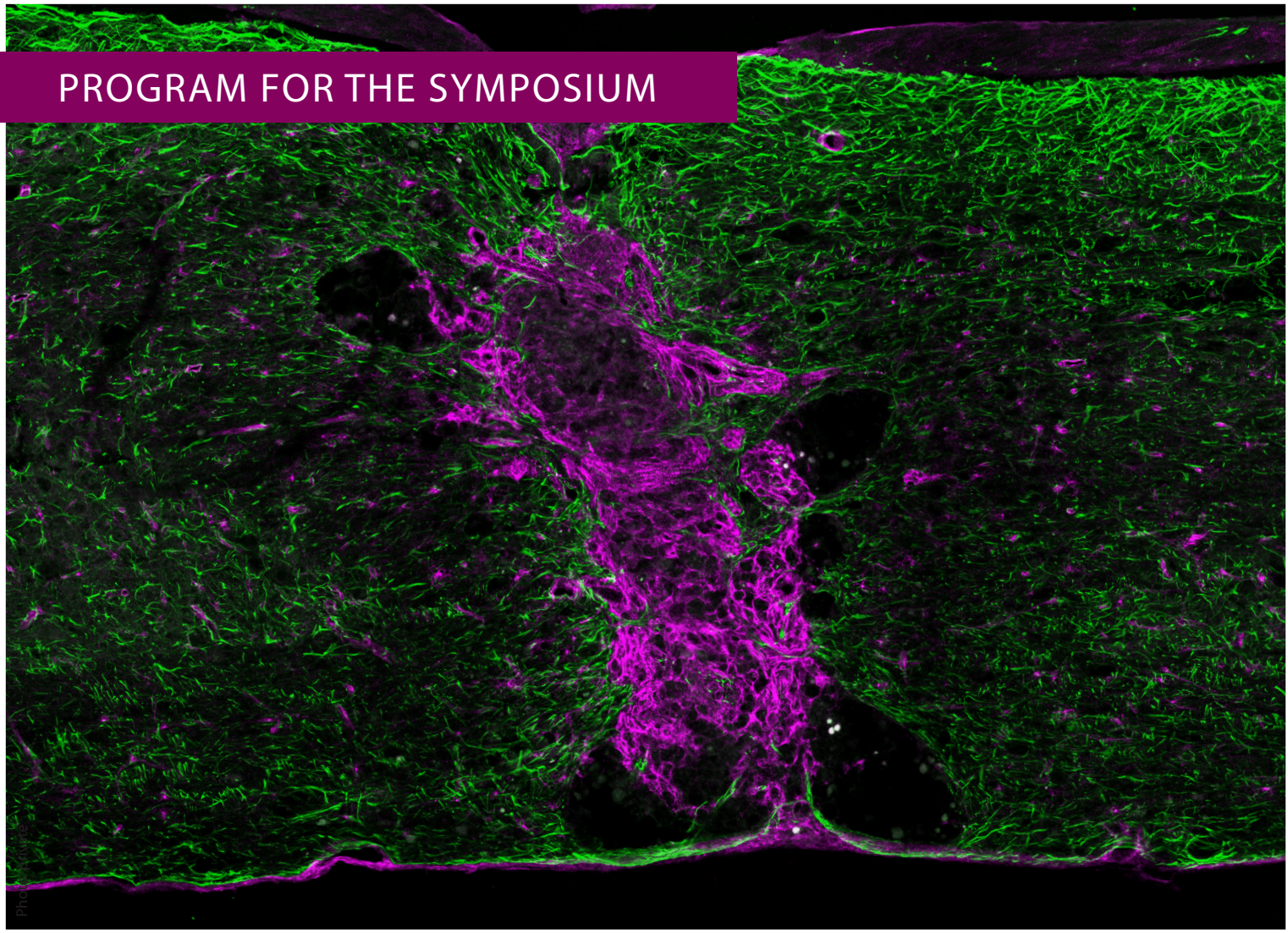
PROGRAM FOR THE SYMPOSIUM



CNS Injuries and Repair

3 April 2019 | Nobel Forum, Karolinska Institutet, Solna

Karolinska Institutet

FOREWORD

Damage to the adult central nervous system most often leads to persistent deficits due to limited tissue regeneration and the inability of mature axons to regenerate after injury. Reduced inherent axonal growth capacity and local inhibition at the lesion site are the two main obstacles for axons to regenerate. At the lesion, inhibitory molecules associated with myelin, inflammatory cells and different scar components have been identified as impediment for regrowing axons. Secondary damage and limited remyelination further exacerbates injury. These barriers collectively present a great challenge in restoring the original circuitry. Despite the number of obstacles, our understanding of the complex injury mechanisms is growing and promising therapeutic approaches are emerging.

This symposium gathers some of the leading scientists working on critical aspects regarding neuron intrinsic axon growth inhibitors, extrinsic inhibition associated with myelin components and glial and fibrotic scar elements and remyelination as well as neurotechnology development, which has led to the development of therapeutic strategies to promote recovery following CNS injuries.

I am looking forward to an exciting symposium.

Christian Göritz

WEDNESDAY, APRIL 3 2019, NOBEL FORUM
KAROLINSKA INSTITUTET, SOLNA | 08.30–17.40

08.30–09.00	REGISTRATION
09.00–09.10	WELCOMING ADDRESS
	SESSION I: MOLECULAR MEDIATORS OF AXONAL GROWTH
09.10–10.00	NEURONAL INTRINSIC INHIBITORS REGULATING AXON REGENERATION Kai Liu, HKUST, Hong Kong, China
10.00–10.50	MECHANISMS OF AXON GROWTH AND REGENERATION. Frank Bradke, DZNE Bonn, Germany
10.50–11.20	COFFEE BREAK
	SESSION II: OVERCOMING EXTRINSIC INHIBITION
11.10–12.00	FUNCTIONAL REGENERATION AFTER CHRONIC SPINAL CORD INJURY Jerry Silver, Case Western Reserve University, USA
12.00–12.50	SUCCESSFUL SPINAL CORD REPAIR IN ZEBRAFISH Catherina Becker, The University of Edinburgh, UK
12.50–13.50	LUNCH BREAK
13.50–14.40	ANTI-NOGO-A THERAPY FOR STROKE AND SPINAL CORD INJURY: FROM BENCH TO CLINIC Martin Schwab, University and ETH Zurich, Switzerland
14.40–15.30	FIBROTIC SCARRING AND REPAIR Christian Göritz, Karolinska Institutet, Sweden
15.30–15.50	COFFEE BREAK
	SESSION III: CELL REPLACEMENT AND NEUROTECHNOLOGIES
15.50–16.40	REDIRECTING THE RESPONSE OF RESIDENT NEURAL STEM CELLS TO SPINAL CORD INJURY Jonas Frisén, Karolinska Institutet, Sweden
16.40–17.30	TARGETED NEUROTECHNOLOGIES TO RESTORE FUNCTION AFTER SPINAL CORD INJURY Quentin Barraud, EPFL Geneva, Switzerland
17.30–17.40	CLOSING REMARKS

Kai Liu
Division of Life Science, HKUST, Hong Kong, China

"NEURONAL INTRINSIC INHIBITORS REGULATING AXON REGENERATION"

Kai Liu is currently Cheng Associate Professor of Science in Division of Life Science at The Hong Kong University of Science and Technology (HKUST). Liu received his Bachelor degree from School of Life Sciences at Peking University in 1998, and received his Ph.D. from Rutgers University at New Brunswick in 2006. Then he did his postdoc research at Children's Hospital Boston/Harvard Medical School. In 2011, Liu joined Division of Life Science at HKUST as Assistant Professor. His research interest focuses on the intrinsic mechanisms regulating axonal regeneration, and he has authored 19 scientific publications on neural injury, regeneration, and repair.

Selected publications

Wang H, Wang X, Zhang K, Wang Q, Cao X, Wang Z, Zhang S, Li A#, Liu K#, Fang Y#. Rapid depletion of ESCRT protein Vps4 underlies injury-induced autophagic impediment and Wallerian degeneration. Science Advances 2019 Feb 13:Vol. 5, no. 2.

Weng Y-L, Wang X, Ran A, Cassin J, Vissers C, Liu Y, Liu Y, Xu T, Wang X, Wong S, Joseph J, Dore L, Dong Q, Zheng W, Jin P, Wu H, Shen B, Zhuang X, He C, Liu K, Song H, Ming G-L. Epitranscriptomic m6A Regulation of Axon Regeneration in the Adult Mammalian Nervous System. Neuron, 2018 Jan:97(2), 313-325. e6

Li S*, Yang C*, Zhang L, Gao X, Wang X, Liu W, Wang Y, Jiang S, Wong YH, Zhang Y, Liu K. Promoting axon regeneration in the adult CNS by modulation of the melanopsin/GPCR signaling. Proc. Natl. Acad. Sci. USA. 2016 Feb 16;113(7):1937-42.

Du K*, Zheng S*, Zhang Q*, Li S, Gao X, Wang J, Jiang L, Liu K. Pten deletion promotes regrowth of corticospinal tract axons 1 year after spinal cord injury. Journal of Neuroscience 2015 July 1;35(26): 9754-9763.

Li S*, He Q*, Wang H, Tang X, Ho KW, Gao X, Zhang Q, Shen Y, Cheung A, Wong F, Wong YH, Ip NY, Jiang L, Yung WH, Liu K. Injured adult retinal axons with Pten and Socs3 co-deletion reform active synapses with suprachiasmatic neurons. Neurobiology of Disease 2014 Oct 16;73C:366-376. [Epub ahead of print].

Homepage: https://life-sci.ust.hk/team/kai-liu/

Franke Bradke
German Center for Neurodegenerative Diseases, Bonn, Germany

"MECHANISMS OF AXON GROWTH AND REGENERATION"

After studying at the Freie Universität Berlin and University College London, Bradke carried out research at the European Molecular Biology Laboratory (EMBL) in Heidelberg as part of his doctoral thesis. As a postdoctoral researcher, he moved to the University of California in San Francisco and Stanford University in 2000. In 2003, he was appointed a group leader at the Max Planck Institute of Neurobiology in Martinsried. In 2011, he was awarded the IRP Schellenberg Prize, one of the most prestigious awards in the field of regeneration research. In the same year he became full professor at the University of Bonn, and was appointed head of the Axon Growth and Regeneration research group at the DZNE. Bradke is an elected a member of the Leopoldina (the German National Academy of Sciences), the Academia Europaea, and the European Molecular Biology Organization (EMBO). In 2016, he was awarded the Leibniz Prize, which is the most important research award in Germany. In 2018, he received the Roger de Spoelberch Prize.

Selected publications

Hilton BJ, Blanquie O, Tedeschi A, Bradke F (in press). High-resolution 3D imaging and analysis of axon regeneration in unsectioned spinal cord with or without tissue clearing. Nature Protocols.

Tedeschi A, Dupraz S, Laskowski C, Xue J, Ulas T, Beyer M, Schultze J, Bradke F (2016). The Calcium Channel Subunit Alpha2delta2 Suppresses Axon Regeneration in the Adult CNS. Neuron 92: 419–434

Ruschel J, Hellal F, Flynn KC, Dupraz S, Elliott DA, Tedeschi A, Bates M, Sliwinski C, Brook G, Dobrindt K, Peitz M, Brüstle O, Norenberg MD, Blesch A, Weidner N, Bunge MB, Bixby JL, Bradke F (2015). Systemic administration of epothilone B promotes axon regeneration and functional recovery. Science 348: 347-352.

Flynn KC, Hellal F, Neukirchen D, Jacobs S, Tahirovic S, Dupraz S, Stern S, Garvalov BK, Gurniak C, Shaw A, Meyn L, Wedlich-Söldner R, Bamburg JR, Small JV, Witke W, Bradke F (2012). ADF/cofilin-mediated Actin Retrograde Flow Directs Neurite Formation in the Developing Brain. Neuron 76:1091-107.

Ertürk A, Mauch CP, Hellal F, Förstner F, Keck T, Becker K, Jährling N, Steffens H, Richter M, Hübener M, Kramer E, Kirchhoff F, Dodt HU, Bradke F (2011). 3D imaging of the unsectioned adult spinal cord to assess axon regeneration and glial responses after injury. Nature Medicine 18: 166-171.

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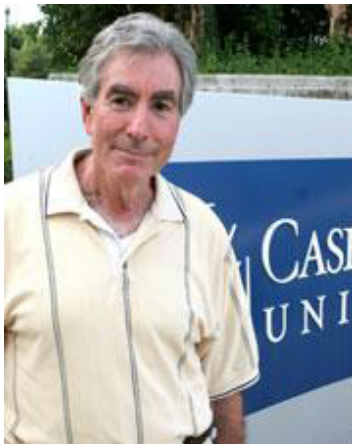

Jerry Silver
Case Western Reserve University School of Medicine, Cleveland, Ohio, USA

"FUNCTIONAL REGENERATION AFTER CHRONIC SPINAL CORD INJURY"

Dr. Silver received his Ph.D. from Case Western Reserve in 1974 and was the recipient of the Herbert S. Steuer Memorial Award for Meritorious Original Research in Anatomy. Jerry did post-doctoral work at Harvard University in the Department of Neurosciences at The Children's Hospital and in the Neuropathology Department at Harvard Medical School. Dr. Silver is currently Professor in the Department of Neurosciences at the Case Western Reserve University School of Medicine. Dr. Silver is a recipient of several prestigious awards. In 2003 he was awarded the Ameritec Prize for significant accomplishments toward a cure for paralysis. In 2003 he was also honored with the Christopher Reeve-Joan Irvine Research Medal (The Reeve-Irvine Medal) for critical contributions that may lead to the promotion of repair of the damaged spinal cord. In 2004 Dr. Silver received a Jacob Javits Neuroscience Investigator Award for his long-standing grant entitled "Factors affecting regeneration through the glial scar." Dr. Silver was named the recipient of the 2008 Erica Nader Award, which is given through the American Spinal Injury Association (ASIA). The award honors "breakthrough research in the field of spinal cord injury". In 2011 he became a fellow of the American Association for the Advancement of Science. Dr. Silver has served on a number of editorial boards including the journals Glia, The Journal of Neurocytology, Developmental Neurobiology, The Journal of Neuroscience, Scientific Reports and Experimental Neurology (where he is a Section Editor). He has served on a variety of NIH study sections since 1982 including the Neurobiology Review Group, Neurology B2, The Visual Sciences C Study Section, and the Clinical Neurology, Neurotransmitters and Transplantation Study Section. He has been appointed as a regular member of the Scientific Board of the International Spinal Research Trust (England). He has served as lead or senior author on more than 175 publications. The ultimate goal of the Silver lab is to understand the basic biology that underlies regeneration failure in the adult spinal cord and then use this knowledge to develop strategies to maximally overcome the lack of regeneration after both incomplete and complete cord injury in order to promote functional repair.

Selected publications

Tran AP, Warren PM and Silver J (2018) The biology of regeneration failure and success after spinal cord injury. Physiol Rev. 98:881-917.

Warren PM, Steiger SC, Dick TE, MacFarlane PM, Alilain WJ and Silver J (2018) Rapid and robust recovery of breathing long after spinal cord injury. Nature Comm 9, 4843 Nov 27, 2018.

Lang BT, Cregg JM, DePaul MA, Tran A, Madalena KM, Weng YL, Li S, Busch SA, Shen Y and Silver J (2015) Systemic modulation of the proteoglycan receptor PTPσ promotes functional recovery after spinal cord injury. Nature 518:404-408.

Alilain WA, Horn KP, Hu H, Dick TE and Silver J (2011) Functional regeneration of respiratory pathways after spinal cord injury. Nature, 475: 196-200.

Shen Y, Tenney AP, Busch SA, Horn KP, Cuascut FX, Liu K, He Z, Silver J and Flanagan JG, (2009) PTPsigma is a receptor for Chondroitin Sulfate Proteoglycan, an inhibitor of neural regeneration. Science express / Science, 23 October, 326: 592-596.

Homepage: https://case.edu/medicine/neurosciences/people/faculty/jerry-silver

Catherina G. Becker, FRSB
University of Edinburgh, Edinburgh, United Kingdom

"SUCCESSFUL SPINAL CORD REPAIR IN ZEBRAFISH"

The Becker group use adult and larval zebrafish to investigate spinal cord regeneration and mechanisms of motor neuron development and repair in motor neuron diseases. Catherina Becker obtained an MRes in Human Genetics and a PhD in Neurosciences from the University of Bremen, Germany, studying development and successful regeneration of the amphibian (frogs and salamanders) central nervous system. For her first postdoctoral training post, she moved to the renowned Swiss Federal Institute of Technology in Zürich, Switzerland on an EMBO-funded postdoctoral fellowship. Her postgraduate studies continued at the University of California, and the Centre for Molecular Neurobiology in Hamburg on German Research Foundation Fellowships. The Becker group moved to the University of Edinburgh in 2005 and Catherina Becker is now Professor for Neural Development and Regeneration and the Deputy Director of the Centre for Discovery Brain Sciences at the University of Edinburgh. Catherina is a founding member of EuFishBioMed, the European Society of Fish Models in Biology and Medicine, she is a Fellow of the Royal Society of Biology (FRSB) and the co-Director of the new Wellcome Trust funded 4 year PhD programme in Tissue Repair.

Selected publications

Tsarouchas TM, Wehner D, Cavone L, Munir T, Keatinge M, Lambertus M, Underhill A, Barrett T, Kassapis E, Ogryzko NV, Feng Y, van Ham TJ, Becker T, Becker CG (2018) Dynamic control of proinflammatory cytokines Il-1β and Tnf-α by macrophages is necessary for functional spinal cord regeneration in zebrafish. Nat Communications 9: 4670

Wehner D, Tsarouchas TM, Michael A, Haase C, Weidinger G, Reimer MM, Becker T*, Becker CG* (2017) Wnt signaling controls a pro-regenerative extracellular matrix in functional spinal cord regeneration, Nature Communications, DOI: 10.1038/s41467-017-00143-0

Becker CG, Becker T (2015). Neuronal Regeneration from Ependymo-radial Glial Cells: Cook, Little Pot, Cook! Developmental Cell 32(4):516-27.

Reimer MM, Norris A, Ohnmacht J, Patani R, Zhong Z, Dias TB, Kuscha V, Scott AL, Chen Y, Rozov S, Frazer SL, Wyatt C, Higashijima S, Patton EE, Panula P, Chandran S, Becker T*, Becker CG* (2013) Dopamine signaling from the brain augments spinal motor neuron generation during development and adult regeneration via hedgehog pathway activation, Dev Cell 25(5): 478-491

Becker T, Becker CG (2014) Axonal regeneration in zebrafish. Curr Opin Neurobiol. 27C:186-191
Reimer MM, Kuscha V, Sörensen, Frank RE, Knüwer M, Becker T*, Becker CG* (2009) Sonic hedgehog is a polarized signal for motor neuron regeneration in adult zebrafish, J Neurosci 29: 15073-82

Homepage: https://www.ed.ac.uk/discovery-brain-sciences/our-staff/research-groups/becker-group

Martin E. Schwab
University of Zurich, Switzerland

"ANTI-NOGO-A THERAPY FOR STROKE AND SPINAL CORD INJURY: FROM BENCH TO CLINIC"

Martin E. Schwab is professor of Neuroscience at the Institute of Regenerative Medicine at the University of Zurich and at the Dept. of Health Sciences and Technology at ETH Zurich. His research focuses on the mechanisms of structural and functional plasticity and repair of the brain and spinal cord. He postulated the concept of specific inhibitors of neurite growth as a cause of the absent regeneration of injured fiber tracts in the CNS. With his group he isolated the membrane protein Nogo-A and showed that Nogo-A neutralization leads to fiber regeneration, enhanced plasticity and functional repair after spinal cord or brain injuries in adult rats and monkeys. These results led to currently on-going clinical trials.

Selected publications

Wahl AS, Omlor W, Rubio JC, Chen JL, Zheng H, Schröter A, Gullo M, Weinmann O, Kobayashi K, Helmchen F, Ommer B, Schwab ME (2014). Neuronal repair. Asynchronous therapy restores motor control by rewiring of the rat corticospinal tract after stroke. Science 13;344 (6189):1250-1255

Kempf A, Tews B, Arzt ME, Weinmann O, Obermair FJ, Pernet V, Zagrebelsky M, Delekate A, Iobbi C, Zemmar A, Ristic Z, Gullo M, Spies P, Dodd D, Gygax D, Korte M, Schwab ME (2014). The Sphingolipid receptor S1PR2 is a receptor for Nogo-A repressing synaptic plasticity. PLOS Biology (12)1:e1001763

Lindau NT, Bänninger BJ, Gullo M, Good NA, Bachmann LC, Starkey ML, Schwab ME (2013). Rewiring of the corticospinal tract in the adult rat after unilateral stroke and anti-Nogo-A therapy. Brain:137,739-756

Bachmann LC, Matis A, Lindau NT, Felder P, Gullo M, Schwab ME (2013). Deep brain stimulation of the midbrain locomotor region improves paretic hindlimb function after spinal cord injury in rats. Science Translational Medicine 5(208):208ra146

Schwab ME, Strittmatter SM. (2014) Nogo limits neural plasticity and recovery from injury. Curr Opin Neurobiol. 27: 53-60

Homepage: https://www.hifo.uzh.ch/en/research/schwab

Christian Göritz
Karolinska Institutet, Stockholm, Sweden

"FIBROTIC SCARRING AND REPAIR"

Associate Professor Christian Göritz is heading a research team at the Department of Cell and Molecular Biology at Karolinska Institutet. He is also a member of the Ming Wai Lau Centre for Reparative Medicine, where he is serving as fellow coordinator. Christian studied Biochemistry at the Free University of Berlin, Germany. He performed his PhD studies in Strasbourg, France, in a joint Max Planck / CNRS research environment in the field of Neuroscience. For his postdoctoral training, he joined the lab of Prof. Jonas Frisén at the Karolinska Institutet. With his research group, Christian investigates the mechanisms that mediate scarring and repair of the central nervous system. He discovered a new type of cells that are associated with blood vessels, named type A pericytes. These cells are the main source of fibrotic scar tissue after spinal cord injury. By comparing several different models of injury and disease, the Göritz team is intending to uncover common mechanisms of scarring and fibrosis with the goal to identify new targets for the treatment of central nervous system lesions. Christian has been awarded with an ERC starting grant and a Wallenberg Academy and Hållsten Academy fellowship.

Selected publications

Dias DO, Kim H, Holl D, Werne Solnestam B, Lundeberg J, Carlén M, Göritz C* and Frisén J. Reducing pericyte-derived fibrosis promotes recovery after spinal cord injury. Cell. 2018 Mar 22;173(1):153-165.e22. *Lead contact author

Dias DO, Göritz C. Fibrotic scarring following lesions to the central nervous system. Matrix Biology. 2018 Feb 9. pii: S0945-053X(17)30480-8.

Magnusson JP*, Göritz C*, Tatarishvili J, Dias DO, Smith EM, Lindvall O, Kokaia Z, Frisén J. A latent neurogenic program in astrocytes regulated by Notch signaling in the mouse. Science. 2014 Oct 10;346(6206):237-41. PMID:25301628; *Equal contribution

Sabelström H, Stenudd M, Réu P, Dias DO, Elfineh M, Zdunek S, Damberg P, Göritz C and Jonas Frisén. Resident neural stem cells restrict tissue damage and neuronal loss after spinal cord injury. Science. 2013 Nov 1;342(6158):637-40.

Göritz C, Dias DO, Tomilin N, Barbacid M, Shupliakov O, Frisén J. A pericyte origin of spinal cord scar tissue. Science. 2011 Jul 8 ;333(6039) :238-42. PMID: 21737741

Barnabé-Heider F, Göritz C, Sabelström H, Takebayashi H, Pfrieger FW, Meletis K, Frisén J (2010). Origin of new glial cells in intact and injured adult spinal cord. Cell Stem Cell. 2010 Oct 8;7(4):470-82. PMID: 20887953

Homepage: https://ki.se/en/cmb/christian-goritzs-group

Jonas Frisén
Karolinska Institutet, Stockholm, Sweden

"REDIRECTING THE RESPONSE OF RESIDENT NEURAL STEM CELLS TO SPINAL CORD INJURY"

Jonas Frisén is the Tobias Foundation Professor of Stem Cell Research at the Karolinska Institutet. After completing his PhD in Neuroscience at the Karolinska Institute, he was a postdoctoral fellow in the laboratory of Mariano Barbacid in Princeton, USA. With his group, Jonas is studying cell turnover in the adult body in health and disease in several organ systems. They are interested in the molecular regulation, extent and functional importance of these processes in model organisms and humans.

Selected publications

Spalding, K.L. Bergmann, O., Alkass, K., Bernard, S., Salehpour, M., Huttner, H.B., Boström, E., Westerlund, I., Vial, C., Buchholz, B.A., Possnert, G., Mash, D.C., Druid, H. and Frisén, J. (2013) Dynamics of hippocampal neurogenesis in adult humans. Cell, 153:1219-1227.

Sabelström, H., Stenudd, M., Reu, P., Dias, D., Elfineh, M., Damberg, P., Göritz, C. and Frisén, J. (2013) Resident neural stem cells restrict tissue damage and neuronal loss after spinal cord injury in mice. Science, 342:637-640.

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Yeung, M.S.Y., Djelloul, M., Steiner, E., Bernard, S., Salehpour, M., Possnert, G., Lou Brundin, L. and Jonas Frisén, J. (2019) Oligodendrocyte generation dynamics in multiple sclerosis. Nature, in press.

Homepage: https://ki.se/en/cmb/jonas-frisens-group

Quentin Barraud
Laboratory of Prof. Courtine, Ecole Polytechnique et Federale de Lausanne (EPFL), Geneva, Switzerland

"TARGETED NEUROTECHNOLOGIES TO RESTORE FUNCTION AFTER SPINAL CORD INJURY"

Quentin Barraud is senior researcher in the Laboratory of Prof. Courtine at EPFL, Switzerland. After completing a PhD in neurobiology at the University of Bordeaux under the direction of Prof. Erwan Bezard (2007-2010), Quentin Barraud completed a postdoctoral stage in the laboratory of Prof Courtine at University of Zurich (2010-2012) and EPFL (2012-2018)., Quentin is developing neurotechnologies that improve functional recovery after neurological disorders such as spinal cord injury. He's studying the mechanisms through which electrochemical spinal cord stimulation and robot-assisted training restore volitional locomotion after spinal cord injury in both rat and non-human primate models. He has authored 12 publications, including some in prestigious scientific journals.

Selected publications

Cortico-reticulo-spinal circuit reorganization enables functional recovery after severe spinal cord contusion. Asboth L, Friedli L, Beauparlant J, Martinez-Gonzalez C, Anil S, Rey E, Baud L, Pidpruzhnykova G, Anderson MA, Shkorbatova P, Batti L, Pagès S, Kreider J, Schneider BL, Barraud Q, Courtine G. Nature Neuroscience 2018 Apr;21(4):576-588. doi: 10.1038/s41593-018-0093-5. Epub 2018 Mar 19. PMID: 29556028

Long-term usability and bio-integration of polyimide-based intra-neural stimulating electrodes. Wurth S, Capogrosso M, Raspopovic S, Gandar J, Federici G, Kinany N, Cutrone A, Piersigilli A, Pavlova N, Guiet R, Taverni G, Rigosa J, Shkorbatova P, Navarro X, Barraud Q, Courtine G, Micera S. Biomaterials. 2017 Apr;122:114-129.

Pronounced species divergence in corticospinal tract reorganization and functional recovery after lateralized spinal cord injury favors primates. Friedli L, Rosenzweig ES, Barraud Q, Schubert M, Dominici N, Awai L, Nielson JL, Musienko P, Nout-Lomas Y, Zhong H, Zdunowski S, Roy RR, Strand SC, van den Brand R, Havton LA, Beattie MS, Bresnahan JC, Bézard E, Bloch J, Edgerton VR, Ferguson AR, Curt A, Tuszynski MH, Courtine G. Science Translational Medicine. 2015 Aug 26;7(302):302ra134. doi: 10.1126/scitranslmed.aac5811. PMID: 26311729

Electronic dura mater for long-term multimodal neural interfaces. Minev IR, Musienko P, Hirsch A, Barraud Q, Wenger N, Moraud EM, Gandar J, Capogrosso M, Milekovic T, Asboth L, Torres RF, Vachicouras N, Liu Q, Pavlova N, Duis S, Larmagnac A, Vörös J, Micera S, Suo Z, Courtine G, Lacour SP. Science. 2015 Jan 9;347(6218):159-63. doi: 10.1126/science.1260318. PMID: 25574019

Restoring voluntary control of locomotion after paralyzing spinal cord injury. R. van den Brand, J. Heutschi, Q. Barraud, J. DiGiovanna, K. Bartholdi, M. Huerlimann, L. Friedli, I. Vollenweider, E. M. Moraud, S. Duis, N. Dominici, S. Micera, P. Musienko, and G. Courtine. Science, vol. 336, no. 6085, pp. 1182–1185, Jun. 2012.

Homepage: https://courtine-lab.epfl.ch

Scientific organizer

Christian Göritz

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