

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
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Nice, France
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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

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 3,419,100 Euros) as a Principal Investigator in last 8 years - direct cost is indicated

- ARC 2022 PJA3 Fondation ARC « Cancer et vieillissement: comprendre la signification clinique des cellules sénescences pour améliorer le traitement du cancer du poumon », 2023-2024, 50000€
- 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 thematique, 2021-2026, 127300€
- FRM Labelisation “Déplétion et remplacement des cellules sénescences 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, Yokohama 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 "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.

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 p16^{High} senescence restricts cellular plasticity during somatic cell reprogramming. <https://doi.org/10.1101/2022.08.24.504108>, **in revision for Nature Cell Biology**
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 Filippini, 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 Filippini, 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, 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]
 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. <https://doi.org/10.1101/2022.08.24.504108>, **in revision for Nature Cell Biology**
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. Filippini 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, 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]
 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, L  pez-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.
28. Shreeram S, Weng KH, Demidov ON, Kek C, Fornace AJ, Anderson CW, Appella E and Bulavin DV. (2006) Regulation of ATM/p53-dependent suppression of myc-induced lymphomas by Wip1 phosphatase. **J. Experimental Medicine**, 203 (13):2793-2799.
29. 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.
30. Phillips, C., Kek, C., Demidov, ON., Saito, S., Fernandes, K., Diot A., Bourbon JC., Lane, DP., Appella, E., Fornace, AJ and Bulavin, DV. (2006) Tumor susceptibility and apoptosis defect in a mouse strain carrying a human p53 transgene. **Cancer Research**, 66(6):2928-36.
31. Belova, GI., Demidov, ON., Fornace AJ., and Bulavin, DV. (2005) Chemical Inhibition of Wip1 phosphatase contributes to suppression of tumorigenesis. **Cancer Biology and Therapy**, 4(10):1154-8.
32. Jirmanova,L., Bulavin, DV., and Fornace, AJ (2005) Inhibition of the ATR/Chk1 Pathway Induces a p38-Dependent S-phase Delay in Mouse ES Cells. **Cell Cycle**, 30 (10):1428-34.
33. Khaled, AR., Bulavin, DV., Kittipatarin, C., Li, WQ., Alvarez, M, Kim K, Young, HA., Fornace, AJ., and Durum, SK (2005) Cytokine-driven cell cycling is mediated through Cdc25A. **J.Cell Biol**, 169 (5), 765-775.
34. Timofeev,O., Lee, T.Y., and Bulavin, D.V. (2005) A subtle change in p38 MAPK activity is sufficient to suppress in vivo tumorigenesis. **Cell Cycle**, 30 (1), 118-120.
35. Bulavin, D. V.*, Phillips, C., Nannenga, B., Timofeev, O., Donehower, L. A., Anderson, C. W., Appella, E., and Fornace, Jr, A. J. (2004). Inactivation of the Wip1 Phosphatase Inhibits Mammary Tumorigenesis through p38 MAPK-mediated Activation of the Ink4a/Arf Pathway (Article). **Nat Genet**, 36, 343-350. Commentary: Bernard R., Wip-ing out cancer. *Nat Genet*, 36, 319-320.* corresponding author
36. Goloudina A., Yamaguchi H., Chervyakova D.B, Appella E., Fornace A.J., and Bulavin D.V. (2003) Regulation of Human Cdc25A Stability by Serine 75 Phosphorylation Is Not Sufficient to Activate an S-phase Checkpoint. **Cell Cycle**, 2, 473-478. Commentary: Neely, K.E. and Piwnica-Worms, H. Cdc25A regulation, To destroy or not to destroy? Is that the only question? **Cell Cycle** 2: 455-7, 2003.
37. Bulavin D.V.*, Higashimoto Y., Demidenko Z.N., Meek S., Graves P., Phillips C., Zhao H., Moody S.A., Appella E., Piwnica-Worms H. and Fornace A.J. (2003) Dual phosphorylation controls Cdc25 phosphatases and mitotic entry. **Nature Cell Biology**, 5, 545-551. * corresponding author
38. Bulavin D.V., Kovalsky O., Hollander M.C., Fornace A.J.,(2003) Abrogation of oncogenic H-ras-induced cell-cycle arrest and p38 MAPK activation by disruption of *Gadd45a*. **Mol Cell Biol**, 23, 3859-3871.
39. Bulavin D.V., Demidenko Z.N., Phillips C., Moody S.A., and Fornace A.J. (2003) Phosphorylation of *Xenopus* Cdc25C at Ser285 interferes with ability to activate a DNA damage replication checkpoint in the pre-midblastula embryos. **Cell Cycle**, 2, 263-266. Commentary: Manke, I. A, & Yaffe, M. B., Chk'n Out in Mitosis. *Cell Cycle* 2: 236-237, 2003.
40. Dmitrieva N.I., Bulavin D.V., Burg M.B. (2003) High NaCl causes Mre11 to leave the nucleus, disrupting DNA damage signaling and repair. **Am J Physiol Renal Physiol**, 285, F266-274.
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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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