct phenotypic and functional properties. However, there is very few information on the molecular and functional differences between OCLs from both sexes.
Thus, our goal is to further characterize murine OCLs from both sexes combining scRNAseq, flow cytometry and functional assays in order to better understand this sexual dysmorphism.

scRNAseq analysis on purified murine OCLs from 8-week-old male and female mice confirmed the existence of different subsets that interestingly, are differentially represented between samples. Computational analysis revealed that subset C0 strongly associates with bone resorption genes (Acp5, Mmp9, Ctsk) and is over-represented in males. In contrast, subset C1 having a gene signature of inflammatory OCLs (Fcgr2b, Fcgr3, Tlr2, ...) and subset C2 that is characterized by both resorption and inflammatory features are both more abundant in females. Comparative flow cytometry analysis confirmed differences in the proportion of OCL subsets between sexes. In vitro OCLs differentiation and resorption assays revealed a greater OCL size and resorption capacity in males. They also showed that OCLs resorb mainly intermittently in females (pits), while male OCLs resorb more continuously while they move (trenches), as already reported for human OCLs. Concerning immunological functions of OCLs, OVA antigen processing is more efficient for female OCLs, which is consistent with a greater proportion of inflammatory OCLs in the females observed in the scRNAseq. Experiments are ongoing to further assess their immunological function and to correlate the different OCL progenitors with specific subsets.

In conclusion, by revealing major differences in the composition, characteristics and function of OCLs between males and females, our results shed new light on the sexual dysmorphism of OCLs. They also open new therapeutic perspectives by suggesting that different approaches could be used depending on the sex for pathologies related to OCL dysfunction.

ABSTRACTS
POSTERS
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P-50	*Plant Biology*	ROUSSET Zoé	ISA

Beetle against weed: who wins? The story of the biological control of common ragweed in France

Zoé Rousset

Common ragweed, *Ambrosia artemisiifolia*, is an invasive alien species native to North America that was accidentally introduced in Europe in the mid-19th century. It poses challenges for both agriculture, where it leads to significant yield losses, and public health, due to its highly allergenic pollen that can trigger severe allergic reactions. In Europe, the public health costs associated with ragweed allergies have been estimated up to €7.4 billion a year. The current ragweed management is ineffective and at a standstill. Consequently, a classical biological control (CBC) program has been initiated by INRAE in 2021, relying on the leaf beetle *Ophraella communa* (Coleoptera: Chrysomelidea) as a biological control agent. My PhD is part of this project. Following worldwide scientific methods and recommendations, I'm studying the host range of the beetle, as well as its current geographical dispersion in France, and different parameters linked to the biological control of common ragweed in France, like winter survival and dispersal factors.

P-51	*Cancer/Immunology*	DELABY Chloé	C3M

Immunological effects of post-transplant therapies in acute myeloid leukemia: focus on FLT3 kinase inhibitors

Chloé DELABY, Emeline KERRENEUR, Morgane FAJOLLES, Arnaud CHOPIN, Juliette CHARLES, Maxence BOURGOIN, Alexandre PUISSANT, Guillaume ROBERT, Patrick AUBERGER, Michael LOSCHI and Arnaud JACQUEL

Patent: EP23307236.2

Allogeneic hematopoietic stem cell transplantation remains the only curative treatment for selected patients with high-risk acute myeloid leukemia (AML). FLT3 mutations or internal tandem duplications, present in ~30% of AML cases, are associated with a significant risk of post-transplant relapse. FLT3 inhibitors, such as sorafenib—the current standard for post-transplant maintenance—have shown promise by modulating immune responses. However, the immunological effects of next-generation inhibitors, like Gilteritinib, remain poorly characterized, particularly in the context of anti-tumor immunity.

This study investigates the immunomodulatory effects of FLT3 inhibitors using both ex vivo and in vivo approaches. Ex vivo, we analyzed the impact of these compounds on the proliferation and polarization of macrophages and T cells from healthy donors. Monocyte-derived macrophages (MDMs) were generated and polarized into M0, M1, or M2 phenotypes. Naive CD4+ T cells were polarized toward Th1, Th2, or Treg subsets. Functional and phenotypic analyses were performed using spectral flow cytometry, RT-qPCR and ELISA. In vivo, we evaluated the therapeutic and immunological effects of FLT3 inhibitors in a graft-versus-leukemia (GVL) mouse model designed to mimic the post-transplant setting.

Our data show that:
(i) Gilteritinib reprogram IL-4-induced M2-like macrophages by downregulating key M2 markers and chemokines;
(ii) FLT3 receptor expression increases during macrophage polarization;
(iii) FLT3 knockdown inhibits M2, but not M1, polarization;
(iv) Gilteritinib promotes Th1 polarization of CD4+ T cells, increasing pro-inflammatory markers and reducing Th2-associated genes.
In vivo, Gilteritinib treatment significantly reduced leukemia burden and improved survival in the GVL model. The characterization of the immune populations in this setting is ongoing.

Our findings highlight an immunomodulatory role for FLT3 inhibitors in shaping macrophage and T cell responses. This work supports their potential use not only as anti-leukemic agents but also as immunotherapeutic modulators in post-transplant AML, potentially extending benefits beyond FLT3-mutated patients.

ABSTRACTS
POSTERS
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P-52	*Physiopath/Neuro*	LELIEVRE Quentin	LP2M

Biophysical properties of two-pore domain potassium channel TWIK1 in black lipid membranes

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Leak potassium channels (K2P) have two pore domains and are involved in many processes such as cell volume regulation and excitability. They are open at all membrane potentials and therefore define the resting potential of the cells.
The first K2P discovered was TWIK1 (Tandem of P domains in a Weak Inward rectifying K^+ channel). The particular interest in this channel comes from its high expression in the brain, heart and kidney. However, its characterization has long been made difficult by the lack of functional activity observable in whole-cell patch-clamp. It was established that this was due to the channel being mainly localized in subcellular compartments such as recycling endosomes.

We therefore propose to study TWIK1 by inserting it into artificial lipid membranes made of a bilayer of phospholipids. This technique allows us to investigate the unitary biophysical properties of the channel such as its unitary conductance and its open probability according to different physicochemical parameters, such as pH. Indeed, a particularity of TWIK1 is that its selectivity changes when the pH becomes acidic and the channel then becomes permeable to sodium ions. The physiological relevance of this permeability switch is yet to be determined. Our findings show that TWIK1 has a very low open probability (≃1%) compared to TWIK1-I293-294A-K274E, a known membrane-localized functional mutant with a greater open probability (≃15%). The latter, contrary to the wild type, produces strong currents and polarizes the reverse potential (Erev≃-70mV) near to the K^+ equilibrium potential in CHO cells, in the whole cell configuration.
In addition to its fast internalization, the poor open probability of TWIK1 could explain its low functional activity in mammalian cells.

ABSTRACTS
POSTERS
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P-53	*Bioinformatics/Omics*	LAGHRISSI Hiba	iBV

Aging is a complex process characterized by a progressive decline in physiological and cognitive abilities. Over the year, numerous studies have explored the molecular, cellular and systemic signatures contributing to aging, thus showing that aging disrupts the coupling between mRNA transcription and translation. The molecular mechanisms underlying this decoupling, however, are still unknown.

Our objective is to understand how translation is modulated in the context of brain aging. We use Drosophila Melanogaster, a powerful model in aging studies due to its short lifespan and the fact that ~77% of genes associated with age-related diseases in humans are expressed in the equivalent fly tissues. To first characterize age-dependent changes in translation patterns at a transcriptome-wide level, we performed Ribosome Profiling and Bulk RNA-seq at three different timepoints. Our first analysis of the ribo-seq data uncovered the existence of specific populations of transcripts with concordant and discordant patterns upon aging, highlighting potential regulatory mechanisms. To understand the observed regulatory changes, we compared the molecular characteristics at both the cis-acting and trans-acting levels (GC content, uORFs, RNA sequence, binding to RBPs, etc.). We also use Machine Learning algorithms to link molecular signatures we identified at the translational level in order to predict mRNA regulation patterns upon aging. This work will not only deepen our understanding regarding the poorly studied translational regulatory mechanisms but will also open further questions regarding the differences between healthy and pathological aging.

ABSTRACTS
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P-54	*Physiopathology*	GALLEGO LOPEZ Maria Del Carmen	Ulysseus

Folic acid supplementation improves hepatic aldosterone clearance and systolic blood pressure in binge drinking adolescent rats

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Background/Aims: Alcohol is the most consumed drug worldwide. Among adolescents, binge drinking (BD)- an acute pattern of alcohol intake with pro-oxidant effects - is increasingly prevalent and poses major public health risks, including hypertension linked to renal dysfunction. BD also alters folic acid (FA) homeostasis in adolescent rats. This antioxidant vitamin is crucial for cardiovascular health, but its protective effects against BD-induced damage in adolescents remain unclear. We aimed to evaluate whether FA supplementation prevents renal-cardiovascular damage in adolescent BD-exposed rats.

Methods: Four groups of adolescent male Wistar rats were treated for 3 weeks: control, BD (3 weekly 20% alcohol/i.p. injections), control FA-supplemented group, and BD-FA supplemented group. Dietary FA content in control groups was 2 ppm, and 8 ppm in supplemented groups. Oxidative status was assessed via malondialdehyde (MDA) levels, the end-product of lipid peroxidation, in serum, liver, and kidney (spectrophotometry). Renal-cardiovascular function was evaluated by measuring systolic blood pressure (SBP) (indirect tail-cuff method), serum/urine aldosterone levels (ELISA), and serum/urine creatinine levels (clinical biochemistry tests). Creatinine clearance was calculated as a glomerular filtration rate (GFR) marker, and relative aldosterone clearance was also calculated. Hepatic UDP-glucuronosyltransferase 1 (UGT1) expression was evaluated (Western blot) to assess metabolic function.

Results: BD significantly increased MDA levels, confirming that oxidative stress (OS) was established. This OS is one of the mechanisms by which acute ethanol stimulates the sympathetic nervous system, hypothalamus–pituitary–adrenal axis, and renin- angiotensin-aldosterone system, leading to high aldosterone levels, low GFR, and elevated SBP. This was observed in BD rats. BD also upregulated UGT1 expression, indicating that the enzyme was overwhelmed by the high alcohol load, impairing its ability to metabolize other substrates such as aldosterone. Consequently, the lower aldosterone clearance in BD rats resulted in increased serum levels due to reduced urinary excretion. FA supplementation reduced OS, improving UGT1 bioavailability and enhancing aldosterone clearance. This partially reduced serum aldosterone and SBP in BD rats, though GFR was not restored.

Conclusions: This study shows that FA supplementation mitigates BD-induced OS and improves hepatic aldosterone clearance, partially lowering SBP in adolescent rats. However, it fails to restore GFR, highlighting the need for further research, as adolescent renal- cardiovascular dysfunction may predispose to adult heart disease.

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Metabolic and Genetic engineering for the efficient production of industrially value chemicals.

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Pseudomonas putida is a bacterium endowed with wide metabolic versatility, which provides it with a high ability to adapt and grow in the presence of xenobiotics chemicals. This ability makes it an ideal candidate for productions of industrially valuable chemicals using waste as a carbon source. Among other capability, Pseudomonas putida can metabolize simple carbon sources such as glucose, glycerol, and fatty acids, and produce various types of polyhydroxyalkanoates (PHA's) as products. These PHA's can be used to create biodegradables plasticswith multiple physicochemical characteristics, serving as an alternative to polypropylene, which is the main chemical used in the plastic industry.

Our research group, in collaboration with the Universidad de Santiago de Chile (USACH), has identified lipase-coding genes involving in the β oxidation pathway of fatty acids. Theses lipases appear to be involved in the bioavailability of oil, promoting its bioconversion by Pseudomonas putida.

Currently our group is characterizing the lipases and their role in the bioavailability of oil, while also researching ways to enhance oil bioavailability to facilitate its metabolism by Pseduomonas putida. With all this, our goal is bioremediation of waste oil to transform the carbon into PHA's (bioplastics), as an alternative to addressing the current pollution problem caused by non-biodegradable plastics.