

Conseil de laboratoire du 28 octobre 2020

Etaient présents :

Eric GILSON

Membres nommés

Gaël CRISTOFARI

Chloé FERAL

Cédric GAGGIOLI

Laurence GENET

Paul HOFMAN, excusé (vote par procuration)

Eric RÖTTINGER

Sabine SCARZELLO (Assistante de prévention)

Nadir DJERBI (Assistant de prévention suppléant)

Membres élus

- Représentants des Chercheurs et enseignants-chercheurs permanents

Etienne BOULTER

Laurence BIANCHINI

- Représentantes des Ingénieurs et Techniciens permanents

Sabrina PISANO

Marielle MARET, excusée (vote par procuration)

- Représentants des Personnels non permanents

Marie Angela DOMDOM

Mounir EL MAI

- Représentants des Etudiants

Lou DURET

Anaïs HAGEGE

Invités : Delphine BENNARROCH, Roser BUSCA, Julien CHERFILS, Olivier CROCE, Miguel FERREIRA, Agnès LLORED, Gilles PAGES, Véronique PAQUIS, Marina SKHRELI, Valérie VOURET

Ouverture de la séance : 9 h 15

Les deux objectifs de ce conseil de laboratoire exceptionnel sont

- Avis sur la candidature de Dmitry BULAVIN à la direction de l'IRCAN en janvier 2023
- Avis sur les candidatures des 2 nouvelles équipes « junior »

Sous réserve des contraintes imposées par la faculté, 2 espaces seront disponibles :

- Au 5^{ème} étage – utilisation des locaux libérés par l'ouverture du PEMED PCV.
- 2^{ème} étage : locaux de l'équipe de Thierry Magnaldo

1. Création « Junior Group leader »

Concernant les candidatures pour la création des deux équipes « junior », Eric rappelle que nous avons reçu 28 candidatures. Les Pls ont sélectionné, début août, 7 candidats qui ont été auditionnés par le SAB le 7 octobre dernier.

Il ressort des entretiens par le SAB (*cf. pièce jointe - rapport d'audition par le président du SAB, Jean-Marc EGLY*)

- Une candidature “sort du lot” : **Eirini Trompouki**,

PI au « Department of Cellular and Molecular Immunology » à Max-Planck-Institute, Eirini Trompouki a été classée 1^{ère} par le SAB. (cf CV)

Nouvelle thématique : Hematopoïèse

Modèle utilisé : zebrafish

Eirini Trompouki devrait postuler à l'AAP “Chairs of Excellence Labex SIGNALIFE”

Pour rappel : 5 chaires d'excellence sont proposées (1 par institut : C3M IBV IPMC IRCAN ISA).

Le scientifique sélectionné par le comité d'évaluation recevra un kit de démarrage SIGNALIFE (jusqu'à 600 000 euros) pour une durée de cinq ans.

- 3 autres candidats ont été présélectionnés par le SAB
- **Julien CHERFILS** : prioritaire pour créer son équipe. Retenu par le SAB comme « group leader » sous réserve qu'il obtienne un financement substantiel lui permettant d'être autonome financièrement (ANR JC, ERC, ARC, INCA...).

Candidatures à examiner à nouveau dans une année dépendant de leur évolution et en concertation avec le prochain directeur de l'IRCAN

- **Lorenzo Giordani**
- **Lida Katsimpardi**

Le SAB suggère de reconsidérer l'an prochain les candidatures de L.Katsimpardi et L. Giordani s'ils remplissent deux conditions : (i) intégration d'un organisme de recherche Inserm ou CNRS et (ii) obtention d'un contrat FRM, ANR, ARC, Ligue ou, mieux, européen.

2. Examen de la Candidature de Dmitry BULAVIN

L'audition par le SAB s'est tenue le 7 octobre dernier.

Le SAB a émis un avis très positif. Candidature de grande qualité avec une vision claire du domaine "Ageing et Cancer» et une très belle projection dans le futur.

Le CL doit donner son avis sur le candidat qui sera proposé aux tutelles pour assurer la future direction de l'IRCAN 3.

Si l'avis est négatif : proposer un plan B

Si l'avis est positif : proposer aux tutelles la candidature de Dmitry BULAVIN pour la position de Directeur de l'IRCAN à partir de 2023 sur recommandations du SAB et avis du CL

Organisation du vote à bulletin secret, pour ou contre la candidature de Dmitry BULAVIN.

Résultat du vote 13 OUI et 3 NON, aucun vote blanc.

La candidature de Dmitry BULAVIN sera donc proposée aux tutelles.

3. Problème RH – Plateformes d'expérimentation du vivant

Le sous-effectif dont souffre les plateformes d'expérimentation animale (rongeurs et zebrafish) est un problème majeur.

Les tutelles ont été alertées à de nombreuses reprises de ce problème.

Les postes demandés sont en cours d'arbitrage par les tutelles.

Une réunion « intra-IRCAN » doit être organisée très prochainement par Marina afin d'élaborer une procédure de fonctionnement en mode dégradé, refaire le point sur les besoins RH à court et moyen terme et les équipements nécessaires pour le PEMED.

4. Crise sanitaire – Covid 19

De nouvelles mesures devraient être annoncées ce soir pour faire face à la deuxième vague de la COVID-19

Point de vigilance : Le risque de contamination reste plus élevé au moment de la pause déjeuner. **Il est donc fortement recommandé de Privilégier l'extérieur** tout en respectant la distanciation physique.

Remettre le masque quand on a fini de manger.

Eviter les regroupements.

CONTINUER A RESPECTER LES GESTES BARRIERES.

La séance est levée à 11H10

Illkirch, le 13 octobre 2020

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Compte-rendu du SAB effectué à Nice le 8 octobre 2020

A la demande d'Eric Gilson, Directeur de l'IRCAN, le SAB, composé U Prof. Hugues de Thé (Collège de France, et Hôpital St Louis), Thomas Krieg (Dir. Dept. de Dermatologie et Venerologie, Université de Koln), Prof. Rudolf Lenhard (Dir. du Leibnitz Institute of Ageing), Prof et moi-même, avec les commentaires écrits du Prof. Tomas Lindahl (Kribs Institute, Prix Nobel 2015) et ce, en présence des représentants de l'Université (Laurent Counillon), de l'Inserm (Alain Eychène), et du CNRS (Yvan Delaunoy), s'est penché au cours de la journée du 7 octobre 2020, sur le dossier de Dmitry Bulavin qui postulait pour la Direction de l'IRCAN à partir de janvier 2023 ainsi que sur la candidature de 7 jeunes chercheurs à deux positions de chefs d'équipe.

Suite à un bref résumé d'Eric Gilson, et après avoir écouté D. Bulavin, les membres du SAB ont jugé sa candidature de grande qualité tant par l'exposé que par la profession de foi écrite qui leur avait été fournie. Il fut jugé un excellent candidat avec une vision claire du domaine "Ageing et Cancer" et une très belle projection dans le futur, fortement documentée, voulant faire de ce Centre une référence dans le domaine au sein d'un réseau où seraient impliqués outre des unités CNRS/Inserm locales, la Faculté de Médecine, l'Hôpital et le Centre Lacassagne notamment. Cette initiative a été fortement encouragée par le SAB. La qualité des travaux de D. Bulavin publiés récemment dans des revues parmi les plus prestigieuses, plaident en sa faveur. Quelques soucis furent émis par certains membres du SAB, quant à la gouvernance, à savoir le côté administratif et les relations avec les tutelles qui voudraient l'avoir comme direct interlocuteur, tout en comprenant sa volonté de consensus et de travailler dès le départ, avec un « Deputy Directeur ». Il lui a été demandé d'être plus précis quant aux attributions du « Deputy Directeur » qu'il serait bon de désigner dans un temps relativement proche. Il a également été rappelé que les tutelles voulaient avoir D. Bulavin comme premier interlocuteur.

Au cours de cette audition, le SAB a émis le souhait d'une collaboration plus étroite entre le toujours Directeur Eric Gilson et D. Bulavin sur des sujets engageant l'avenir et dans des prises de décisions qui ne devraient pas amputer l'exercice de ce dernier à partir de janvier 2023. De plus, le SAB a

d'ores et déjà émis un avis concernant les recrutements prochains, suggérant que le second poste ouvert (et qui, comme documenté plus bas, ne trouve pas preneur) devrait être réservé à une thématique plus en adéquation avec la philosophie de D. Bulavin. Le SAB, comme il l'a fait remarquer, étant prêt à revenir à l'automne prochain.

Il a été conclu à l'unanimité l'excellence de la candidature de D. Bulavin et le SAB encourage les tutelles à accepter cette candidature. Le SAB a également apprécié comment le projet Bulavin s'inscrivait dans ce qu'avait réalisé E. Gilson, dont tous ont reconnu le succès pour la création de l'IRCAN.

Dans une seconde partie de ses travaux, le SAB a examiné les diverses candidatures aux deux postes ouverts à l'IRCAN pour courant 2021.

Le SAB s'est basé sur la philosophie mise en place à l'IRCAN et qui a vu le recrutement de Chloé Feral, Gael Cristofari (également titulaire d'un ERC), Gianni Liti, Eric Rottinger et Marina Shkreli sur des programmes d'excellence Atip/Avenir proposés par l'Inserm et le CNRS. Le SAB avait, en son temps, évalué ces candidats pour être recrutés en tant que PIs et actuellement membres à part entière de l'IRCAN.

Après avoir écouté les 7 candidats, le SAB a émis les commentaires suivants :

- **Elrini Trompouki** a été classée au 1er rang, suite à une prestation et une discussion de grande qualité. Le travail passé ainsi que les technologies et l'expertise existantes à l'IRCAN étaient pour elle un facteur primordial de sa candidature, même si elle était consciente des difficultés dans l'obtention d'un poste et de la faiblesse de son salaire en comparaison de sa situation à Fribourg (Allemagne). Il restait, cependant, quelques préoccupations quant à une proximité plus affirmée avec les thématiques de l'IRCAN sachant le lien déjà connus inflammation/différentiation, sujet qu'elle aborde au travers de mécanismes de signalisation.

- **Lida Katsimpardi** : le projet est clair et ambitieux en vue d'étudier les mécanismes en relation avec le vieillissement du cerveau et ceux permettant de les retarder. Cependant la candidate n'a pas obtenu de poste au CNRS et n'a pas de contrats de type ANR, ARC, Ligue, FRM ou AFM et ne peut donc pas en l'état devenir PI à l'IRCAN, restant dans l'attente de papiers soumis ou en voie de.

- **Lorenzo Giordani** : il montré une compétence technique dans le domaine single cell (scChIP-, scRNA seq, sc-omics) et combien il pouvait exploiter ces résultats en mêlant Imagerie/Protéomique dans un projet pouvant intéresser l'IRCAN. A noter que, malgré un contrat ANR jeune chercheur, ce jeune chercheur n'a pas été sélectionné dans le programme ATIP/Avenir, ni à intégrer un organisme.

Le SAB suggère donc de reconsidérer l'an prochain les candidatures de L. Katsimpardi et L. Giordani s'ils remplissent deux conditions : (i) intégration d'un organisme de recherche Inserm ou CNRS et (ii) obtention d'un contrat FRM, ANR, ARC, Ligue ou, mieux, européen.

- **Julien Cherfils**, pur produit de l'IRCAN où (sous la houlette d'Eric Gilson), il s'est familiarisé avec les thématiques Vieillissement. En tant que « Baby team » jouissant d'une certaine indépendance thématique, il s'est dessiné un projet visant à comprendre la relation entre cellules sénescences et système

immunitaire, mêlant ainsi l'expérience acquise à Nice à celle obtenue lors de sa thèse chez Hervé. Fridman aux Cordeliers. Ayant suivi ce jeune chercheur doté d'un poste au CNRS depuis quelque temps, le SAB suggère que J. Cherfils puisse être considéré comme partie intégrante de l'IRCAN s'il réussit dans le courant de l'année qui suit, à publier ses travaux et à obtenir un financement ANR, ERC, ARC ou INCA. Le SAB suggère que ce cas ne serait pas inclus dans l'un des 2 postes mis au concours à l'IRCAN.

Le second poste mis au concours par l'IRCAN est donc en attente et pourrait être reconsidéré comme indiqué ci-dessus.

Le SAB a par ailleurs estimé que les 3 autres candidats (Noelia Diaz, Luca Lignitto, Dominic van Essen) ne satisfaisaient pas aux critères évoqués ci-dessus, à savoir un passif certain en termes de publications, un projet bien structuré pour prétendre à diriger une équipe et une thématique en adéquation avec les projets IRCAN.

Par ailleurs, à titre personnel, j'ai énormément apprécié la qualité des travaux en cours à l'IRCAN et l'excellente tenue de la réunion organisée par E. Gilson le jeudi 8 octobre, tant dans la compétence et la modestie des exposés, que dans celles des commentaires et des questions qui ne manquaient pas de suivre. Bien sûr, il y aura quelques directions de recherche à modifier, mais cela fait partie de la vie d'un laboratoire que l'on pourrait citer en exemple. Au cours de la journée précédente, le SAB a par ailleurs encouragé plusieurs chercheurs à postuler aux programmes d'excellence européens.

Comme les années précédentes, le SAB a pu apprécier l'évolution de l'IRCAN sous la houlette d'Eric Gilson et de ses équipes dont on ne doute pas de la qualité.



Jean-Marc Egly
DRE Inserm
Membre de l'Académie des Sciences
Président du Conseil Scientifique de l'IRCAN

Eirini Trompouki Ph.D. CV

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EDUCATION

Harvard Extension School

Master of Management

Boston, USA

2015

Cold Spring Harbor Laboratories

Next Generation Sequencing Course

Cold Spring Harbor,
2011

National and Kapodistrian University of Athens Medical School.

Biomedical Sciences Research Center “Al. Fleming”

Ph.D. Cell and Molecular Biology

Dissertation: “The role of transcription factor NF- κ B in the development of neoplasms”

Athens, Greece

2006

National and Kapodistrian University of Athens Department of Biology.

B.S. Biology

Athens, Greece

2001

RESEARCH EXPERIENCE

Max Planck Institute of Immunobiology and Epigenetics

Department of Cellular and Molecular Immunology
Group Leader

Freiburg, Germany

September 2013-
present

Children’s Hospital Boston, Harvard Medical School

Boston, MA

Postdoctoral Fellow; Advisor: Dr. Leonard I. Zon

2007-2013

The Wnt and BMP signaling pathways in hematopoietic differentiation and regeneration

National and Kapodistrian University of Athens Medical School.

Biomedical Sciences Research Center “Al. Fleming”

Postdoctoral Fellow

Athens, Greece

Advisor: G. Mosialos, Ph.D.

2006-2007

CYLD as a negative regulator of the NF- κ B signaling pathway

National and Kapodistrian University of Athens Medical School.

Biomedical Sciences Research Center “Al. Fleming”

Graduate student

Athens, Greece

Thesis Advisor: G. Mosialos, Ph.D.

2001-2006

CYLD as a negative regulator of the NF- κ B signaling pathway

Peer-reviewed publication list

- Stylianos Lefkopoulos, Aikaterini Polyzou, Marta Derecka, Veronica Bergo, Pierre Cauchy, Thomas Clapes, Carolina Jerez Longres, Megumi Onishi-Seebacher, Na Yin, Natalia Martagon, Kathryn S Potts, Lheanna Klaeyle, Feng Liu, Teresa V. Bowman, Thomas Jenuwein, Marina Mione, and **Eirini Trompouki**. Repetitive elements induce a RIG-I-like receptor-mediated inflammation to regulate HSPC emergence *Immunity* (provisionally accepted). (I.F.21.522)
- Jingmei Hsu, Hsuan-Ting Huang, Chung-Tsai Lee², Avik Choudhuri, Nicola K. Wilson, Brian J. Abraham, Victoria Moignard, Shuqian Yu, R. Katherine Hyde, **Eirini Trompouki**, Joanna Tober, Xiongwei Cai, Yan Li, Vy Nguyen, Alireza Ghamari, Fernando J. Calero-Nieto, Jing Jiang, Katie L. Kathrein, Anne L. Robertson, Ellen M. Durand, Michael Superdock, Song Yang, Yalin Guo, Peng Gao, Long Gao, Iannis Aifantis, Scott A. Gerber, Wei Tong, Kai Tan, Alan B. Cantor, Yi Zhou, P. Paul Liu, Richard A. Young, Berthold Göttgens, Nancy A. Speck, and Leonard I. Zon. CHD7 and Runx1 interaction provides a braking mechanism for hematopoietic differentiation. *PNAS* (*in press*). (I.F. 9.412)
- Kozyra EJ, Pastor VB, Lefkopoulos S, Sahoo SS, Busch H, Voss RK, Erlacher M, Lebrecht D, Szvetnik EA, Hirabayashi S, Pasaulienė R, Pedace L, Tartaglia M, Klemann C, Metzger P, Boerries M, Catala A, Hasle H, de Haas V, Kállay K, Masetti R, De Moerloose B, Dworzak M, Schmugge M, Smith O, Starý J, Mejstrikova E, Ussowicz M, Morris E, Singh P, Collin M, Derecka M, Göhring G, Flotho C, Strahm B, Locatelli F, Niemeyer CM, **Trompouki**

E, Wlodarski MW; European Working Group of MDS in Childhood (EWOG-MDS). Synonymous GATA2 mutations result in selective loss of mutated RNA and are common in patients with GATA2 deficiency. *Leukemia*. 2020 Jun 18. doi: 10.1038/s41375-020-0899-5. Online ahead of print. (I.F. 10.240).

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- Piragyte I, Clapes T, Polyzou A, Klein Geltink RI, Lefkopoulos S, Yin N, Cauchy P, Curtis JD, Klaeyle L, Langa X, Beckmann CCA, Wlodarski MW, Müller P, Van Essen D, Rambold A, Kapp FG, Mione M, Buescher JM, Pearce EL, Polyzos A, **Trompouki E**. A metabolic interplay coordinated by HLX regulates myeloid differentiation and AML through partly overlapping pathways. *Nat Commun*. 2018 Aug 6;9(1):3090. doi: 10.1038/s41467-018-05311-4 (I.F. 12.353).
- Kapp FG, Perlin JR, Hagedorn EJ, Gansner JM, Schwarz DE, O'Connell LA, Johnson NS, Amemiya C, Fisher DE, Wölfl U, **Trompouki E**, Niemeyer CM, Driever W, Zon LI. Protection from UV light is an evolutionarily conserved feature of the haematopoietic niche. *Nature*. 2018 Jun;558(7710):445-448. doi: 10.1038/s41586-018-0213-0. Epub 2018 Jun 13 (I.F. 41.577).
- Van Rooij JA F.**Trompouki E**., et al, Ganesh SK. Genome-wide trans-ethnic meta-analysis identifies seven genetic loci influencing erythrocyte traits and a novel role for *RBPMS* in erythropoiesis. *American Journal of Human Genetics*, Am J Hum Genet. 2017 Jan 5;100(1):51-63. doi: 10.1016/j.ajhg.2016.11.016. Epub 2016 Dec 22 (I.F. 9.025).
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- Huang J, Liu X, Li D, Shao Z, Cao H, Zhang Y, **Trompouki E**, Bowman TV, Zon LI, Yuan GC, Orkin SH, Xu J. Dynamic Control of Enhancer Repertoires Drives Lineage and Stage-Specific Transcription during Hematopoiesis. *Dev Cell*. 2016 Jan 11;36(1):9-23. doi: 10.1016/j.devcel.2015.12.014 (I.F. 9.174).
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- Ganis JJ, Hsia N, **Trompouki E**, de Jong JL, DiBiase A, Lambert JS, Jia Z, Sabo PJ, Weaver M, Sandstrom R, Stamatoyannopoulos JA, Zhou Y, Zon LI. Zebrafish globin switching occurs in two developmental stages and is controlled by the LCR. *Dev Biol*. 2012 Jun

15;366(2):185-94. Epub 2012 Apr 19 (I.F. 2.89).

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- Tsagaratou A, **Trompouki E**, Grammenoudi S, Kontoyiannis DL, Mosialos G. Thymocyte-specific truncation of the deubiquitinating domain of CYLD impairs positive selection in a NF-kappaB essential modulator-dependent manner. *J Immunol*. 2010 Aug 15;185(4):2032-43. Epub 2010 Jul 19 (I.F. 5.63).
- **Trompouki E**, Tsagaratou A, Kosmidis SK, Dollé P, Qian J, Kontoyiannis DL, Cardoso WV, Mosialos G. Truncation of the catalytic domain of the cylindromatosis tumor suppressor impairs lung maturation. *Neoplasia*. 2009 May;11(5):469-76 (I.F. 5.025).
- Jono H, Lim JH, Chen LF, Xu H, **Trompouki E**, Pan ZK, Mosialos G, Li JD. NF-kappaB is essential for induction of CYLD, the negative regulator of NF-kappaB: evidence for a novel inducible autoregulatory feedback pathway. *J Biol Chem*. 2004 Aug 27;279(35):36171-4. Epub 2004 Jun 28 (I.F. 6.355).
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Reviews, protocols and book chapters

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- de Pater E, **Trompouki E**. Perspective, Bloody Zebrafish: Novel Methods in Normal and Malignant Hematopoiesis. *Front Cell Dev Biol*. 2018 Oct 15;6:124. doi: 10.3389/fcell.2018.00124 (I.F. 5.206).
- **Trompouki E**, Mullen L, Fernandez-Reyes D, Yodoi J, Kim S, Schuettpeitz LG. Editorial: Inflammatory Signaling in Bone Marrow Failure and Hematopoietic Malignancy. *Front Immunol*. 2017 Jun 2;8:660. doi: 10.3389/fimmu.2017.00660. eCollection 2017 (I.F. 5.511).

- **Trompouki E**, Flores-Figueroa E, Lucas D, Bowman TV. From the Bedside to the Bench: New Discoveries on Blood Cell Fate and Function. *Exp. Hematol.* 2017 Mar;47:24-30. doi: 10.1016/j.exphem.2016.11.007. Epub 2016 Dec 5. Review (I.F. 2.436).
- Clapes T, Lefkopoulos S, **Trompouki E**. Stress and Non-Stress Roles of Inflammatory Signals during HSC Emergence and Maintenance. *Frontiers Immunology* 2016 Nov 7;7:487. eCollection 2016. Review (I.F. 5.511).
- **Trompouki E**. Fish provide ID(H) eas on targeting leukemia. *Blood.* 2015 May 7;125(19):2880-2. doi: 10.1182/blood-2015-03-636225 (I.F. 13.164).
- **Trompouki E**, King KY, Will B, Lessard J, Flores-Figueroa E, Kokkaliaris KD, Bowman T. Bloody signals: From birth to disease and death. *Exp Hematol.* 2014 Dec;42(12):989-94. doi: 10.1016/j.exphem.2014.10.007 (I.F. 2.475).
- **Trompouki E**, Bowman TV, Dibiase A, Zhou Y, Zon LI. Chromatin immunoprecipitation in adult zebrafish red cells. *Methods Cell Biol.* 2011;104:341-52 (I.F. 1.877).
- **Trompouki E**, Zon LI. Small molecule screen in zebrafish and HSC expansion. *Methods Mol Biol.* 2010;636:301-16 (I.F. 1.877).

Manuscripts submitted

- Thomas Clapes, Aikaterini Polyzou, Pia Prater, Sagar, Antonio Morales-Hernández, Barbara Hummel, Daniel Maticzka, Stylianos Lefkopoulos, Anne Bridgeman, Josip S. Herman, Ibrahim Ilik, Lhéanna Klaeylé, Jan Rehwinkel, Shannon McKinney-Freeman, Rita Rebollo, Rolf Backofen, Asifa Akhtar, Ritwick Sawarkar, Dominic Grün, **Eirini Trompouki**. Transposable elements enhance hematopoietic regeneration via activation of innate immune signalling *Nature Cell Biology in review*.
- Avik Choudhuri*, **Eirini Trompouki***, Brian J. Abraham*, Leandro M. Colli, Kian Hong Kock, William Mallard, Min-Lee Yang, Alireza Ghamari, Karen Hoi, Sonja Boatman, Victoria Chan, Barbara Hummel, Song Yang, Asher Lichtig, Michael Superdock, Yi Zhou, Teresa V. Bowman, Roby Joehanes, Shinichiro Takahashi, Alan B. Cantor, Santhi K. Ganesh, John L. Rinn, Martha L. Bulyk, Stephen J. Chanock, Richard A. Young and Leonard I. Zon. Mutation in Signaling Transcription Factor Binding Sites Causes Majority of Genetic Traits *Nature Genetics* (revision submitted) * equal first authors.
- Nathalie Faggianelli-Conrozier, Aikaterini Polyzou, Renee Chow, Stéphane Roth, **Eirini Trompouki***, Julien Vermot*. Complementary functions of the mechanosensitive factors *egr1*, *klf2b* and *klf2a* instruct the valvulogenic program. *Development* (in revision) (* equal last authors)
- Ferrari F, Arrigoni L, Franz H, Butenko L, **Trompouki E**, Vogel T., Manke T. DOT1L

Methyltransferase Activity Preserves SOX2-Enhancer Accessibility And Prevents Activation of Repressed Genes In Murine Stem Cells. *Nature Communications* (in revision)

• Mauro Corrado, Joy Edwards-Hicks, Lea Flachsmann, David E. Sanin, Matteo Villa, Francesc Baixauli, Michal Stanczak, Eve Anderson, Mai Azuma, Andrea Quintana, Jonathan D. Curti¹, Thomas Clapes, Carina Zorzi, Katarzyna M. Grzes, Agnieszka M. Kabat, Ryan Kyle, Maaïke Jacobs, Heiko Heerklotz, Ramon Klein Geltink, Borko Amulic⁵, Colin Steward, Douglas Strathdee, **Eirini Trompouki**, David O'Sullivan, Edward J. Pearce, and Erika L. Pearce. Regulated cardiolipin synthesis and remodeling is required for CD8⁺ T cell immunity. Submitted to *Cell*.

References

Dr George Mosialos

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Dr Rudi Grosschedl (head of the department)

Max Planck Institute of Immunobiology and Epigenetics grosschedl@ie-freiburg.mpg.de

Dr Julien Vermot (collaborator)

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Dr Marina Mione

University of Trento mariacaterina.mione@unitn.it



INSTITUT DE RECHERCHE SUR LE CANCER ET LE VIEILLISSEMENT, NICE
INSTITUTE FOR RESEARCH ON CANCER AND AGING, NICE

Attestation

Je soussigné, Éric GILSON, Directeur de l'Institut de recherche sur le cancer et le vieillissement (IRCAN) à Nice, atteste que

L'organisation future de l'IRCAN (mandat 2024/2028) a été présentée par Dmitry BULAVIN en Assemblée générale des personnels en date 27 janvier 2023.

La candidature de Véronique PAQUIS a été proposée au poste de directrice adjointe. Cette candidature n'a soulevé aucune objection de la part de l'ensemble des personnels.

Éric GILSON
Directeur de l'IRCAN

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Scientific Leadership Profile

Major scientific contributions

Dmitry Bulavin is a trained physician who received his medical degree with distinctions from one of the top medical schools in Russia, the Medical Academy of St. Petersburg. Subsequently he completed a PhD program in biochemistry and molecular biology from the same academy. In 1998, he moved to the USA to carry out his postdoctoral training in the laboratory of Albert Fornace (NCI, NIH), the world-renowned expert in stress response who identified the first p53-responsive gene, *Gadd45*. During his PhD, Dmitry Bulavin established a novel role of p38 MAPK in negative regulation of tumorigenesis (EMBO j, 1999; *Nature*, 2001, *Nature Genet*, 2002), the direction that is now widely pursued in the cancer field. His achievements were recognized by the NIH by appointing Dmitry Bulavin in 2002 as a Staff Scientist, a prestigious permanent position at the NIH. During subsequent 4 years as a staff scientist, Dmitry Bulavin made an important discovery in establishing the key role of a novel phosphatase Wip1 as a potent human oncogene. Subsequently, he went on to show that a deficiency of Wip1 phosphatase in mice results in profound tumor resistance (*Nature Genet* 2004), another line of research that is now actively being pursued to improve cancer treatment. After establishing his own lab in Singapore in 2004, Dmitry Bulavin continued interrogating the role of DNA damage and stress-induced signaling in cancer and subsequently in other pathological conditions as well as during aging. Through generation and detailed analysis of multiple novel mouse models, the research lead by Dmitry Bulavin established a key role of DNA damage and stress-induced signaling in cancer (*Mol. Cell* 2006; *JEM* 2006; *Cell Stem Cell* 2007; *Cancer Cell* 2013), atherosclerosis (*Cell Metabolism* 2012) and ageing (*Dev. Cell* 2008; *JCI* 2014). Since moving to France and joining IRCAN in 2014, the research lead by Dmitry Bulavin uncovered an unexpected role of DNA damage-induced signaling in cancer cell reprogramming as an alternative to a Cancer Stem Cell model of tumor relapse (*Mol.Cell*, 2019). More recently, the Dmitry Bulavin's group was involved in analysis of senescence in aging and cancer and generated unique genetic models to track and to eliminate senescent cells (*Cell Metabolism*, 2020). Using these unique mouse models, Dmitry Bulavin's lab has established numerous collaborations with the leading scientific institutions around the world (Harvard and Cambridge Universities, Institute Curie, Pasteur Institute, University of Pennsylvania and Tokyo and many others) to move broadly to understand the fundamental role and significance of senescence with aging. His achievements in his own field as well as interdisciplinary nature of his work have been well-recognized by the scientific communities through regular invitations to speak at international conferences and workshops. The research of Dmitry Bulavin is grounded in solid, high-quality work as demonstrated in high-impact publications include, among others, *Nature*, *Nature Genetics*, *Cancer Cell*, *Cell Stem Cell*, *Cell Metabolism*, *NCB*, *Mol. Cell*, *Genes and Dev*, *Dev. Cell* and many additional publications in high impact journals (*JCI*, *JEM*, *JCB* etc).

Curriculum vitae

Dmitry Bulavin

Director of Research of 1st Class INSERM

Director of Institute for Research on Aging and Cancer (IRCAN)

28 Avenue de Valombrose,

Nice, France

Tel: +33 6 46 75 18 48

Education:

1994 MD, Medical Academy, St.Petersburg, Russia, including one year of clinical internship.

1996 PhD; Medical Academy, St.Petersburg, Russia.

Brief Chronology of Employment

1996 - 1998 Research Scientist, Institute of Cytology, St.Petersburg, Russia.

1998 - 2000 Visiting Fellow NCI, NIH, Bethesda, MD, USA

2000 - 2004 Staff Scientist (semi-independent), NCI, NIH, Bethesda, MD, USA

2004 - 2008 Principal Investigator (Assistant Professor), IMCB, Singapore

2008 - 2014 Senior Principal Investigator (Associate Professor), IMCB, Singapore

since 2014 - DR1 INSERM (Full Professor), IRCAN, Nice, France

since 2024- Director of Institute for Research on Aging and Cancer (IRCAN), Nice, France

Awards and Achievements

- The Fellows Award for Research Excellence 2002, National Institutes of Health, Bethesda, USA
- The 2012 World Technology Awards for doing "the innovative work of the greatest likely long-term significance", finalist.
- Member of the World Technology Network since 2012
- "Accueil de nouveaux talents pour une recherche innovante en cancérologie" Award, ARC Foundation 2012
- Prime d'Excellence INSERM 2014
- ARC Labelization Award, 2018
- Member of Biotech/Medical and Life Extension boards of the Lifeboat Foundation (<https://lifeboat.com/ex/bios.dmitry.v.bulavin>) since 2019
- FRM labelization Award, 2021

Mentoring activities

- PhD students: Dr. Anastasia Goloudina (PhD, April 2004 from the Institute of Cytology, St.Petersburg, Russia); Dr. Oleg Timofeev (PhD, March 2005 from the Institute of Cytology, St.Petersburg, Russia) Ms. Daria Chervyakova (PhD, 2007 from St.Petersburg University, Russia); Ms. Crissy Phillips (PhD, 2007 from the NIH/John Hopkins University); Mr. Yunhua Zhu (PhD, 2010 from the National University of Singapore); Bodgan Grigorash (joint PhD student with University of Burgundy, 2022); Alessandra Pierantoni (INSERM InterAging program, PhD from University of Cote D'Azur, expected in 2025).
- ASTAR scholars (Singapore): 9
- Pre-PhD students through SIPGA program (Singapore): 2
- Master students: 15

- Postdocs: 12
- Lab biologists: 16

Teaching activities

- Cell Cycle Course for PhD students (10h)
- Cancer Biology Course for PhD student (10h)

Editorial and advisory boards

- Cancer Biology and Therapy;
- Frontiers in Radiation Oncology;
- Biotech/Medical and Life Extension boards of the Lifeboat Foundation (<https://lifeboat.com/ex/bios.dmitry.v.bulavin>)

Current and past grant support (total >4 000 000 Euros) as a Principal Investigator direct cost is indicated

- AAP INCa 2023 - Projets libres de Recherche «Biologie et Sciences du Cancer», 2023-2026, 240000€
- Bourses FRM, programme SPF, 2023-2025 - 107000€
- ARC 2022 PJA3 Fondation ARC « Cancer et vieillissement: comprendre la signification clinique des cellules sénescentes pour améliorer le traitement du cancer du poumon », 2023-2024, 50000€
- Bourses Excellence Jeunes Chercheurs 2023-2025 IDEX UCA - 120000€
- ANR France, “Role of macrophage p16High senescence-like state in inflammaging” (MacrophAge). 2022-2026, 341000 €
- The European University Ulysseus Postdoctoral fellowship, 2022-2023, 60000€
- Interaging, programme de coordination thématique, 2021-2026, 127300€
- FRM Labelisation “Déplétion et remplacement des cellules sénescentes comme stratégie pour prolonger significativement l’espérance de vie” 2021-2023, 382500€
- AGEMED2, INSERM Consortium, 2020-2023, 157400€
- ANR France, “Senescence as a pivotal point of healthy aging” (SENAGE). 2019-2023, 345000 €
- Canceropole PACA, Special grant for finalizing the experiments for high profile journals – “Boosting publication”, 2018, 24100 €
- Foundation ARC grant “La signalisation des dommages à l'ADN comme une force motrice de l'hétérogénéité tumorale”, 2018-2020, 450000€
- Canceropole PACA, Pilot project of Single cell analysis, 20000€
- PLAN CANCER 2015, 2015-2016, 61800€
- Appel à projets Fondation ARC 2011, Accueil de nouveaux talents pour une recherche innovante en cancérologie (2013-2017), 1400000 €

Invited Talks (partial)

- Annual Meeting of Radiation Research Society/North American Hyperthermia Society, San Juan, Puerto Rico, April 21-25, 2001
- Gordon Research Conference on Stress-Induced Gene Expression, July 27-August 1, 2003, Queen’s College, Oxford, UK

- The 10th Annual Symposium of the Danish Cancer Society, August 23-25, 2004, Copenhagen, Denmark.
- The 12th International p53 Workshop, November 6-10, 2004, Dunedin, New Zealand.
- The 3rd International Mdm2 Workshop, Konstanz, Germany September 9th-12th, 2005
- Croucher ASI: Signaling in Cell Growth & Differentiation, Jan 16-20, 2006, Hong Kong
- FASEB meeting "Spindle Assembly and Function", Fall 2007, Vermont, USA
- 9th Australian Cell Cycle Workshop, St. Vincent's Institute of Medical Research, Melbourne, Australia, 23- 25 November 2006
- CNIO Workshop "Stress Signaling and Cancer", October 12-15, 2008, Madrid, Spain
- Europhosphatases 2009: Protein Phosphatases in development and disease. Egmond aan Zee, The Netherlands 14-18 July 2009
- 1st Singapore-Italy Joint Symposium on Biomedical Sciences, Biopolis, Singapore, December 10-11, 2009
- Stem Cells, Tissue Homeostasis and Cancer Conference, Heidelberg, 12-15 May 2010
- The ISSCR 10th ISSCR Annual Meeting, Yokahama Japan, June 13-16, 2012
- 2014 FASEB conference on Protein Phosphatases, July 20-25, 2014, Nassau, Bahamas.
- "Europhosphatase" meeting, June 24-29th, 2015, Turku, Finland.
- "Zing" scientific conference "Genomic Integrity", August 1-5, 2015, Cairns, Australia.
- FASEB Protein Phosphatase meeting, Steamboat Springs, Colorado from July 17-22, 2016.
- ICAD 2016, International Society on Aging and Disease, Li Ka Shing Learning and Knowledge conference center, Stanford University, California, United States, September 30 – October 3.
- Europhosphatase 2017: Phosphatases in cell fates and decisions" Paris, France, July 23- 28, 2017.
- Jena Aging Meeting (JAM) September 6-8, 2018 Venue: Friedrich Schiller University, Jena, Germany
- ICAD 2018, International Society on Aging and Disease, Convention Center at at "The Saint-Paul", Nice, France, October 5-7, 2018
- Undoing Aging 2019, the Umspannwerk Alexanderplatz, Berlin, Germany, March, 28 to 30, 2019
- Cologne Spring meeting 3rd Ageing Conference "From mechanism to disease", Cologne, Germany, March 17-21, 2020 (moved to 2022)
- DINGO meeting on "Diversity of DNA Damage Signaling Pathways", Marseille, France, 19-20 May 2020 (moved to 2021)
- The 39th Sapporo International Cancer Symposium, Sapporo, Japan, 2020/6/30-2020/7/2 (moved to 2021)
- International Conference on Cancer Science: Research & Development (ICSR 2021), June 11-12, 2021, Czech Republic, Prague.
- A Keynote lecture at the ceremony of opening of the Aging Center at Ruijin Hospital, Shanghai, May 12, 2021
- Nouvelles idées pour le problème séculaire du vieillissement, Intitute de France, Academie des Sciences, Paris 05/10/2021
- Invited Talk, Insitute Pasteur, September 27, 2022, Paris France
- Invited Talk, EUR-LIVE, September 29-30, Paris France
- Invited Talk, IRB Barcelona, November 2, Barcelona Spain
- Invited online lecture, ISAR, Interaging – Shanghai Jiotong University School of Medicine, December 7th, 2022.
- 14th international symposium on DNA Damage Response & Human Disease (isDDRHD-2023), Shenzhen, China Nov. 3-5th, 2023.
-

Patents

1. United States Provisional Patent Application # 60/246,912; PCT Application #US01/47669. Title: "Enhanced Efficacy and Safety of Genotoxic Therapy by p38 MAPK Modulation." Inventors: Bulavin DV and Fornace J.
2. United States Provisional Patent Application # 60/366,883. Title: "Materials and Methods for Inhibiting Wip1." Inventors: Bulavin DV, Fornace J, Appella E, Kallioniemi A.
3. Patent application EP15305361.6 filed on 10 March 2015 "Method and Kit for reprogramming of somatic cells". Inventors: Bulavin DV, Filipponi D.
4. SG patent application 10201702209V filed on 17 March 2017 "A novel method of the lung cancer treatment via blocking the tumor-promoting functions of macrophages". Inventors: Bulavin DV, Brichkina A, Antipova M, Novoselova M, Loh HM, Brzozowska AM
5. International PCT No. PCT/EP2021/082221, 18 november 2021, "COMPOUNDS FOR TREATING A DISEASE ASSOCIATED WITH MACROPHAGE SENESENCE" Inventors: Bulavin DV, Triana-Martinez F.
6. B220026EPA/VEM/CPO, 08 April 2022, METHOD OF GENERATING iPSC LINES WITH TOTIPOTENT PROPERTIES. Inventors: Bulavin DV, Grigorash B

Main Research and clinical collaborations

- "Generation of single cell senescent atlas in normal and cancerous tissues", together with Pr. Masashi Narita, CRUK, Cambridge University, UK
- "The role of senescent cells in Alzheimer's Disease", together with Pr. Bart de Strooper, Crick Institute, London, UK
- "Genome-wide analysis of epigenetic marks in senescence in cancer", Pr. V. Gladishev, Harvard University, USA
- "Developing an approach to remove senescent cells by CART to improve cancer treatment", Pr. Zoltan Arany, University of Pennsylvania, USA
- "Chromatin regulation in senescence of normal and cancer cells", Dr. O. Bischof, Pasteur Institute, Paris, France
- "The role of senescent cells in lung fibrosis and lung cancer", Dr. A. Londono, Curie Institute, Paris, France
- "The role of senescent cells in osteoarthritis", Dr. JM Brondello, INSERM U844, Montreuil, France
- "Role of Runx3 in Wip1-dependent regulation of DNA damage response", co-PI Dr. Y. Ito, CSI, Singapore
- "Role of fibroblast senescence in cancer", co-PI C. Gaggioli, IRCAN, Nice, France

Ad-hoc reviewer for

Apoptosis, Biology of the Cell, Breast Cancer Research, Cancer Biology and Therapy, Cancer Cell, Cancer Research, Cell, Cell Cycle, Cell Death and Differentiation; Cell Division; Cell Reports; Cell Stem Cell, Current Biology; EMBO journal; Genes and Development; Journal of Biological Chemistry; Journal of Cellular Biochemistry; Journal of Clinical Investigation; Molecular and Cellular Biology; Molecular Cancer Research; Oncogene; Nature, Nature Cell Biology, Nature Chemical Biology; Nature Structural and Molecular Biology; Nature Genetics; Science; Science Signaling; Stem Cell Reports

Top Publications as a senior and corresponding author

1. Bogdan B. Grigorash, Dominic van Essen, Laurent Grosse, Alexander Emelyanov, Benoît Kanzler, Clement Molina, Elsa Lopez, Oleg N. Demidov, Carmen Garrido, Simona Sacconi, Dmitry V. Bulavin (2023) p16^{High} senescence restricts cellular plasticity during somatic cell reprogramming. **Nature Cell Biology** 25(9):1265-1278. Highlighted in "Depletion of p16^{High} senescent cells for stem cell reprogramming and tissue rejuvenation" (2023) **Nature Cell Biology** 25: 1252–1253 (2023).

2. Grosse L, Wagner N, Emelyanov A, Molina C, Lacas-Gervais S, Wagner KD, Bulavin DV. (2020) Defined p16^{High} Senescent Cell Types Are Indispensable for Mouse Healthspan. **Cell Metab.** 32(1):87-99. Highlighted by 2 Faculty Opinion Recommendations- <https://facultyopinions.com/prime/738059169>;
3. Doria Filipponi, Alexander Emelyanov, Julius Muller, Clement Molina, Jennifer Nichols and Dmitry V. Bulavin (2019) DNA Damage Signaling - induced Cancer Cell Reprogramming as a Driver of Tumor Relapse. **Mol. Cell**, 74(4):651-663.e8. Highlighted by F1000Prime - <https://f1000.com/prime/735479648>
4. Brichkina A, Bertero T, Loh HM, Nguyen TMN, Emelyanov A, Rigade S, Ilie M, Hofman P, Gaggioli C, Bulavin DV. (2016) p38 MAPK builds a hyaluronan cancer niche to drive lung tumorigenesis. **Genes and Development**, 30(23):2623-2636
5. Yunhua Zhu, Oleg N.Demidov, Amanda M. Goh, David M. Virshup, David P. Lane, Dmitry V. Bulavin. (2014) Wip1 regulates adult neurogenesis and Wnt signaling during aging. **Journal of Clinical Investigation**, 124(7):3263-73.
6. Doria Filipponi, Julius Muller, Alexander Emelyanov, and Dmitry V Bulavin. (2013) WIP1 controls global heterochromatin silencing via ATM/BRCA1-dependent DNA methylation. **Cancer Cell**, 24(4):528-41. Highlighted in "Epigenetics: WIP1 creates hush and havoc". [Nat Rev Cancer. 2013] and in "Wiping DNA methylation: Wip1 regulates genomic fluidity on cancer." [Cancer Cell. 2013]
7. Yunhua Zhu, Yi-Fu Huang, Calvina Kek and Bulavin DV. (2013). Apoptosis differently affects lineage tracing of Lgr5 and Bmi1 intestinal stem cell populations. **Cell Stem Cell**, 12(3):298-303. Highlighted by F1000Prime and in "If a stem cell dies in the crypt, and no one is around to see it...." [Cell Stem Cell. 2013]
8. Le Guezennec X, Brichkina A, YF Huang, Kostromina A, Han W, Bulavin DV. (2012). Wip1-dependent regulation of autophagy, obesity, and atherosclerosis. **Cell Metabolism**, 16(1):68-80.
9. Esther Sook Miin Wong, Xavier Le Guezennec, Oleg N.Demidov, Nicolette Theresa Marshall, Siew Tein Wang, Janakiraman Krishnamurthy, Norman E. Sharpless, N. Ray Dunn, and Dmitry V. Bulavin. (2009). p38MAPK Controls Expression of Multiple Cell Cycle Inhibitors and Islet Proliferation with Advancing Age. **Dev Cell**, 17(1):142-9.
10. Demidov ON, Timofeev O, Lwin N, Kek C, Appella E and Bulavin DV. (2007). Regulation of p53-dependent apoptosis of stem cells and intestinal tumorigenesis by Wip1 phosphatase. **Cell Stem Cell**, 1:170-180.
11. Shreeram S, Demidov ON, Weng KH, Yamaguchi H, Onishi N., Kek C., Timofeev O, Dungeon C, Fornace AJ, Anderson CW, Minami Y., Appella E and Bulavin DV. (2006) Wip1 Phosphatase Modulates ATM-dependent Signaling Pathways. **Molecular Cell**, 23: 757-764.

Full List of publications

1. Bogdan B. Grigorash, Dominic van Essen, Laurent Grosse, Alexander Emelyanov, Benoît Kanzler, Clement Molina, Elsa Lopez, Oleg N.Demidov, Carmen Garrido, Simona Sacconi, Dmitry V.Bulavin p16^{High} senescence restricts cellular plasticity during somatic cell reprogramming. (2023) **Nature Cell Biology** 25(9):1265-1278. Highlighted in "Depletion of p16^{high} senescent cells for stem cell reprogramming and tissue rejuvenation" (2023) **Nature Cell Biology** 25: 1252–1253.
2. Emmanuelle Born, Larissa Lipskaia, Marielle Breau, Amal Houssaini, Delphine Beaulieu, Elisabeth Marcos, Remi Pierre, Marcio Do-cruzeiro, Marine Lefevre, Genevieve Derumeaux, Dmitry V. Bulavin, et al. Eliminating senescent cells can promote pulmonary hypertension development and progression. **Circulation** <https://doi.org/10.1161/CIRCULATIONAHA.122.058794>
3. Grosse L., Wagner N., Emelyanov A., Lacas-Gervais S., Wagner KW., Bulavin DV. (2020) Defined p16^{High} Senescent Cell Types Are Indispensable for Mouse Healthspan. **Cell Metab.** 32(1):87-99.
4. Filipponi D, Emelyanov A., Muller J., Molina C., Nichols J. and Bulavin DV. (2019). DNA Damage Signaling - induced Cancer Cell Reprogramming as a Driver of Tumor Relapse. **Mol.Cell**, 74(4):651-663.e8. Highlighted by

F1000Prime - <https://f1000.com/prime/735479648>

5. Bertero T., Oldham WM, Grasset EM, et al *. Tumor-stroma mechanics coordinate amino acid availability to sustain tumor growth and malignancy. **Cell Metabolism**, 2019 Jan 8;29(1):124-140.
6. Brichkina A, Bertero T, Loh HM, Nguyen TMN, Emelyanov A, Rigade S, Ilie M, Hofman P, Gaggioli C, Bulavin DV. (2016) p38 MAPK builds a hyaluronan cancer niche to drive lung tumorigenesis. **Genes and Development**, 30(23):2623-2636.
7. Brichkina A, Nguyen NT, Baskar R, Wee S, Gunaratne J, Robinson RC, Bulavin DV. (2016) Proline isomerisation as a novel regulatory mechanism for p38MAPK activation and functions. **Cell Death Differ**, 23(10):1592-1601.
8. Cortez I, Bulavin DV, Wu P, McGrath EL, Cunningham KA, Wakamiya M, Papaconstantinou J, Dineley KT. (2016) Aged dominant negative p38 α mapk mice are resistant to age-dependent decline in adult-neurogenesis and context discrimination fear conditioning. **Behav Brain Res**, S0166-4328(16)30826-9.
9. Klionsky DJ,Bulavin DV, ... Zoladek T, Zong WX, Zorzano A, Zughaier SM. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). **Autophagy**. 2016 Jan 2;12(1):1-222.
10. Papaconstantinou J, Wang CZ, Zhang M, Yang S, Deford J, **Bulavin DV**, Ansari NH. Attenuation of p38 α MAPK stress response signaling delays the in vivo aging of skeletal muscle myofibers and progenitor cells. **Aging** (Albany NY). 2015 Sep;7(9):718-33.
11. Huang YF, **Bulavin DV**. Oncogene-mediated regulation of p53 ISGylation and functions. **Oncotarget**. 2014 Jul 30;5(14):5808-18.
12. Huang YF, Wee S, Gunaratne J, Lane DP, **Bulavin DV**. Isg15 controls p53 stability and functions. **Cell Cycle**. 2014;13(14):2200-10.
13. Yunhua Zhu, Oleg N.Demidov, Amanda M. Goh, David M. Virshup, David P. Lane, Dmitry V. Bulavin. (2014) Wip1 regulates adult neurogenesis and Wnt signaling during aging. **Journal of Clinical Investigation**, 124 (7):3263-73.
14. Doria Filipponi, Julius Muller, Alexander Emelyanov, and Dmitry V Bulavin. (2013) WIP1 controls global heterochromatin silencing via ATM/BRCA1-dependent DNA methylation. **Cancer Cell**, 24(4):528-41. Highlighted in "Epigenetics: WIP1 creates hush and havoc". [Nat Rev Cancer. 2013] and in "Wiping DNA methylation: Wip1 regulates genomic fluidity on cancer." [Cancer Cell. 2013]
15. Yunhua Zhu, Yi-Fu Huang, Calvin Kek and Bulavin DV. (2013). Apoptosis differently affects lineage tracing of Lgr5 and Bmi1 intestinal stem cell populations. **Cell Stem Cell**, 12(3):298-303. Highlighted by F1000Prime and in "If a stem cell dies in the crypt, and no one is around to see it...." [Cell Stem Cell. 2013]
16. Dudgeon C, Shreeram S, Tanoue K, Mazur SJ, Sayadi A, Robinson RC, Appella E, **Bulavin DV**. Genetic variants and mutations of PPM1D control the response to DNA damage. **Cell Cycle**. 2013 Aug 15;12(16):2656-64.
17. Le Guezennec X, Brichkina A, YF Huang, Kostromina A, Han W, Bulavin DV. (2012). Wip1-dependent regulation of autophagy, obesity, and atherosclerosis. **Cell Metabolism**, 16(1):68-80.
18. Demidov ON., Zhu Y., Kek C., A.Goloudina, Motoyama N, Bulavin DV. (2012). Gadd45a is a haploinsufficient gene in Wip1-dependent regulation of intestinal tumorigenesis, **Cell Death and Differentiation**, 19(11):1761-8.
19. Fernandez F., Soon I., Li Z., Kuan TC., Min DH., Wong ESM., Demidov ON., Paterson MC., Dawe G., Bulavin DV*. Xiao ZX*. (2012). Wip1 phosphatase positively modulates dendritic spine morphology and memory processes through the p38MAPK signaling pathway, **Cell Adhesion and Migration**, 6(4), on line; (* -corresponding author)
20. Goloudina AR, Tanoue K, Hammann A , Fourmaux E , Le Guezennec X, Bulavin DV, Mazur SJ, Appella E, Garrido C, Demidov ON. (2011). Wip1 promotes RUNX2-dependent apoptosis in p53 negative tumors and protects normal tissues during treatment with anti-cancer agents. **PNAS**, 2012;109(2):E68-75.
21. Cha H, Lowe JM, Li H, Lee JS, Belova GI, Bulavin DV, Fornace AJ Jr. (2010). Wip1 directly dephosphorylates gamma-H2AX and attenuates the DNA damage response. **Cancer Res**. 2010;70(10):4112-22.
22. Esther Sook Miin Wong, Xavier Le Guezennec, Oleg N.Demidov, Nicolette Theresa Marshall, Siew Tein Wang, Janakiraman Krishnamurthy, Norman E. Sharpless, N. Ray Dunn, and Dmitry V. Bulavin. (2009). p38MAPK Controls Expression of Multiple Cell Cycle Inhibitors and Islet Proliferation with Advancing Age. **Dev Cell**,

- 17(1):142-9.
23. Yun-Hua Zhu, Cheng-Wu Zhang, Li Lu, Oleg N. Demidov, Li Sun Lan Yang, Dmitry V. Bulavin*, Zhi-Cheng Xiao* (2009). Wip1 Regulates The Generation Of New Neural Cells In The Adult Olfactory Bulb Through p53 Dependent Cell Cycle Control. **Stem Cells**, 27(6):1433-1442. (* -corresponding author)
 24. Chew J., Biswas S, Shreeram S, Humaidi M, Wong ET, Dhillon MK, Teo H, Hazra A, Fang CC, López-Collazo E, Bulavin DV & Tergaonkar V (2009). Wip1 phosphatase is a negative regulator of Nf-kB signaling. **Nature Cell Biology**, 11(5):659-66.
 25. Shreeram S., WK Hee and Bulavin DV. Cdc25A Serine 123 phosphorylation couples centrosome duplication with DNA replication and regulates tumorigenesis (2008) **Mol Cell Biol** 28(24):7442-50.
 26. Demidov ON, Timofeev O, Lwin N, Kek C, Appella E and Bulavin DV. (2007). Regulation of p53-dependent apoptosis of stem cells and intestinal tumorigenesis by Wip1 phosphatase. **Cell Stem Cell**, 1:170-180.
 27. Demidov, ON., Kek,C., Shreeram, S., Timofeev, O., Fornace, AJ., Appella, E., and Bulavin, DV. (2007) The role of MKK6/p38 MAPK pathway in Wip1-dependent regulation of ErbB2-driven mammary gland tumorigenesis. **Oncogene**, 26(17): 2502-2506.
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Scientific Achievements

Scientific Achievements

The increase in life expectancy worldwide and the resulting increase in proportion of people over 60 years old makes research on aging a public health priority. In this respect, understanding how aging organism contributes to multiple diseases is a key to treat such diseases. It would be correct to say that most of known diseases manifest with age, so aging should be considering the most frequent and significant risk factor in development of multiple types of cancer. How we age, what cell types undergo age-induced deterioration first, what can be done to delay or even to prevent it and how this ultimately contributes to aging and development of aging-related diseases remains largely unknown. In this respect, in the course of the last 25 years, my research remains focused on the role of DNA damage-induced and stress response signaling as a mechanism and the role of senescence as a cellular phenotype in aging and aging-related pathologies with main focus on cancer. Below are several examples of my work that can be divided into several axes: 1) A role for stress- and DNA damage-induced signaling in regulation of tumorigenesis and aging; 2) A role for a DNA damage-induced cancer cell reprogramming as an alternative to a Cancer Stem Cell Model of tumor relapse; 3) understanding the role of senescence, the mechanism(s) of its induction and overall significance in aging and aging-related pathologies including cancer.

1. Role of the stress- and DNA damage-induced signaling in regulation of tumorigenesis and aging.

In the past 2 decades, my lab was working on better understanding of the role of Wip1 phosphatase as a regulator of DNA damage-induced signaling and p38 MAPK, a key player in stress-induced signaling - both in controlling cancer and aging. We previously showed that Wip1 signaling plays an important role in suppressing tumorigenesis *in vivo*¹⁻³, however the precise molecular network regulated by Wip1 phosphatases had to be fully characterized. Using extensive biochemical protocols, my lab identified ATM (the Ataxia-Telangiectasia Mutated kinase) as the key player in the regulation of tumor-resistant properties downstream of Wip1^{4,5}. We found that Wip1 phosphatase is directly involved in regulation of ATM activity. In turn, activation of ATM was required to suppress Em-myc-induced B-cell lymphomas, the onset of which was dramatically delayed in Wip1-deficient mice in an ATM- dependent manner. Thus, we proposed that a non-genotoxic activation of ATM, as seen in Wip1 deficient cells, could be a promising approach for cancer therapy. This suggested to us that inhibition of Wip1 could be the basis for a therapeutic approach in a broad spectrum of tumor types, including breast cancer. As a step into translational research, we have identified chemical compounds with the properties to inhibit Wip1 phosphatase and tested their ability to attenuate cancer cell proliferation⁶.

Understanding the mechanisms underlying the behavior of stem cells and their implications in tumorigenesis and aging are of great importance and paramount to the design of more effective treatments for human diseases. In many, if not all, instances, *in vivo* interrogation of stem cells is intimately linked to lineage tracing protocols, which, in turn, depends on the identification of appropriate stem cell markers. To this end, my lab identified several such markers, including Wip1 phosphatase, which is a key stem cell regulator in the mouse brain and small intestine^{7,8}. We further used several reporter mouse strains to label different stem cell populations in the mouse intestine. Activation of oncogenes in stem cells, an early event in tumorigenesis, results in conversion of stem cells into tumor-initiating/cancer stem cells. My lab found that if Wip1 is deleted or inactivated during this conversion process, p53 undergoes hyperactivation and, consequently, a newly formed cancer stem cell is eliminated via apoptosis⁷. This mechanism is critical in cancer prevention and could provide the basis for the development of therapies for patients with cancer-prone mutations such as APC and BRCA1/BRCA2.

In parallel with our efforts to understand the role of stress and DNA damage-induced pathways in tumorigenesis, we also investigated the role of these pathways in aging. The process of organismal aging is characterized by the functional decline and diminished capacity of different tissues to respond to injury or stress. My lab found that both p38MAPK and Wip1 phosphatase are critically involved in organismal aging. We have generated a p38 knock-in mouse strain that specifically modulates Ink4a expression with age, a gene responsible for age-related decline in functional competence of different tissues⁹. We further showed that these knock-in mice or overexpression of Wip1 results in efficient suppression of an aging-induced decline in functional competence of pancreatic beta cells. As a follow up to these studies, we investigated the role of Wip1 phosphatase in the regulation of aging-induced decline in neural stem cells and neurogenesis. Using mouse models with both overexpression and deletion of Wip1 phosphatase we found that in fact, Wip1 is a critical player in controlling aging-induced changes in brain morphology and functions⁸.

To further understand the network of molecular pathways in controlling tumorigenesis downstream of Wip1, my lab decided to investigate the role of Wip1 in other pathologies that manifest with age. We found that deletion of Wip1 results in efficient suppression of a fat diet-induced weight gain and atherosclerosis when mice are crossed on an ApoE-deficient background¹⁰. Further analysis revealed that this effect was through a non-canonical ATM-mTor pathway and regulation of autophagy. After identifying that autophagy could be a part of Wip1-deficient phenotypes, we are now investigating its contribution to tumorigenesis in defined mouse cancer genetics models as well as using *in vitro* systems. This knowledge could be important in understanding the mechanisms responsible for a metabolic switch towards glycolysis that is common in cancer cells as well as in cancer stem cells.

2. A role for a DNA damage-induced cancer cell reprogramming as an alternative to the Cancer Stem Cell Model of tumor relapse.

Therapies that have either broad targeting anti-cancer activity or target specific signaling molecules that are mutated in cancers often have significant favorable short-term effects. Nevertheless, the presence of resistant cancer cells or acquisition of resistance in the course of tumor evolution or in response to drug treatment are major barriers to a full cure¹¹. Appearance of secondary mutations could contribute to resistance however in a significant number of cases there are no clear genetic changes. The cancer stem cell (CSC) model has been broadly accepted as an explanation for the clinical behavior of some cancers. CSCs represent a distinct population of drug-resistant cells capable of clonal long-term repopulation and self-renewal, which can stably maintain their identity both in primary and relapsed tumors. However, accumulating evidence raised the possibility of existence of rare and most importantly transient non-genetic cell variants that are resistant to cancer therapy and ultimately contribute to tumor spreading and relapse. The origin of such cells remains largely unclear. One line of evidence came from the analysis of human melanoma cells that showed profound transcriptional variability at the single-cell level¹². This variability involves infrequent, semi-coordinated transcription of a number of genes (that could contribute to drug resistance) at high levels in a very small number of cells. It has been argued that addition of cancer drugs could induce epigenetic reprogramming in these cells, converting the transient transcriptional state to a stably resistant state.

Activation of DNA damage response (DDR) with subsequent elimination of cancer cells remains the main route for efficient cancer treatment in response to chemo- and radiotherapy. It is also well documented however that gaps in radiation therapy worsen the outcome of patients suffering from epithelial cancers of the head and neck region and of the breast¹³. The mechanisms of this phenomenon are not completely understood, but are generally attributed to the increased growth rate of the cancer during treatment gaps. Moreover, cancer patients who have received chemotherapy often relapse, and most go on to develop more advanced diseases following their initial therapy. The role of low dose irradiation in cancer initiation is also well documented. DNA damage, via an increased mutation rate, is believed to either activate oncogenes or disable tumor suppressors, thus favoring tumorigenesis. However, low doses of chemo- or radiotherapy may also exert immediate tumor-promoting effects in a large population of cancer cells *in vitro*¹⁴, an effect that cannot be explained by changes in mutation rates.

Our strategy has been to use a Wip1-depleting approach both *in vitro* and *in vivo* as a model to re-capitulate a constitutive activation of DDR signaling. Our prior work revealed that DDR signaling drives heterochromatin silencing during both development and tumorigenesis^{15,16}. Subsequently, we identified a novel role for DDR signaling in overall re-organization of chromatin landscape to favor tumorigenesis. We found that in the case when DDR signaling strength is not sufficient to eliminate cancer cells, it can drastically change their transcriptional profiles¹⁷. Our work provided evidence that treatment-induced DDR can play a priming role in epigenetic reprogramming of cancer cells, by inducing a transient activation of stem cell-specific and pluripotency genes, including Oct4a. In turn, this CSC-like state contributed to acquisition of drug resistance and tumor relapse. These results highlight the mechanistic basis and the phenotypic effect of DDR-induced cancer cell reprogramming as a driver of tumor relapse. Based on our finding we proposed that 1) Stochastic or DDR-induced epigenetic changes in individual cancer cells can lead to re-activation of pluripotency-associated factors and consequently to transient and/or reversible acquisition of a stem-like cellular phenotype. In this scenario, re-activation of the prototypical pluripotency gene Oct4a is a predominant event associated with cancer cell reprogramming; 2) Stochastically- or transiently-induced stem-like phenotypes in cancer cell subpopulations can cause or contribute to drug-resistance and tumor relapse in specific cancers and/or clinical scenarios. Specifically, we proposed that the rare cell subpopulations that act as ‘founders’ for tumor relapse after treatment or DDR-induced signaling may exhibit stem-like phenotypes in a reversible fashion; 3) Specific pluripotency factors not only confer a stem-like phenotype onto individual cancer cells, but they also mechanistically contribute to the induction of gene expression programs and epigenetic changes that endow drug resistance, or other cellular properties that promote tumor relapse (such as metabolic rewiring and/or transient quiescence).

Our analysis of cancer cell reprogramming is based on a series of original and novel approaches, which are grounded in the proof-of-principle studies. This enables us to make significant advances in the understanding of tumor epigenetic heterogeneity of cancers in the course of tumor evolution, with an emphasis on cancer cell reprogramming and transcriptional networks responsible for acquisition of drug resistance.

3. Understanding the role of senescence, the mechanism(s) of its induction and overall significance in aging and aging-related pathologies including cancer. Aging is the major risk factor for many chronic diseases accounting for the bulk of morbidity, mortality, and health costs in the world. Multiple chronic diseases, including cancer manifest with increasing age and tend to prevail in older individuals. Importantly, there is significant evidence that the accumulation of senescent cells can drive many of these phenotypes and pathologies associated with aging but also during cancer development and treatment. However, how senescence mechanistically or dynamically contributes to the aging process and affect the cancer treatment outcome remains largely unknown.

Identifying the full repertoire of senescent cells *in vivo* is critical in understanding how their removal or attenuation could affect tumorigenesis and outcome of cancer treatment. The complexity of targeting senescent cells in aged organism comes from the fact of high abundance of senescence among different cell types and thus overall complexity of targeting cancer-related senescence. In this respect, my lab recently showed that senescent liver sinusoid endothelial cells (LSECs) are not replaced by non-senescent neighbors, but instead their removal activates another type of regenerative response — fibrosis^{18,19}. As such, non-selective senescent cell removal should be considered with great caution while improving protocols for cancer treatment as it could have a serious negative health impact in older organisms. This problem however could be solved by using drugs that selectively remove defined senescent cell types related to cancer. Alternatively, targeting senescence without killing senescent cells with the drugs called senomorphics could be considered as a viable option for improvement of cancer treatment. Both directions are currently under detailed analysis in my lab.

Data obtained from genetically modified mouse models by my lab suggest a detrimental role for p16^{High} senescent cells in physiological aging and age-related pathologies including cancer. Our recent analysis of aging mice revealed a continuous and noticeable accumulation of LSECs expressing numerous senescence markers, including p16. At early stage, senescent LSECs show an enhanced ability to clear macromolecular waste and toxins

including oxidized LDL (oxLDL). Later in life, however, the efficiency of this important detoxifying function rapidly declines potentially due to increased endothelial thickness and senescence-induced silencing of scavenger receptors and endocytosis genes. This inability to detoxify toxins and macromolecular waste, which can be further exacerbated by increased intestinal leakiness with age, might be an important contributing factor to cancer progression and reduced response to cancer treatment. Our work proposes how LSEC senescence could serve as an endogenous clock that ultimately controls longevity and outlines possible approaches to improve this function directly reducing the onset of cancer as well as improving different cancer treatment protocols including in the presence of immune checkpoint therapeutics.

The unique mouse models to track and to eliminate p16 senescence cells developed by my lab have a tremendous potential to dissect the role of senescence in aging and cancer and by setting-up numerous collaboration with world-leading scientific centers, this is currently under broad investigation. This multi-collaborative approach could yield advancement in the field of aging but also in better understanding and treatment of multiple age-related pathologies including cancer.

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- Membre du conseil scientifique de l'Association contre les Maladies Mitochondriales (AMMi), et de l'Association contre le syndrome de Wolfram, de la FSMR FILSAN
- Membre du CA de l'ARC depuis 2018
- Expert dans les jurys de différents AAP (ANR, PHRC, IDEX...) et reviewer dans différents journaux (Brain, Nat Com, Am J Hum Genet...)

Fonctions universitaires/Enseignement

- Coordinatrice locale du DES de Biologie Médicale depuis 2012.
- Responsable locale FST Génétique et Médecine Moléculaire Bioclinique
- Responsable de l'enseignement de la génétique pour les étudiants en médecine

Diplômes et formation

- Internat des Hôpitaux (promotion 1984)
- D.E.A de Microbiologie et Biologie Cellulaire (1987)
- Doctorat en Médecine (1991)
- D.E.S. de Pédiatrie (1992)
- Assistante en Biologie Cellulaire à la Faculté de Médecine de Nice (1992-1996)
- Doctorat des Sciences de la Vie de l'UNSA (1993)
- Maître de Conférences des Universités (1996-2002)
- Qualification en Génétique Médicale (1997)
- Habilitation à Diriger les Recherches (1997)
- Professeur des Universités en Génétique à la Faculté de Médecine de Nice, depuis le 1er septembre 2002
- Agrément pour la pratique des examens de génétique moléculaire à des fins médicales et pour le diagnostic prénatal, depuis le 31 juillet 2001

Prix et distinctions

- Prix Fabrice LE MOUHAËR, Fondation pour la Recherche Médicale (FRM), 2021

- Prix d'Excellence Université Côte d'Azur, 2021
- Prime d'Encadrement Doctoral et de Recherche (PEDR) depuis 2016
- Chevalier de la Légion d'honneur, 2010

Sélection de responsabilités scientifiques antérieures

- Responsable scientifique du Laboratoire de Données Médicales (MDLab), IDEX UCA JEDI de 2017-22.
- Présidente de la commission nationale 5 de l'ARC (Recherche clinique), 2006-12.
- Membre du conseil scientifique de l'ARC, 2006-12.
- Membre du CNU de Génétique, 2006-12.
- Membre du conseil scientifique de l'INPS (Institut National de Police Scientifique) jusqu'en 2019.

Principaux financements au cours des 5 dernières années

- **ANR 2021**: « MITOMICS - mitochondrial disease database : an integrated multi-OMICS approach » 1.397M€, partenaire
- **FRM – Maladies neurodégénératives 2020** : Disséquer les mécanismes moléculaires responsables d'un défaut mitochondrial conduisant à la mort du motoneurone, 600 000€, principal investigateur
- **PHRC 2020** : “ Intérêt du multi-omics (WES/RNA-Seq) pour lutter contre l'impasse diagnostique dans les maladies mitochondriales”, 247.103€, partenaire
- **AFM projet stratégique 2019** : Identifying candidate drugs in mitochondrial cardiomyopathies : From Mouse to Human, 1.8M€, partenaire
- **IDEX UCA Jedi 2017** : *CHCHD10* mutations : a mouse model to understand how mitochondrial dysfunction leads to fronto-temporal dementia (FTD), 200 000€, co-principal investigateur
- **IDEX UCA Jedi 2017** Mise en place d'une plateforme de spectrophotométrie/fluorométrie sur microplaques pour le diagnostic de maladies mitochondriales et l'exploration de modèles murins », 60 000€, principal investigateur

Conférences invitées (sélection)

- FENS, Federation of European Neuroscience Societies, Juin 2024, Vienne
- EUROMIT, International meeting on mitochondrial pathology, Juin 2023, Bologne
- Phenomin celebrates X years, Juillet 2021, Strasbourg
- Conférence plénière e-JR6 SLA-MN, Octobre 2020, Paris
- SFEIM, Novembre 2019, Paris
- Fondation Maladies Rares, Mai 2019, Paris
- Congrès de Bioénergétique, Septembre 2017, Lacanau
- UMDF Mitochondrial Medicine, Juillet 2017, Washington DC (Award price)

Organisation de congrès

- MitoNice2022, Presidents Valerio Carelli & Véronique Paquis-Flucklinger, September 2022, Acropolis, Nice
- Winter School : “Mitochondria in Health, Disease and Aging”, 2nd édition, Décembre 2021, Nice; <https://life.univ-cotedazur.fr/winter-school-2021>, organisée tous les 2 ans (EUR “Life and Health Sciences), couplée à un DU sur les maladies mitochondriales
- Winter School : “Mitochondria in Health and Disease”, Décembre 2018, Nice.

Activités de diffusion et d'information

Nombreuses activités pour les associations de patients : Journées annuelles des centres de référence pour les maladies rares, Journée internationale des maladies rares, Care2022, Fête de la science, Téléthon...

Dix publications significatives dans les 5 dernières années

1. Genin* EC, Bannwarth* S, Ropert B, Lespinasse F, Mauri-Crouzet A, Augé G, Fragaki K, Cochaud C, Donnarumma E, Lacas-Gervais S, Wai T, **Paquis-Flucklinger V**. CHCHD10 and SLP2 control the stability of the PHB complex: a key factor for motor neuron viability. *Brain*. 2022 Jun 3;awac197. (*co-first authors). doi: 10.1093/brain/awac197. Epub ahead of print. PMID: 35656794.
2. Baek M, Choe Y-J, Bannwarth S, Kim J, Maitra S, Dorn II GW, Taylor JP, **Paquis-Flucklinger V**, Kim NC. Dominant toxicity of ALS-FTD-associated *CHCHD10*^{S59L} is mediated by TDP-43 and PINK1. *Nat Com*, 2021; 74 :20-38.
3. Labory J, Fierville M, Ait-El-Mkadem S, Bannwarth S, **Paquis-Flucklinger V*** and Bottini S* (*co-last authors). Multi-Omics approaches to improve mitochondrial disease diagnosis: challenges, advances and perspectives. *Frontiers in Molecular Biology*, 2020; Nov 2; 7:590842.
4. Zereg E, Chaussenot A, Morel G, Bannwarth S, Sacconi S, Soriani MH, Attarian S, Cano A, Pouget J, Bellance R, Tranchant C, Lannes B, de Paula AM, Saadi Ait-El-Mkadem S, Chafino B, Berthet M, Fragaki K, **Paquis-Flucklinger V***, Rouzier C* (*co-last authors). Single-fiber studies for assigning pathogenicity of eight mitochondrial DNA variants associated with mitochondrial diseases. *Hum Mut*, 2020; 41:1394-1406.
5. Vaillant-Beuchot L, Mary A, Pardossi-Piquard R, Bourgeois A, Lauritzen I, Eysert F, Kinoshita PF, Cazareth J, Badot C, Fragaki K, Bussiere R, Martin C, Mary R, Bauer C, Pagnotta S, **Paquis-Flucklinger V**, Buée-Scherrer V, Buée L, Lacas-Gervais S, Checler F, Chami M. Accumulation of amyloid precursor protein C-terminal fragments triggers mitochondrial structure, function, and mitophagy defects in Alzheimer's disease models and human brains. *Acta Neuropathol*, 2020 Oct 20. doi: 10.1007/s00401-020-02234-7.
6. Genin EC, Madji Hounoum B, Bannwarth S, Fragaki K, Lacas-Gervais S, Mauri-Crouzet A, Lespinasse F, Neveu J, Ropert B, Augé G, Cochaud C, Lefebvre-Omar C, Bigou S, Chiot A, Mochel F, Boillée S, Lobsiger CS, Bohl D, Ricci JE, **Paquis-Flucklinger**. Mitochondrial defect in muscle precedes neuromuscular junction degradation and motor neuron death in *CHCHD10*^{S59L/+} mouse. *Acta Neuropathol*, 2019 Mar 14. doi: 10.1007/s00401-019-01988-z.
7. Genin EC, Bannwarth S, Lespinasse F, Ortega-Vila B, Fragaki K, Itoh K, Villa E, Lacas-Gervais S, Jokela M, Auranen M, Ylikallio E, Mauri-Crouzet A, Tynnismaa H, Vihola A, Augé G, Cochaud C, Sesaki H, Ricci JE, Udd B, Vives-Bauza C, **Paquis-Flucklinger V**. Loss of MICOS complex integrity and mitochondrial damage, but not TDP-43 mitochondrial localisation, are likely associated with severity of *CHCHD10*-related diseases. *Neurobiol Dis*, 2018 ; Nov;119:159-171. doi: 10.1016/j.nbd.2018.07.027.
8. Plutino M, Chaussenot A, Rouzier C, Ait-El-Mkadem S, Fragaki K, **Paquis-Flucklinger V**, Bannwarth S. Targeted next generation sequencing with an extended gene panel does not impact detection in mitochondrial diseases. *BMC Med Genet*, 2018; Apr 7;19(1):57. doi: 10.1186/s12881-018-0568-y.

9. Rouzier C, Moore D, Delorme C, Lacas-Gervais S, Ait-El-Mkadem S, Fragaki K, Burté F, Serre V, Bannwarth S, Chaussenot A, Catala M, Yu-Wai-Man P, **Paquis-Flucklinger V**. A novel *CISD2* mutation associated with a classical Wolfram syndrome phenotype alters Ca^{2+} homeostasis and ER-mitochondria interactions. *Hum Mol Genet*, 2017; 26:1599-1611.
10. Ait-El-Mkadem S, Dayem-Quere M, Mirjana Gusic M, Chaussenot A, Bannwarth S, François B, Genin E.C, Fragaki K, Volker-Touw C, Vasnier C, Valérie Serre S, van Gassen K.L.I, Lespinasse F, Richter S, Eisenhofer G, Rouzier C, Mochel F, De Saint-Martin A, Abi Warde MT, de Sain M, Judith Jans J, van Hasselt P, Amiel J, Avsec Z, Mertes C, Haack T.B, Strom T, Meitinger T, Bonnen P.E, Taylor R.W, Gagneur J, Rötig A, Delahodde A, Prokisch H, Fuchs S, **Paquis-Flucklinger V**. Mutations in *MDH2*, encoding a Krebs cycle enzyme, cause early-onset severe encephalopathy. *Am J Hum Genet*, 2017; 100:151-159.