BIOGRAPHICAL SKETCH

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NAME: Michael Fainzilber (ORCID I.D. # 0000-0001-8173-8557)

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

POSITION TITLE: The Chaya Professor in Molecular Neuroscience

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Hebrew University of Jerusalem	B.Sc.	06/1986	Biology
Hebrew University of Jerusalem	M.Sc.	12/1988	Biochemistry
Hebrew University of Jerusalem	Ph.D.	10/1993	Neurobiochemistry
Vrije Universiteit Amsterdam	Postdoc	10/1995	Molecular Neurobiology
Karolinska Institute, Stockholm	Postdoc	11/1997	Molecular Neurobiology

A. Personal Statement

My work has focused on integration of cytoplasmic and nuclear transport in neurons. We described a novel axonal transport route based on importins and dynein, demonstrating that local translation of importin β1 mRNA upon injury triggers formation of an importins complex transported retrogradely by dynein. We then showed that local translation and proteolysis of an intermediate filament links phosphorylated MAP kinases to the complex in a phosphatase-protected manner, thus establishing a novel mechanism for long distance transport of an activated kinase. Furthermore, we demonstrated that Ran GTPase and its associated effectors regulate the formation of importin signaling complexes in axons, providing a locally regulated 'safety catch' for the system, and challenging the dogma of a strict nucleus/cytoplasm RanGTP/GDP gradient. Recent findings reveal that locally activated transcription factors integrate axonal signaling with transcription networks in injured neurons. Generation of subcellular knockouts of axonal importin β1 and its carrier RNA binding protein Nucleolin validated the central role of local axonal synthesis in retrograde injury signaling, and recently generated UTR mutants for mTOR shed new light on local regulation of protein synthesis in axons. Additional recent work has highlighted roles for importins in CNS neurons, including in anxiety regulating circuits, MeCP2 dependent processes, and in chronic pain. Finally, a major effort in my group has extended RNA localization and local protein synthesis mechanisms to control of cell size and neuron length.

B. Positions, Scientific Appointments, and Honors

2022 - present: Head, Dept. of Biomolecular Sciences, Weizmann Institute of Science.

2021 - present: Professor, Dept. of Molecular Neuroscience, Weizmann Institute of Science.

2013 - present: Professor, Dept. of Biomolecular Sciences (formerly Biological Chemistry), Weizmann Institute of Science.

2005 - 2013: Associate Professor, Dept. of Biological Chemistry, Weizmann Institute of Science.

1998 - 2005: Senior Scientist, Dept. of Biological Chemistry, Weizmann Institute of Science.

Other Appointments/Activities

2004-2009: Editorial Board member: *Journal of Biological Chemistry*.

2004-2010: Editorial Board member: *Developmental Neurobiology*.

2007, 2009, 2013: Lead Organizer, EMBO Conferences on Spatial Dynamics of Intracellular Signaling.

2006-2008: Steering Committee, Neural Repair Program, Adelson Medical Research Foundation.

2007-2009: Member, Inter-Senate Committee for Protection of Academic Freedom

2008: Chair, International NGF Meeting (NGF2008)

2009-present: Editorial Board member, *Molecular & Cellular Proteomics*.

2010: Chair, ISF-Legacy Meeting on New Approaches to Neurodegenerative Diseases.

2010-2013: Member, International Affairs Advisory Committee, Society for Neuroscience.

2013: Lead organizer, Keystone Symposium on Cell Biology and Pathology of Axons.

2014-2020: Reviewing Editor, *eNeuro*.

2015-2021: Chair, Postdoctoral Training Program, Weizmann Institute of Science.

2016, 2021: Lead organizer, EMBO Workshops on Cell Size Regulation.

2021: Chair, Katzir/ISF Conference on Intrinsic Mechanisms of Neuronal Growth.

2021-present: Cajal Advanced Training Program, Member of the Expert Committee on "*Neurons and Glia: Intrinsic Properties, Cell Biology and Cell Types*".

2021-present: Head, Weizmann Center for Research on Neurodegeneration, Weizmann Institute of Science.

2022-present: Editorial Advisory Board, *Oxford Open Neuroscience*.

Honors

1997: Clore Prize, Weizmann Institute of Science.

1997: Allon Fellowship, Israel Academy of Sciences.

1998: Daniel Koshland Sr. Career Development Chair, Weizmann Institute of Science.

2004: Hestrin Prize, Israel Society for Biochemistry & Molecular Biology (ISBMB).

2006-present: Chaya Professorial Chair in Molecular Neuroscience, Weizmann Institute of Science.

2009: NARSAD Independent Investigator Award.

2011: IRP-Schellenberg Prize, International Foundation for Research in Paraplegia.

2013-2018: ERC Advanced Grant (European Research Council).

2024-2029: ERC Advanced Grant (European Research Council).

Main Research Grants (last 5 years)

European Research Council (ERC) – Advanced, 2024-2029.

Adelson Medical Research Foundation – 2022-2025.

Israel Science Foundation (ISF) – 2018-2023.

C. Contributions to Science

1. Retrograde Injury Signaling in Injured Nerve: We discovered a novel axonal transport route based on importins and dynein, showing that local translation of importin β1 mRNA upon injury triggers formation of an importins complex transported retrogradely by dynein.

Hanz, S., Perlson, E., Willis, D., Zheng, J.Q., Massarwa, R., Huerta, J.J., Koltzenburg, M., Kohler, M., van-Minnen, J., Twiss, J.L., & **Fainzilber, M.**, 2003: Axoplasmic importins enable retrograde injury signaling in lesioned nerve. *Neuron 40*, 1095-1104.

Perlson, E., Hanz, S., Ben-Yaakov, K., Segal-Ruder, Y., Seger, R. & **Fainzilber, M.**, 2005: Vimentin dependent spatial translocation of an activated MAP kinase in injured nerve. *Neuron 45*, 715-726.

Yudin, D., Hanz, S., Yoo, S.M., Iavnilovitch, E., Willis, D., Gradus, T., Vuppalanchi, D., Segal-Ruder, Y., Ben-Yaakov, K., Hieda, M., Yoneda, Y., Twiss, J.L., & **Fainzilber, M.**, 2008: Localized regulation of axonal RanGTPase controls retrograde injury signaling in peripheral nerve. *Neuron 59*, 241-252.

Perry, R.B., Doron-Mandel, E., Iavnilovitch, E., Rishal, I., Dagan, S.Y., Tsoory, M., Coppola, G., McDonald, M.K., Gomes, C., Geschwind, D.H., Twiss, J.L., Yaron, A., & **Fainzilber, M.**, 2012: Subcellular knockout of importin β1 perturbs axonal retrograde signaling. *Neuron 75*, 294-305.

Terenzio, M., Koley, S., Samra, N., Rishal, I., Zhao, Q., Sahoo, P.K., Urisman, A., Marvaldi, L., Oses-Prieto, J.A., Forester, C., Gomes, C., Kalinski, A.L., Di Pizio, A., Perry, R.B., Doron-Mandel, E., Koppel, I., Twiss, J.L., Burlingame, A.L., & **Fainzilber, M.**, 2018: Locally translated mTOR controls axonal local translation in nerve injury. *Science 359*, 1416-1421.

Alber, S., Di-Matteo, P., Zdradzinski, M.D., Dalla Costa, I., Medzihradszky, K.F., Kawaguchi, R., Di Pizio, A., Freund, P., Panayotis, N., Marvaldi, L., Doron-Mandel, E., Okladnikov, N., Rishal, I., Nevo, R., Coppola, G., Lee, S.J., Sahoo, P.K., Burlingame, A.L., Twiss, J.L., & **Fainzilber, M.**, 2023: PTBP1 regulates injury responses and sensory pathways in adult peripheral neurons. *Science Advances 9*, eadi0286, doi:10.1126/sciadv.adi0286.

2. Cell Length Sensing and Axonal Growth Control: We proposed a novel mechanism for cell size and axon length sensing, progressing from in silico modeling to experimental validation of the involvement of anterograde mRNA transport, local translation and retrograde transport of the size sensing factors.

Kam, N., Pilpel, Y., & **Fainzilber, M**., 2009: Can molecular motors drive distance measurements in injured neurons? *PLOS Comput Biol 5(8)*, e1000477.

Rishal, I., Kam, N., Perry, R.B., Shinder, V., Fisher, E.M., Schiavo, G., & **Fainzilber, M**., 2012: A Motor Driven Mechanism for Cell Length Sensing. *Cell Reports 1*, 608-616.

Perry R.B., Rishal, I., Doron-Mandel, E., Kalinski, A., Medzihradszky, K.F., Terenzio, M., Alber, S., Koley, S., Lin, A., Rozenbaum, M., Yudin, D., Sahoo, P.K., Gomes, C., Shinder, V., Geraisy, W., Huebner, E.A., Woolf, C.J., Yaron, A., Burlingame, A.L., Twiss, J.L., & **Fainzilber, M.**, 2016: Nucleolin-mediated RNA localization regulates neuron growth and fibroblast cell size. *Cell Reports 16*, 1664–1676.

Doron-Mandel, E., Koppel, I., Abraham, O., Rishal, I., Smith, T.P., Buchanan, C.N., Sahoo, P.K., Kadlec, J., Oses-Prieto, J.A., Kawaguchi, R., Alber, S., Zahavi, E.E., Di-Matteo, P., Di-Pizio, A., Song, D-A., Okladnikov, N., Gordon, D., Ben-Dor, S., Haffner-Krausz, R., Coppola, G., Burlingame, A.L., Jungwirth, P., Twiss, J.L., & **Fainzilber, M.**, 2021: The glycine arginine rich domain of the RNA-binding protein nucleolin regulates its subcellular localization. *EMBO J. 40*, e107158.

3. Long-Distance Signaling and Axonal Proteomics: We have used advanced proteomics approaches to identify and characterize protein complexes and protein dynamics in neuronal function. Recent methods developed to this end enable molecular and biochemical studies on nascent proteomes to a degree not previously possible.

Perlson, E., Michaelevski, I., Kowalsman, N., Ben-Yaakov, K., Shaked, M., Seger, R., Eisenstein, M., & **Fainzilber, M**., 2006: Vimentin binding to phosphorylated Erk sterically hinders enzymatic dephosphorylation of the kinase. *J. Mol. Biol. 364*, 938–944.

Michaelevski, I., Medzihradszky, K.F., Lynn, A., Burlingame, A.L. & **Fainzilber, M**., 2010: Axonal transport proteomics reveals mobilization of translation machinery to the lesion site in injured sciatic nerve. *Mol. Cell. Proteomics 9*, 976-987.

Michaelevski, I., Segal-Ruder, Y., Rozenbaum, M., Medzihradszky, K.F., Shalem, O., Coppola, G., Horn-Saban, S., Ben-Yaakov, K., Dagan, S., Rishal, I., Geschwind, D.H., Pilpel, Y., Burlingame, A.L., & **Fainzilber, M**., 2010: Signaling to transcription networks in the neuronal retrograde injury response. *Science Signaling 3*, ra53.

Ben-Yaakov, K., Dagan, S., Segal-Ruder, Y., Shalem, O., Vuppalanchi, D., Willis, D.E., Yudin, D., Rishal, I., Rother, F., Bader, M., Blesch, A., Pilpel, Y., Twiss, J.L., & **Fainzilber, M**., 2012: Axonal transcription factors signal retrogradely in lesioned peripheral nerve. *EMBO J. 31*, 1350 - 1363.

Song, D-A., Alber, S., Doron-Mandel, E., Schmid, V., Albus, C., Leitner, O., Hamawi, H., Oses-Prieto, J.A., Burlingame, A.L., **Fainzilber, M.**, & Rishal, I., 2022: A new monoclonal antibody enables BAR analysis of subcellular Importin β1 interactomes. *Mol. Cell. Proteomics 21*, 100418.

4. Importin functions in neuronal physiology: We identified critical regulatory nodes controlled by importins in neurobehavioral circuits controlling anxiety, chronic pain and memory. This is a recent and accelerating research effort in the group.

Panayotis, N., Sheinin, A., Dagan, S.Y., Tsoory, M.M., Rother, F., Vadhvani, M., Meshcheriakova, A., Koley, S., Marvaldi, L., Song, D.-A., Reuveny, E., Eickholt, B., Hartmann, E., Bader, M., Michaelevski, I., & **Fainzilber, M.**, 2018: Importin α5 regulates anxiety through MeCP2 and Sphingosine kinase 1. *Cell Reports 25*, 3169–3179.

Marvaldi, L., Panayotis, N., Alber, S., Dagan, S.Y., Okladinikov, N., Koppel, I., Di Pizio, A., Song, D-A., Tzur, Y., Terenzio, M., Rishal, I., Gordon, D., Rother, F., Hartmann, E., Bader, M., & Fainzilber, M., 2020: Importin α3 regulates chronic pain pathways in peripheral sensory neurons. *Science 369*, 842-846.

Panayotis, N., Freund, P.A., Marvaldi, L., Shalit, T., Brandis, A., Mehlman, T., Tsoory, M., & Fainzilber, M., 2021: β-sitosterol reduces anxiety and synergizes with established anxiolytic drugs. *Cell Reports Medicine 2*, 100281.

5. Neurotrophin Signaling and Biology: We identified molecular and cell biological mechanisms of intracellular signaling by neurotrophic factors that contribute to death signaling in neurons and in pediatric neural tumors.

Tcherpakov, M., Bronfman, F.C., Vaskovsky, A., Conticello, S.G., Levy, Z., Niinobe, M., Yoshikawa, K., Arenas, E., & **Fainzilber, M**., 2002: The p75 neurotrophin receptor interacts with multiple MAGE proteins. *J. Biol. Chem. 277* , 49101-49104 *(Accelerated Publication)*.

Bronfman, F.C., Tcherpakov, M., Jovin, T.M., & **Fainzilber. M**., 2003: Ligand-induced internalization of the p75 neurotrophin receptor: a slow route to the signaling endosome. *Journal of Neuroscience 23*, 3209-3220.

Harel, L., Costa, B., Tcherpakov, M., Zapatka, M., Oberthuer, A., Hansford, L.M., Vojvodic, M., Levy, Z., Chen, Z.Y., Lee, F.S., Avigad, S., Yaniv, I., Shi, L., Eils, R., Fischer, M., Brors, B., Kaplan, D.R., & **Fainzilber, M**., 2009: CCM2 mediates death signaling by the TrkA receptor tyrosine kinase. *Neuron 63*, 585-591.

Costa, B., Kean, M., Ast, V., Knight, J.D.R., Mett, A., Levy, Z., Ceccarelli, D.F., Badillo, B.G., Eils, R., Koenig, R., Gingras, A.C., & **Fainzilber, M**., 2012: Stk25 Mediates TrkA and CCM2 dependent death in pediatric tumor cells of neural origin. *J. Biol. Chem. 287*, 29285–29289 *(Report)*.

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