BIOGRAPHICAL SKETCH

NAME: **Alexandre Dubrac**

eRA COMMONS USER NAME (credential, e.g., agency login): ADUBRAC

POSITION TITLE: Assistant professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Toulouse III, France	M.Sc	12/2005	Molecular, Cellular and Developmental Biology
University of Bordeaux I, France	Ph.D.	12/2008	Molecular and Cell Biology
Yale University	Postdoctoral	08/2018	Cardiovascular Biology

A. Personal Statement

I earned my Ph.D. at the University of Bordeaux I, where I worked with Prof. Andreas Bikfalvi on tumoral angiogenesis. I then did postdoctoral research with Prof. Anne Eichmann at Yale University, where I learned developmental angiogenesis by studying neurovascular guidance and endothelial cell polarity. As an assistant professor in the Department of Pathology and Cellular Biology at the University of Montreal Medical School, my lab studies vascular cells heterogeneity and TGFβ signaling in developmental and pathological angiogenesis. During angiogenesis, specialized endothelial cells, called tip cells, govern organotypic vascular patterning by guiding the new vessel growth. We have recently described that retina vascularization depends on tip cells heterogeneity in development and ischemic retinopathy. Indeed, we have uncovered a new neurovascular paradigm in which TGFβ signaling governs specialized tip cells (or D-tip cells) specification, blood-retina barrier formation, and mouse neuroretina vascularization. My lab developed new EC enrichment/isolation methods, and we built a unique pipeline for single-cell RNA sequencing analysis of vascular cells (ECs and perivascular cells from retina and brain). We now study the brain EC heterogeneity, and we are testing whether TGFβ-induced D-tip cell sprouting is conserved in brain development and ischemic stroke. We have shown that TGFβ signaling controls the retina vascularization independently of the canonical transcription factor SMADs. Thus, we investigate new TGFβ-induced transcription factors and non-canonical signaling, such as the polarity protein PAR6, in neuro-angiogenesis.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2005-2008 Graduate Student (Ph.D.) Inserm U1029 Bordeaux (Advisor: A. Bikfalvi).
2009-2011 Postdoctoral Fellow INSERM UMR1037 Eq. 5 Toulouse, France (Advisor: H. Prats).
2012-2016 Postdoctoral Fellow, Yale University School of Medicine New Haven, CT, U.S (Advisor: A. Eichmann).
2016-2018 Associated Research Scientist, Yale University School of Medicine (Advisor: A. Eichmann).
2018-present Assistant professor, Department of Pathology and cellular biology, school of medicine, University of Montreal

Honors

2009 Poster presentation award, 1st French Society of Angiogenesis meeting, Vineuil St Firmin Chantilly, France.
2014 American Heart Association, 2 years postdoctoral fellowship award (14POST20380207).
2015 Poster presentation award, Vascular Biology and Therapeutics (VBT) and Cardiovascular Medicine annual retreat, Yale University, New Haven, CT, USA.
2015 Poster presentation award, Gordon Research Conference, Vascular Cell Biology, Ventura, CA, USA.
2017 Chair of the 2017 Gordon Research Seminar, Vascular Cell Biology, Ventura, CA, USA (with Natalie Kofler).
2017 American Heart Association, Scientist Development Grant award (17SDG33700124).
2019 Research Scholars - Junior 1, Fonds de recherche du Québec - Santé (FRQS).

C. Contributions to Science

Google Scholar: https://scholar.google.com/citations?user=xYgYGj0AAAAJ&hl=fr
Articles: 27, H-Index: 21, Citations: 1465.

1. Vascular heterogeneity and guidance. During angiogenesis, specialized endothelial cells, called tip cells, mediate guided vascular patterning. Following tip cells, stalk cells proliferate and form the capillary lumen. VEGF and NOTCH signaling regulates endothelial tip and stalk cells specification. We have shown a new pivotal function of neuropilin-1 (NRP1), which suppresses the stalk-cell phenotype by limiting SMAD2/3 activation. Endothelial cells develop the blood-brain barrier (BBB) in the central nervous system, a unique barrier essential for neuronal health. This suggests that tip cell heterogeneity is required to develop organotypic vascular features. We have recently uncovered a new neurovascular paradigm in which TGFβ signaling governs specialized tip cells (or D-tip cells) specification, blood-retina barrier formation, and mouse neuroretina vascularization.
    a. Zarkada G, Howard JP, Xiao X, Park H, Bizou M, Leclerc S, Künzel SE, Boisseau B, Li J, Cagnone G, Joyal JS, Andelfinger G, Eichmann A[#], **Dubrac A[#,$].** Specialized endothelial tip cells guide neuroretina vascularization and blood-retina-barrier formation. Dev Cell. 2021 Aug 9;56(15):2237-2251.e6. doi: 10.1016/j.devcel.2021.06.021. Epub 2021 Jul 16. **[#] co-corresponding author. [$] Lead contact.**
    b. Aspalter IM*, Gordon E*, **Dubrac A,** Ragab A, Narloch J, Vizán P, Geudens I, Thomas Collins R, Franco CA, Abrahams CL, Thurston G, Fruttiger M, Ian Rosewell3, Anne Eichmann2,9,10†, Holger Gerhardt1, 6,11, †. Alk1 and Alk5 inhibition by Nrp1 controls vascular sprouting downstream of Notch. Nat Commun. 2015 Jun 17;6:7264. * equal contribution.
    c. Poulet M, Sirois J, Boyé K, Uetani N., Hardy S, Daubon T, **Dubrac A,** Tremblay ML, Bikfalvi A. PRL-2 is essential for NOTCH1 signaling and retinal angiogenesis. Commun Biol. 2020 Oct 23;3(1):603. doi: 10.1038/s42003-020-01343-z.

2. Polarized endothelial cell migration. Migratory tip cells exhibit characteristic features, as filopodia, to guide the new vessel growth in response to gradients of growth factors. We demonstrated that fibroblast growth factors (FGFs) regulate tip cell glycolysis, migration, and retinal vessel growth. Cell polarity controls all aspects of sprouting angiogenesis. We have shown that axonal guidance molecules SLIT2/ROBO1&2 regulate tip cell front-rear polarity to promote retinal vessel growth in development and retinopathy. Mechanistically, ROBO1&2 interact with NCK adaptor proteins to polarize the VEGF-induced tip cell migration.
    a. Rama N*, **Dubrac A*,** Mathivet T, Ní Chárthaigh RA, Genet G, Cristofaro B, Pibouin-Fragner L, Ma L, Eichmann A and Chédotal A. Slit2 signaling through Robo1 and Robo2 is required for retinal neovascularization. Nat Med. 2015 May;21(5):483-91.*** equal contribution.**
    b. **Dubrac A,** Genet G, Ola R, Zhang F, Pibouin-Fragner L, Han J., Zhang J., Thomas JL, Chedotal A, Schwartz MA, Eichmann A. Targeting NCK-mediated endothelial cell front-rear polarity inhibits neovascularization. Circulation. 2016 Jan 26;133(4):409-21.
    c. Yu P, Wilhelm K*, **Dubrac A***, Tung JK*, Alves TC, Fang JS, Xie Y, Zhu J, Chen Z, De Smet F, Zhang J, Jin SW, Sun L, Sun H, Kibbey RG, Hirschi KK, Hay N, Carmeliet P, Chittenden TW, Eichmann A,

Potente M, Simons M. FGF-dependent metabolic control of vascular development. Nature. 2017 May 11;545(7653):224-228. *** equal contribution / co-second author**.

d. Genet G, Boyé K, Mathivet T, Ola R, Zhang F, **Dubrac A**, Li J, Genet N, Benedetti L, Künzel S, Pibouin-Fragner L, Thomas JL, Eichmann A. EndophilinA2 dependent VEGFR2 endocytosis promotes sprouting angiogenesis. Nat Commun. 2019 May 28;10(1):2350. doi: 10.1038/s41467-019-10359-x.

3. TGFβ and vascular malformations. TGFβ signaling is essential for vessel maturation and morphogenesis. The TGFβ superfamily is highly conserved and includes two main subfamilies: TGFβs and bone morphogenetic proteins (BMPs). In humans, heterozygous mutations in BMPs receptor *Alk1* gene cause Hereditary Hemorrhagic Telangiectasia (HHT), a disease characterized by arteriovenous malformations (AVMs). We have shown that a neonatal endothelial-specific deletion of *Alk1* leads to hypersprouting and AVMs. In addition, we have demonstrated that blood flow promotes BMP-mediated vessel maturation to prevent vascular malformation. Recently, we have shown that endothelial SMAD4 is the primary signaling pathway downstream of ALK1 to prevent AVMs.

   a. Ola R, Künzel HS, Zhang F, Genet G, Chakraborty R, Pibouin-Fragner L, Martin K, Sessa W, **Dubrac A***, Eichmann A*. SMAD4 prevents arterial-venous malformations by inhibiting Casein Kinase 2. Circulation. 2018 Jul 5. pii: CIRCULATIONAHA.118.033842.*** equal contribution / co-last author.**
   b. Ola R, **Dubrac A**, Han J, Angulo Urarte A, Zhang F, Fang JS, Larrivée B, Lee M, Genet G, Hirschi KK, Sessa WC, Vinals Canals F, Graupera M, Yan M, Young LH, Oh SP, Eichmann A. PI3Kinase inhibition improves vascular malformations in mouse models of hereditary hemorrhagic telangiectasia type 2. Nat Commun. 2016 Nov 29;7:13650.
   c. Baeyens N*, Larrivée B*, Ola R, Hayward B, **Dubrac A**, Huang B, Ross TD, Coon BG, Tsarfati M, Tong H, Eichmann A and Schwartz MA. Defective fluid shear stress mechanotransduction mediates hereditary hemorrhagic telangiectasia (HHT). J Cell Biol. 2016 Sep 26;214(7):807-16. * equal contribution.
   d. Pardanaud L, Pibouin-Fragner L, **Dubrac A**, Mathivet T, Brunet I, Simons M, Eichmann A. Sympathetic innervation promotes arterial fate by enhancing endothelial ERK activity. Circ Res. 2016 Aug 19;119(5):607-20.

4. Vascular permeability and pericyte function in retinopathy. Newly formed blood vessels are composed of endothelial tubes that are highly unstable and require further maturation to prevent vascular leakage. We have shown that endothelial ROBO4 signaling is required for retinal blood vessel permeability during development and disease. Endothelial cells (ECs) recruit pericytes to stabilize nascent sprouts and promote vascular permeability through the blood-retina barrier formation. We have shown that pericyte dysfunction can contribute to the onset and progression of retinopathy. Abnormal, α-SMA-expressing pericytes promote VEGFA-induced pathological EC proliferation and permeability defects in a mouse model of oxygen-induced retinopathy. We have also recently shown that VEGFA regulates lymphatic vessels permeability in the gut and obesity.

   a. **Dubrac A**†, Künzel ES, Künzel HS, Li J, Radhamani Chandran R, Martin K, Greif DM, Adams R, Eichmann A†. NCK-dependent pericyte migration promotes pathological neovascularization in ischemic retinopathy. Nat Commun. 2018 Aug 27;9(1):3463. doi: 10.1038/s41467-018-05926-7. † co-corresponding author.
   b. Zhang F, Prahst C, Mathivet T, Pibouin-Fragner L, Genet G, Zhang J, Tong R, Ye W, **Dubrac A**, Eichmann A. The Robo4 cytoplasmic domain is dispensable for vascular barrier protection and inhibition of neovascularization. Nat Commun. 2016 Nov 24;7:13517**.**
   c. Zhang F, Zarkada G, Han J, Li J, **Dubrac A**, Ola R, Genet G, Boy. K, Michon P, Künzel SE, Camporez JP, Singh AK, Fong GH, Simons M, Tso P, Fernandez-Hernando C, Shulman GI, Sessa WC, Eichmann A. Lacteal junction zippering protects against diet-induced obesity. Science. 2018 Aug 10;361(6402):599-603.

5. During tumor development, cancer cells grow in metabolically adverse conditions, such as hypoxia and glucose deprivation, which will trigger endoplasmic reticulum stress (ER stress). This cellular adaptation

regulates the expression of angiogenic growth factors, including VEGF-A. We have shown how ER stress regulates tumor angiogenesis and tumor invasion.

a. Philippe C*, **Dubrac A*,** Hieblot C, Desquesnes A, Cintas C, Van den Berghe L, Brousset P, Prats H, Touriol C. Selective PERK mediated translational activation of the angiogenic growth factor by the unfolded protein response following ischemic stress. Sci Signal. 2016 May 3;9(426):ra44. *** equal contribution**.
b. Cammas A*, **Dubrac A*,** Morel B, Lamaa A, Touriol C, Teulade-Fichou MP, Prats H, and Millevoi S. Stabilization of the G-quadruplex at the VEGF IRES represses cap-independent translation. RNA Biol. 2015;12(3):320-9. *** equal contribution.**
c. Jabouille A, Delugin M, Pineau R, **Dubrac A**, Soulet F, Lhomond S, Pallares-Lupon N, Prats H, Bikfalvi A, Chevet E, Touriol C, Moenner M. Glioblastoma invasion and cooption depend on IRE1α_endoribonuclease activity. Oncotarget. 2015 Sep 22;6(28):24922-34.
d. Sorli SC, Colié S, Albinet V, **Dubrac A**, Touriol C, Guilbaud N, Bedia C, Fabriàs G, Casas J, Ségui B, Levade T, Andrieu-Abadie N. The nonlysosomal β-glucosidase GBA2 promotes endoplasmic reticulum stress and impairs tumorigenicity of melanoma cells. FASEB J. 2012 Oct 16. Epub 2012 Oct 16.

D. Research Support and/or Scholastic Performance

Ongoing Research Support

ALK5-PAR6A signaling pathway regulates endothelial cells proliferation and vascular leakage.
CIHR (2019PJT-421339) - 10/01/2019 – 09/30/2024 - $766,750
P.I. : Dubrac Alexandre
Collaborators : Dr. Andelfinger G.; Dr. Dehaes M.; Dr. Joyal, J.S.

Molecular mechanisms governing pericyte activation and function during blood vessel morphogenesis in development and diseases.
FRQ-S (269587) - 07/01/2019 – 06/30/2023 - $375,451
P.I. : Dubrac Alexandre

Role of endothelial glycolysis in pericyte recruitment and function.
NSERC (RGPIN-2022-04726) - 04/01/2022 – 03/31/2027 - $177,500
P.I. : Dubrac Alexandre

The role of the TGFB-SOX9 signaling pathway in brain angiogenesis.
CIHR (202203PJT-481084) - 10/01/2022 – 09/30/2027 - $ 826,200
P.I. : Dubrac Alexandre

Completed Research Support

The Angiogenesis & Vascular Bioreactor Platform: endothelium-pericyte interaction in development and vascular diseases.
Canada Foundation for Innovation (CFI) John R. Evans Leaders Fund - $288,482

Identifying vascular mural cells in the retinopathy of prematurity.
Réseau de recherche en santé de la vision - FRQS PROJET - PILOTE for young investigator - $50,000

Guidance of pericyte patterning.
17SDG33700124 AHA Dubrac (PI) 07/01/2017-06/30/2020
Collaborators: Daniel Greif, Yale University; Martin A Schwartz, Yale University; Christer Betsholtz, Uppsala University

Defining the function of Slit ligands and Robo receptors in angiogenesis.
14POST20380207 AHA Dubrac (PI) 07/01/2014-06/30/2016

E. Selected Peer-reviewed Abstracts and Scientific Presentations

Lectures

2019 2nd International Symposium on Retinal and Choroidal Angiogenesis, Montréal, Qc.
2020 Seminar series at l'ICM, Montréal, Qc. *Virtual*.
2021 Inserm U1034 Webinar Series, Bordeaux, France.
2021 Virtual seminar series for our Alberta Vision Net research group (the University of Alberta and University of Calgary).
2021 Seminar series at McGill ophthalmologic department, Montreal, Canada. *Virtual.*
2022 Institut du cerveau et de la moelle épinière (ICM), Paris, France.

National and international contributions

2015 Gordon Research Seminar, Vascular Cell Biology, Ventura, CA, US.
2017 NAVBO Vascular Biology 2017, Monterey, CA, US.
2017 Gordon Research Seminar, Angiogenesis, Newport, RI, US.
2020 NAVBO Vascular Biology 2020, Newport, RI, US. Virtuelle.
2021 Cold Spring Harbor Laboratory on Brain barrier, Cold Spring Harbor, NY, US. Virtuelle.
2022 Kloster Seeon on Angiogenesis, Germany.