

# BIOMETEC – TORRE BIOLOGICA F. LATTERI

**Course title:** Intracellular transport of proteins and lipids

**Lecturer name:** Doron Rapaport

**Affiliation:** Interfaculty Institute of Biochemistry, University of Tübingen, Germany

**Target audience:** Master and Doctoral students

**Type of course:** seminar (in English)

**Course outline:** The course will include 12 academical hours of seminars

**Topics that will be discussed:**

<b>General aspects of protein transport</b>	<b>22/11 15-17 Aula 1</b>
<b>Protein import into mitochondria</b>	<b>24/11 15-17 Aula 1</b>
<b>Protein transport to chloroplasts and peroxisomes</b>	<b>29/11 13-15 Aula 4</b>
<b>The ER and bacteria translocation machineries</b>	<b>30/11 15-17 Aula 1</b>
<b>Transport of proteins through the nuclear pore complex</b>	<b>01/12 15-17 Aula 4</b>
<b>Membrane contact sites and lipids distribution in the euk. cell</b>	<b>05/12 16-18 Aula D</b>

## **Prof. Doron Rapaport - Biosketch**

**Date and Place of Birth:** 26.10.1962 in Tel-Aviv, Israel  
**Marital State:** Married + two  
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Hoppe-Seyler-Str. 4, 72076 Tübingen, Germany  
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### **Education:**

1985-1989 B.Sc. Degree. School of Chemistry, Faculty of Exact Sciences, Tel-Aviv University, Tel-Aviv, Israel. Degree with Magna Cum Laude.  
1989-1991 M.Sc. Degree. The Feinberg Graduate School, The Weizmann Institute of Science, Rehovot, Israel. Degree with distinction.  
1992-1995 Ph.D. Degree. The Feinberg Graduate School, The Weizmann Institute of Science, Rehovot, Israel. Degree with distinction.  
November 2003 Habilitation in the Faculty of Medicine, Ludwig-Maximilians University, Munich, Germany

### **Professional Experience**

*10.1995 – 9.1997* Post-doctoral fellow with Prof. Walter Neupert, Institute for Physiological Chemistry, Ludwig-Maximilians University, Munich, Germany. Supported by EMBO long term fellowship.  
*10.1997 - 10.2000* Scientific Assistant, Institute for Physiological Chemistry, Ludwig-Maximilians University, Munich, Germany  
*11.2000 - 09.2001* Senior Lecturer, The Hebrew University – Hadassah Medical School, Jerusalem, Israel  
*10.2001 - 11.2003* Scientific Assistant, Institute for Physiological Chemistry, Ludwig-Maximilians University, Munich, Germany  
*12.2003 – 09.2006* Group Leader (Assistant Proessor), Institute for Physiological Chemistry, Ludwig-Maximilians University, Munich, Germany  
*10.2006 - present* Professor of Biochemistry, Interfaculty Institute of Biochemistry, University of Tübingen, Germany  
*09.2010 - 12.2010* Visiting Professor at the Weizmann Institute of Science, Israel  
*10.2011 - 09.2014* Speaker of the Department of Biochemistry and Pharmacy  
*10.2016 - 11.2016* Visiting Professor at the Kyoto Sangyo University, Japan  
*01.2017 - 03.2017* Visiting Professor at Tel-Aviv University, Israel  
*10.2017 - present* Speaker of the Department of Biochemistry and Pharmacy  
*04.2018 - present* Speaker of the Research Training Group “MOMbrane”

## Doron Rapaport – List of Publications (since 2011)

1. **Rapaport, D.** (2011) Protein translocation across or insertion into membranes (Editorial Preface for Special Review Issue). *Biochim. Biophys. Acta* **1808**, 840. doi: 10.1016/j.bbamem.2010.11.032.
2. Dukanovic, J. and **D. Rapaport** (2011) Multiple pathways in the integration of proteins into the mitochondrial outer membrane. *Biochim. Biophys. Acta* **1808**, 971-980. doi: 10.1016/j.bbamem.2010.06.021.
3. Müller, J.E.N., D. Papić, T. Ulrich, I. Grin, M. Schütz, P. Oberhettinger, J. Tommassen, D. Linke, K.S. Dimmer, I.B. Autenrieth, and **D. Rapaport** (2011) Mitochondria can recognize and assemble fragments of a  $\beta$ -barrel structure. *Mol. Biol. Cell* **22**, 1638-1647. doi: 10.1091/mbc.E10-12-0943.
4. Papić, D., K. Krumpe, J. Dukanovic, K.S. Dimmer, and **D. Rapaport** (2011) Multispan mitochondrial outer membrane protein Ugo1 follows a unique Mim1-dependent import pathway. *J. Cell Biol.* **194**, 397-405. doi: 10.1083/jcb.201102041.
5. Engl, G., S. Florian, L. Tranebjærg, and **D. Rapaport** (2012) Alterations in expression levels of Deafness Dystonia Protein 1 affect mitochondrial morphology. *Hum. Mol. Gen.* **21**, 287-299. doi: 10.1093/hmg/ddr458.
6. Merklinger, E., Y. Gofman, A. Kedrov, A.J.M. Driessen, N. Ben-Tal, Y. Shai and **D. Rapaport** (2012) Membrane-integration of a mitochondrial signal-anchored protein does not require additional proteinaceous factors. *Biochem. J.* **442**, 381-389. doi: 10.1042/BJ20111363.
7. Dimmer, K.S. and **D. Rapaport** (2012) Unresolved mysteries in the biogenesis of mitochondrial membrane proteins. *Biochim. Biophys. Acta* **1818**, 1085-1090. doi: 10.1016/j.bbamem.2011.08.027.
8. Körner, C., M. Barrera, J. Dukanovic, K. Eydt, M. Harner, R. Rabl, F. Vogel, **D. Rapaport**, W. Neupert, and A.S. Reichert (2012) Formation of crista junctions depends on the C-terminal domain of Fcjl and the TOB/SAM complex. *Mol. Biol. Cell* **23**, 2143-2155. doi: 10.1091/mbc.E11-10-0831.
9. Ulrich, T., L.E. Gross, M.S. Sommer, E. Schleiff, and **D. Rapaport** (2012) Chloroplast  $\beta$ -barrel proteins are assembled into the mitochondrial outer membrane in a process that depends on the TOM and TOB complexes. *J. Biol. Chem.* **287**, 27467-27479. doi: 10.1074/jbc.M112.382093.
10. Dimmer, K.S., D. Papić, B. Schumann, D. Sperl, K. Krumpe, D.M. Walther, and **D. Rapaport** (2012) A crucial role of Mim2 in the biogenesis of mitochondrial outer membrane proteins. *J. Cell Sci.* **125**, 3464-3473. doi: 10.1242/jcs.103804.
11. Krumpe, K., I. Frumkin, Y. Herzig, N. Rimon, C. Özbalci, B. Brügger, **D. Rapaport**, and M. Schuldiner (2012) Ergosterol content specifies targeting of tail-anchored proteins to mitochondrial outer membranes. *Mol. Biol. Cell* **23**, 3927-3935. doi: 10.1091/mbc.E11-12-0994.

12. Kato, H., Q. Lu, **D. Rapaport**, and V. Kozjak-Pavlovic (2013) Tom70 is essential for PINK1 import into mitochondria. *PLOS One* **8(3)**: e58435. doi: 10.1371/journal.pone.0058435
13. Tan, T. C. Özbalci, B. Brügger, **D. Rapaport**, and K. S. Dimmer (2013) Mcp1 and Mcp2, two novel proteins involved in mitochondrial lipid homeostasis. *J. Cell Sci.* **126**, 3563-3574. doi: 10.1242/jcs.121244.
14. Krumpe, K. and **D. Rapaport** (2013) An assay to monitor the membrane integration of single-span proteins. In D. Rapaport and J. Herrmann (Eds.) *Methods in Molecular Biology*, Vol. "Membrane Biogenesis: Methods and protocols", pp. 301-306, Humana Press, New-York. doi: 10.1007/978-1-62703-487-6\_19.
15. Papić, D., Y. Elbaz-Alon, S.N. Koerdt, K. Leopold, D. Worm, M. Jung, M. Schuldiner, and **D. Rapaport** (2013) The role of Djpl in import of the mitochondrial protein Mim1 demonstrates specificity between a co-chaperone and its substrate protein. *Mol. Cell. Biol.* **33**, 4083-4094. doi: 10.1128/MCB.00227-13.
16. Grau, T., L.F. Burbulla, G. Engl, C. Delettre, B. Delprat, K. Oexle, B. Leo-Kottler, T. Roscioli, R. Krüger, **D. Rapaport**, B. Wissinger, and S. Schimpf-Linzenbold (2013) A novel heterozygous *OPA3* mutation located in the mitochondrial target sequence results in altered steady-state levels and fragmented mitochondrial network. *J. Med. Genet.* **50**, 848-858. doi: 10.1136/jmedgenet-2013-101774.
17. Burbulla, L., J. Fitzgerald, K. Stegen, J. Westermeier, A.-K. Thost, H. Kato, D. Mokranjac, J. Sauerwald, L. Martins, D. Voitalla, **D. Rapaport**, O. Riess, T. Proikas-Cezanne, T. Rasse, and R. Krueger (2014) Mitochondrial proteolytic stress induced by loss of mortalin function is rescued by Parkin and PINK1. *Cell Death Dis.* **5**, e1180.
18. Hermesh, O., C. Genz, I. Yofe, M. Sinzel, **D. Rapaport**, M. Schuldiner, and R.-P. Jansen (2014) Yeast phospholipid biosynthesis is linked 1 to mRNA localization. *J. Cell Sci.* **127**, 3373-3381. doi: 10.1242/jcs.149799.
19. Ulrich, T., P. Oberhettinger, M. Schütz, K. Holzer, A. S. Ramms, D. Linke, I.B. Autenrieth, and **D. Rapaport** (2014) Evolutionary Conservation in Biogenesis of  $\beta$ -Barrel Proteins Allows Mitochondria to Assemble a Functional Bacterial Trimeric Autotransporter Protein. *J. Biol. Chem.* **289**, 29457-29470. doi: 10.1074/jbc.M114.565655.
20. Synofzik, M., T.B. Haack, R. Kopajtich, M. Gorza, **D. Rapaport**, M. Greiner, C. Schönfeld, C. Freiberg, R. Holl, M.A. Gonzalez, A. Fritsche, H. Wolburg, R. Zimmermann, T.M. Strom, T. Meitinger, S. Züchner, R. Schüle, L. Schöls, and H. Prokisch (2014) Absence of BiP co-chaperone DNAJC3 causes diabetes mellitus and multisystemic neurodegeneration. *Am. J. Hum. Genet.* **95**, 689-697. doi: 10.1016/j.ajhg.2014.10.013

21. Ulrich, T., and **D. Rapaport** (2015) Biogenesis of  $\beta$ -barrel proteins in evolutionary context. *Int. J. Med. Microbiol.* **305**, 259-264. doi: 10.1016/j.ijmm.2014.12.009.
22. Sauerwald, J., T. Jores, M. Eisenberg-Bord, S.G. Chuartzman, M. Schuldiner, and **D. Rapaport** (2015) Genome-wide screens in yeast highlight a role for cardiolipin in biogenesis of mitochondrial outer membrane multispan proteins. *Mol. Cell. Biol.* **35**, 3200-3211. doi: 10.1128/MCB.00107-15.
23. Ulrich, T., P. Oberhettinger, I.B. Autenrieth, and **D. Rapaport** (2015) Yeast mitochondria as a model system to study the biogenesis of bacterial  $\beta$ -barrel proteins. In S. Buchanan and N. Noinaj (Eds.) *Methods in Molecular Biology*, Vol. "The BAM Complex: Methods and protocols", pp. 17-31, Humana Press, New-York. doi: 10.1007/978-1-4939-2871-2\_2
24. Casadei, N., P. Sood, T. Ulrich, N. Kieper, S. Helling, C. May, E. Glaab, J. Chen, S. Nuber, K. Marcus, **D. Rapaport**, T. Ott, O. Riess, R. Krüger, and J.C. Fitzgerald (2016) Mitochondrial Defects and Neurodegeneration in Mice Overexpressing Wild Type or G399S Mutant HtrA2. *Hum. Mol. Gen.* **25**, 459–471. doi: 10.1093/hmg/ddv485.
25. Zabezhinsky, D., B. Slobodin, **D. Rapaport** and J.E. Gerst (2016) An essential role for COPI in mRNA localization to mitochondria and mitochondrial function. *Cell Rep.* **15**, 540-549. doi: 10.1016/j.celrep.2016.03.053.
26. Sinzel, M., T. Tan, P. Wendling, H. Kalbacher, C. Özbalci, X. Chelius, B. Westermann, B. Brügger, **D. Rapaport** and K.S. Dimmer (2016) Mcp3 is a novel mitochondrial outer membrane protein that follows a unique IMP-dependent biogenesis pathway. *EMBO Rep.* **17**, 965-981. doi: 10.15252/embr.201541273.
27. Jores, T., A. Klinger, L. Groß, S. Kawano, N. Flinner, E. Duchardt-Ferner, J. Wöhnert, H. Kalbacher, T. Endo, E. Schleiff, and **D. Rapaport** (2016) Characterization of the targeting signal in mitochondrial  $\beta$ -barrel proteins. *Nature Comm.* **7**, 12036. doi: 10.1038/ncomms12036.
28. Hoseini, H., S. Pandey, T. Jores, A. Schmitt, M. Franz-Wachtel, B. Macek, J. Buchner, K. S. Dimmer, and **D. Rapaport** (2016) The cytosolic co-chaperone Sti1 is relevant for mitochondrial biogenesis and morphology. *FEBS J.* **283**, 3338-3352. doi: 10.1111/febs.13813.
29. Pfitzner, A.K., N. Steblau, T. Ulrich, P. Oberhettinger, I.B. Autenrieth, M. Schütz, and **D. Rapaport** (2016) Mitochondrial-bacterial hybrids of BamA/Tob55 suggest variable requirements for the membrane integration of  $\beta$ -barrel proteins. *Sci. Reports* **6**, 39053. doi: 10.1038/srep39053.
30. Dimmer, K.S., and **D. Rapaport** (2017) Mitochondrial contact sites as platforms for phospholipid exchange. *Biochim. Biophys. Acta* **1862**, 69-80. doi: 10.1016/j.bbaliip.2016.07.010.

31. Jores, T. and **D. Rapaport** (2017) Early stages in the biogenesis of eukaryotic  $\beta$ -barrel proteins. *FEBS Lett.* **591**, 2671-2681. doi: 10.1002/1873-3468.12726.
32. Singhal, R.K., C. Kruse, J. Heidler, V. Strecker, K. Zwicker, L. Düsterwald, B. Westermann, J.M. Herrmann, I. Wittig, and **D. Rapaport** (2017) Coil is a novel assembly factor of the yeast complex III-complex IV supercomplex. *Mol. Biol. Cell* **28**, 2609-2622. doi: 10.1091/mbc.E17-02-0093.
33. Peter, A.T.J, B. Herrmann, D. Antunes, **D. Rapaport**, K.S. Dimmer, and B. Kornmann (2017) Vps13-Mcp1 interact at the vacuole-mitochondria interface and bypass ERMES-mediated ER-mitochondria contact sites. *J. Cell Biol.* **216**, 3219-3229. doi: 10.1083/jcb.201610055.
34. Vitali, D.G., M. Sinzel, E. Bulthuis, A. Kolb, S. Zabel, D.G. Mehlhorn, A. Clancy, A. Farkas, B. Costa, M. Schuldiner, C. Grefen, B. Schwappach, N. Borgese, and **D. Rapaport** (2018) The GET pathway can increase the risk of mitochondrial outer membrane proteins to be mistargeted to the ER. *J. Cell Sci.*, **131**. doi: 10.1242/jcs.211110.
35. Weill, U., I. Yofe, E. Sass, B. Stynen, D. Davidi, J. Natarajan, R. Ben-Menachem, Z. Avihou, O. Goldman, N. Harpaz, S. Chuartzman, K. Kniazev, B. Knoblach, J. Laborenz, J. Kowarzyk, S. Ben-Dor, E. Zalckvar, J.M. Herrmann, R.A. Rachubinski, O. Pines, **D. Rapaport**, S.W. Michnick, E.D. Levy, and M. Schuldiner (2018) Exploring the yeast proteome using a whole genome SWAp-Tag (SWAT) library. *Nature Methods*, doi: 10.1038/s41592-018-0044-9.
36. Vitali, D.G., S. Käser, A. Kolb, K.S. Dimmer, A. Schneider, and **D. Rapaport** (2018) Independent evolution of functionally exchangeable mitochondrial outer membrane import complexes. *eLife*, **7**:e34488. doi: 10.7554/eLife.34488.
37. Jores, T., J. Lawatscheck, V. Beke, M. Franz-Wachtel, K. Yunoki, J.C. Fitzgerald, B. Macek, T. Endo, H. Kalbacher, J. Buchner, and **D. Rapaport** (2018) Cytosolic Hsp70 and Hsp40 chaperones enable the biogenesis of mitochondrial  $\beta$ -barrel proteins. *J. Cell Biol.*, **217**, 3091-3108. doi: 10.1083/jcb.201712029.
38. Cichocki, B.A., K. Krumpe, D.G. Vitali, and **D. Rapaport** (2018) Pex19 is involved in importing dually targeted tail-anchored proteins to both mitochondria and peroxisomes. *Traffic*, **19**, 770-785. doi: 10.1111/tra.12604.
39. Weinhäupl, K., C. Lindau, A. Hessel, Y. Wang, C. Schütze, T. Jores, L. Melchionda, B. Schönfisch, H. Kalbacher, B. Bersch, **D. Rapaport**, M. Brennich, K. Lindorff-Larsen, N. Wiedemann, and P. Schanda (2018) Structural basis of membrane protein chaperoning through the mitochondrial intermembrane space. *Cell*, **175**, 1365-1379. doi: 10.1016/j.cell.2018.10.039
40. Antunes, D., A. Chowdhury, A. Aich, S. Saladi, N. Harpaz, M. Stahl, M. Schuldiner, J.M. Herrmann, P. Rehling, and **D. Rapaport** (2019) Overexpression of Branched-Chain Amino Acid Aminotransferases rescues the growth defects of cells lacking the Barth Syndrome related gene TAZ1. *J. Mol. Med.*, **97**, 269-279. doi: 10.1007\_s00109-018-1728-4.

41. Makki, A., P. Rada, V. Žárský, S. Kerešiče, L. Kováčik, M. Novotný, T. Jores, **D. Rapaport**, and J. Tachezy (2019) Triplet-pore structure of a highly divergent TOM complex of hydrogenosomes of *Trichomonas vaginalis*. *PLOS Biol.*, doi: 10.1371/journal.pbio.3000098.
42. Eisenberg-Bord, M., H.S. Tsui, D. Antunes, L. Fernández-del-Río, C.D. Dunn, **D. Rapaport**, C.F. Clarke, and M. Schuldiner (2019) The ER-Mitochondria contact site coordinates coenzyme Q biosynthesis. *Contact*, **2**, 1-14. doi: 10.1177/2515256418825409.
43. Grossmann, D., C. Berenguer-Escuder, M.E. Bellet, D. Scheibner, J. Bohler, F. Massart, **D. Rapaport**, A. Skupin, A. Fouquier d'Hérouël, M. Sharma, J. Ghelfi, A. Rakovic, P. Lichtner, P. Antony, E. Glaab, P. May, K.S. Dimmer, J.C. Fitzgerald, A. Gruenewald, and R. Krüger (2019) Mutations in RHOT1 disrupt ER-mitochondria contact sites interfering with calcium homeostasis and mitochondrial dynamics in Parkinson's disease. *Antioxid. Redox Signal.*, **31**, 1213-1234. doi: 10.1089/ars.2018.7718.
44. Odendall, F., S. Backes, T. Tatsuta, U. Weill, M. Schuldiner, T. Langer, J.M. Herrmann, D. Rapaport, and K.S. Dimmer (2019) The mitochondrial intermembrane space-facing proteins Mcp2 and Tgl2 are involved in yeast lipid metabolism. *Mol. Biol. Cell*, **30**, 2681–2694. doi: 10.1091/mbc.E19-03-0166.
45. Natarajan, J., N. Singh, and **D. Rapaport** (2019) Assembly and targeting of Secretins in the bacterial outer membrane. *Int. J. Med. Microbiol.*, **309**, 151322. doi: 10.1016/j.ijmm.2019.06.002.
46. Rapaport, D. (2019) Protein translocation- The mitochondrial gate reveals its secrets. *Nat. Struc. Mol. Biol. (News & Views)*. **26**, 1083-1085. doi:10.1038/s41594-019-0346-3.
47. Natarajan, J., A. Moitra, S. Zabel, N. Singh, S. Wagner, and D. Rapaport (2020) Yeast can express and assemble bacterial secretins in the mitochondrial outer membrane. *Microbial Cell*, **7**, 15-27. doi: 10.15698/mic2020.01.703.
48. Vitali, D.G., L. Drwesh, B.A. Cichocki, A. Kolb, and **D. Rapaport** (2020) The biogenesis of mitochondrial outer membrane proteins show variable dependence on import factors. *iScience*, **23**, 100779. doi: 10.1016/j.isci.2019.100779.
49. Drwesh, L., and **D. Rapaport** (2020) Biogenesis pathways of  $\alpha$ -helical mitochondrial outer membrane proteins. *Biol. Chem.*, **401**, 677-686. doi: 10.1515/hsz-2019-0440.
50. Bykov, Y.S., **D. Rapaport**, J.M. Herrmann, and M. Schuldiner (2020) Cytosolic events in the biogenesis of mitochondrial proteins. *Trends Biochem. Sci.*, **45**, 650-667. doi: 10.1016/j.tibs.2020.04.001.
51. Rosenthal, M., E. Metzl-Raz, J. Bürgi, E. Yifrach, L. Drwesh, A. Fadel, Y. Peleg, **D. Rapaport**, M. Wilmanns, N. Barkai, M. Schuldiner, and E. Zalckvar (2020) Uncovering targeting priority to yeast peroxisomes using an in-cell competition assay. *Proc. Natl. Acad. Sci. USA*, **117**, 21432-21440. doi: 10.1073/pnas.1920078117.

52. Ferdigg, A., K.S. Dimmer, **D. Rapaport**, and D.G. Vitali (2020) Hydrogenosomal tail-anchored proteins are targeted to both mitochondria and ER upon their expression in yeast cells. *PLOS One*, **15**, e0237982. doi: /10.1371/journal.pone.0237982.
53. Sucec, I., Y. Wang, O. Dakhlaoui, K. Weinhäupl, T. Jores, D. Costa, A. Hessel, M. Brennich, **D. Rapaport**, K. Lindorff-Larsen, B. Bersch, and P. Schanda (2020) Structural basis of client specificity in mitochondrial membrane-protein chaperones. *Science Advances*, **6**, eabd0263. doi: 10.1126/sciadv.abd0263.
54. Bus, C, L. Zizmare, M. Feldkaemper, S. Geisler, M. Zarani, A. Schaedler, F. Klose, J. Admard, C. Mageean, G. Arena, P. Fallier-Becker, A. Ugun-Klusek, K.K. Maruszczak, K. Kapolou, B. Schmid, **D. Rapaport**, M. Ueffing, N. Casadei, R. Krüger, T. Gasser, D. Vogt-Weisenhorn, P.J. Kahle1, C. Trautwein, C.J. Gloeckner, and J.C. Fitzgerald (2020) Human dopaminergic neurons lacking PINK1 exhibit disrupted dopamine metabolism related to vitamin B6 co-factors. *iScience*, **23**, 101797. doi: 10.1016/j.isci.2020.101797.
55. Backes, S., Y.S. Bykov, T. Flohr, M. Räschle, J. Zhou, S. Lenhard, L. Krämer, T. Mühlhaus, C. Bibi, C. Jann, J.D. Smith, L.M. Steinmetz, **D. Rapaport**, Z. Storchová, M. Schuldiner, F. Boos, and J.M. Herrmann (2021) The chaperone-binding activity of the mitochondrial surface receptor Tom70 protects the cytosol against mitoprotein-induced stress. *Cell Rep.*, **35**, 108936. doi: 10.1016/j.celrep.2021.108936.
56. Moitra, A. and **D. Rapaport** (2021) The biogenesis process of VDAC-from early cytosolic events to its final membrane integration. *Frontiers in Physiology*, **12**, 732742. doi: 10.3389/fphys.2021.732742.