Johannes Huppa

Name: **Johannes B. HUPPA**
Academic titles: Assoc.-Prof. Dipl. Biochem. PhD
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MAIN AREAS OF RESEARCH

- Molecular mechanisms underlying T-cell antigen recognition in health and disease
- T-cell-based immunotherapies (Chimeric Antigen Receptor- and TCR-modified T-cells, T-cell Engager)
- Advanced imaging modalities
- Synthetic biology

EDUCATION

1994-1998	PhD thesis conducted at MIT and Harvard Medical School and titled "Biochemical and Cell Biological Aspects of Protein Biosynthesis and Proteolysis in the Context of Adaptive Immunity", degree awarded from the Free University of Amsterdam, Netherlands
1989-1994	Study of Biochemistry, Free University of Berlin, Germany, with internships in the laboratories of C. Nüsslein-Volhard (Tübingen), Y. Yarden (Rehovot), G. Winter (Cambridge) and J. Neefjes (Amsterdam); Diploma thesis conducted with H. Ploegh (Cambridge, MA) titled "Molecular and Cell Biological Aspects of MHC Class II Mediated Antigen Presentation", grade: 1.0 (very good)

ACADEMIC POSITIONS

Starting 09/2024	Full Professor (W3) and Chair at the Institute for Tumor Immunology, Charité Universitätsmedizin Berlin
2015 – 2024	Associate Professor at the Medical University of Vienna, Austria
2012 – 2015	Assistant Professor at the Medical University of Vienna, Austria
2005 – 2011	Basic Science Research Associate at the Dep. of Microbiology and Immunology, Stanford School of Medicine and the Howard Hughes Medical Institute, USA
1999 – 2005	Postdoctoral fellow at the Department of Microbiology and Immunology, Stanford School of Medicine and the Howard Hughes Medical Institute, USA
1997 – 1998	Research Associate at Harvard Medical School, USA
1993 – 1997	Visiting Scientist at MIT, USA

INVITED TALKS

Dr. Huppa presented his research in > 50 invited talks at international conferences (most important are listed)

- ESH 3rd Translational Research Conference: Immune & Cellular Therapies, Malahide, Ireland (2024)
- 6th European CAR T-cell Meeting, Valencia (2024)
- CSH Asia meeting "Immunoreceptor Signaling and Therapeutic Applications", Suzhou (2023)
- 4th international immunology workshop in Lofoten, Kabelvåg (2023)
- ESH 2nd Transl. Research Conference: Focus on Advanced Gene-Engineered Immune Cells, Berlin (2022)
- 51st Annual Meeting of the German Society for Immunology (DGFI) and 50th Annual Meeting of the Austrian Society for Allergology and Immunology (ÖGAI), Hannover (2022)
- EHA-EBMT 2nd European CAR T-cell Meeting (Plenary Session), Sitges, Barcelona (2020)
- 2nd Midwinter Immunology Conference (Advances in Immunology), Seefeld (2017)
- Else Kröner Symposium "Translational Immunology – From Target to Therapy", Würzburg (2013)
- Gordon Conference, "Immunochemistry and Immunobiology", Les Diablerets (2010)
- CSH Meeting, "Gene Expression and Signaling in the Immune System" (Plen. Session), NY (2008)
- Keystone Symposium, "Lymphocyte Activation and Signaling" (Plen. Session), Steamboat Springs (2006)
- FASEB Meeting "Signal Transduction in the Immune System", Snowmass Village (2003)

AWARDS

Gottlieb Daimler- and Carl Benz-Foundation, Germany (fellowship,1993); Boehringer Ingelheim Fonds, Germany (fellowship, 1994); Cancer Research Institute, USA (fellowship, 1999 - also accepted for funding by the Irvington and the Arthritis Foundation); iFREC (Immunology Frontiers Research Center) imaging consortium, Japan (fellowship, 2007); Guy Newton Fellowship, Oxford University, UK (2020)

REVIEWER ACTIVITIES (SELECTION)

- Journals: Science, Nature Methods, Nature Medicine, Nature Immunology, Nature Cancer, Nature Reviews Immunology, Immunity, EMBO J., PNAS, Nature Communications, Communications Biology
- Funding agencies: European Commission (ERC-2017-STG, ERC-2018-COG, ERC-STG-2019), Israel Science Foundation (2015), MRC (Great Britain, 2014, 2019, 2024), OeAD (Austria, 2018, 2019), Human Frontiers Science Program, Lower Austria Research Funding (Life Science Call 2018, 2019), German Research Foundation (DFG), German Cancer Aid

EDITORIAL BOARD MEMBERSHIPS:

Frontiers in Immunology

MOST IMPORTANT FUNDED SCIENTIFIC PROJECTS (TOTAL LUMP SUM: 2,300 K€)

Project title	Role as applicant	Project Duration	Amount funded (k€)	Funding Organization
Devising Advanced TCR-TC to eradicate OsteoSarcoma (DART^{2}OS, Excellence Initiative)	Particip. PI	2024-2029	923	Austrian Science Fund
Innovative Medical Initiative (IMI) Accelerating Development and Improving Access to CAR and TCR engineered T-cell therapy (T^{2}EVOLVE)	Particip. PI	2021 - 2026	285	European Commission
Towards a molecular understanding of T-cell engagers in tumor antigen detection	PI	2020 - 2023	424	Boehringer Ingelheim
European Network on Anti-Cancer Immuno-Therapy Improvement by modification of CAR and TCR Interactions and Nanoscale Geometry (EN-ACTI^{2}NG)	Particip. PI	2016 - 2021	255	European Commission
High-Resolution Imaging to Unravel the Molecular Etiology of Disturbed T-Cell Antigen Recognition	PI	2014 - 2019	291	Vienna Science and Technology Fund (WWTF)

INTERNATIONAL COLLABORATION PARTNERS (LAST 5 YEARS)

Simon Davis (Oxford University, UK), Mark M. Davis (Stanford University, USA), Nicholas Gascoigne (National University of Singapore, Singapore), Michael Hudecek (University Clinics Würzburg, Germany)

STUDENT SUPERVISION

Master theses: **6**, PhD theses: **3** completed, **4** ongoing

SCIENTIFIC PRODUCTION

Publications – metrical overview (*per June 2024*): **76 articles (Pubmed-listed), cumulative impact factor = 1166.417, 7764 citations, HI = 36, i10 = 57**

SHORT STATEMENT OF THE MOST IMPORTANT SCIENTIFIC/SCHOLARLY RESULTS

Diploma/ PhD thesis work, MIT and Harvard University: I demonstrated with the use of a cell-free *in vitro* transcription / translation system that proper folding and assembly for the T-cell antigen receptor (TCR)-CD3 complex in the ER mandates simultaneous translation of TCR- and CD3-subunits (**Ref. 10**). I contributed to

shifting a paradigm in cell biology by showing that misfolded TCRs undergo ER-associated degradation (ERAD) by the proteasome, that is after dislocation from the ER into the cytoplasm (**Ref. 9**).

Postdoc / Research Associate, Stanford University: I focused my research efforts on obtaining a deeper understanding of T-cell antigen recognition within the special constraints of the immunological synapse (**Ref. 7**). To this end I devised (single molecule) life cell imaging modalities to inform about cellular and molecular mechanisms underlying the exquisite sensitivity of antigen detection (**Ref. 6**). I showed that continual synaptic TCR-antigen engagement is mandatory for synapse maintenance and the full T-cell effector potential (**Ref. 8**). I succeeded in visualizing synaptic TCR-antigen binding events by devising and employing a FRET-based scoring system, which allowed me to quantitate for the first time highly accelerated synaptic TCR-antigen binding kinetics (**Ref. 5**).

PI, Medical University of Vienna: Research activities of my laboratory concern molecular mechanisms underlying T-cell antigen recognition with a particular focus on human disease (type I diabetes, cancer, COVID-19) and therapeutic intervention. We developed and applied advanced imaging (i) to visualize and measure mechanical pN forces imposed on single synaptic TCR-engaged peptide-loaded MHCs (pMHCs) (**Ref. 1**), (ii) to assess and quantitate true clustering of membrane-associated proteins based on super-resolution microscopy (dSTORM or PALM)-derived localization maps (**Ref. 2**) and (iii) to reveal the monomeric nature of TCR/CD3 complexes (**Ref. 4**) when these are engaged by pMHCs, which in turn act as autonomous entities to stimulate T-cells (biorxiv). We showed that CAR-T-cells - when compared to virus-specific T-cells - target tumor associated antigens with 1000-times reduced sensitivity with implications for cancer immune escape (**Ref. 3**). At current we work towards building novel, more sensitive CAR formats that are based on the TCR-CD3 architecture (biorxiv), understanding T-cell antigen recognition in autoimmunity, cancer eradication and transplantation medicine.

TEN MOST IMPORTANT RESEARCH PUBLICATIONS (*CORRESPONDING AUTHORSHIP)

1. Temporal Analysis of T-Cell Receptor-Imposed Forces via Quantitative Single Molecule FRET Measurements. Göhring J., Kellner F., Schrangl L., Platzer R., Klotzsch E., Stockinger H., **Huppa J.B.***, Schütz G.J. (**2021**) ***Nature Communications*** 4;12(1):2502. doi: 10.1038/s41467-021-22775-z. PMID: 33947864.
2. Unscrambling Fluorophore Blinking for Comprehensive Cluster Detection via Photoactivated Localization Microscopy. Platzer R., Rossboth B.K., Schneider M.C., Sevcsik E., Baumgart F., Stockinger H., Schuetz G.J., **Huppa J.B.***, Brameshuber M. (2020) ***Nature Communications*** 11:4993 https://doi.org/10.1038/s41467-020-18726-9
3. Inefficient CAR-proximal signaling blunts antigen detection. Gudipati V., Rydzek J. Doel Perez I., Scharf L., Königsberger S., Lobner E., Dos Reis Gonçalves V., Kunert R., Einsele H., Stockinger H., Hudecek M. and **Huppa J.B.*** (**2020**) ***Nature Immunology*** 21:848-856 doi: 10.1038/s41590-020-0719-0. online ahead of print. PMID: 32632291
4. Monomeric TCRs Drive T-Cell Antigen Recognition. Brameshuber M., Kellner F., Rossboth B.K., Ta H., Alge K., Sevcsik E., Göhring J., Axmann M., Baumgart F., Gascoigne N.R.J., Davis S.J., Stockinger H., Schütz G.J. **Huppa J.B.*** (**2018**) ***Nature Immunology***, 19(5):487-496, doi: 10.1038/s41590-018-0092-4
5. TCR-peptide-MHC interactions *in situ* show accelerated kinetics and increased affinity. **Huppa J.B.**, Axmann, M., Mörtelmaier M.A., Lillemeier B.F., Newell E.W, Brameshuber M., Klein L.O., Schütz G.J., Davis M.M.(**2010**) ***Nature***: 463: 963-967
6. T cell killing does not require the formation of a stable mature immunological synapse. Purbhoo M.A., Irvine D.J,. **Huppa J.B.**, Davis M.M. (**2004**) ***Nature Immunology*** 5:524-530, IF = **27.586**, citations: **588**
7. T cell antigen recognition and the immunological synapse. **Huppa J.B.**, Davis M.M. (2003) ***Nature Reviews in Immunology*** 3:973-983
8. Continuous T-cell receptor signaling required for synapse maintenance and full effector potential. **Huppa J.B.**, Gleimer M., Sumen C., Davis M.M. (**2003**) ***Nature Immunology*** 4:749-755, citations: **514**
9. The alpha chain of the T-cell antigen receptor is degraded in the cytosol. **Huppa J.B.**, Ploegh H.L. (1997) ***Immunity*** 7:113-122
10. *In vitro* translation and assembly of a complete T-cell receptor-CD3 complex. **Huppa J.B.**, Ploegh H.L. (**1997**) ***Journal of Experimental Medicine*** 186:393-403