BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Michael Rape	Investigator, Howard Hughes Medical Institute; Dr. K. Peter Hirth Chair of Cancer Biology; Professor of Cell and Developmental Biology
eRA COMMONS USER NAME MPRAPE	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Bayreuth University (Bayreuth, Germany)	Diploma (equ. M.Sc)	1999	biochemistry
Max-Planck Institute of Biochemistry & Bayreuth University (Munich, Germany)	PhD	2002	biochemistry
Harvard Medical School (Boston, USA)	Postdoc	2006	cell biology

A. Personal Statement

My laboratory is using an integrated approach based on genetics, proteomics, microscopy and biochemical reconstitution to reveal molecular mechanisms of human cell fate determination. We are focusing onto the developmental role of ubiquitylation, a posttranslational modification that is essential for cell division, differentiation, and survival in all eukaryotes. As aberrant ubiquitylation results in many diseases, including cancer and neurodegeneration, understanding ubiquitin-dependent mechanisms of differentiation not only offers insight into fundamental steps of human development, but also helps reveal events leading to disease initiation or progression. As our work suggested that compounds targeting ubiquitylation enzymes could provide benefit in treating many pathologies, we were among those spearheading induced protein degradation as a novel therapeutic modality. Our work is therefore revealing fundamental principles of mammalian development to pave the way for novel and specific therapeutics.

It is a central goal of mine to mentor a diverse and collaborative lab, to foster the careers of my students and postdocs, and to help build a scientific community in Berkeley and beyond. As a testament to mentoring, my students and postdocs have secured prestigious positions in academia and industry and received important awards, including the Weintraub Award for the best thesis in the US. As a testament to my helping build community, I have served as Chair for the CSRS study section at NIGMS, as an organizer of multiple international meetings in my field, and as a member of the editorial board of the community-driven journal eLife.

Below are recent key publication from my lab:

1. Manford AG, Rodríguez-Pérez F, Shih KY, Shi Z, Berdan CA, Choe M, Titov DV, Nomura DK, and **Rape M**. (2020). A cellular mechanism to detect and alleviate reductive stress. Cell *in press*
2. Mena E, Jevtic P. et al., and **Rape M.** (2020). Structural basis for dimerization quality control. Nature *in press*
3. Oh E, Mark KG, Mocciaro A, Watson ER, Prabu JR, Cha DD, Kampmann M, Gamarra N, Zhou CY, and **Rape M.** (2020). APC/C-dependent control of gene expression and cell identity. Nature 579(7797):136-140.
4. Mena El, Kjolby RAS, Saxton R, Werner A, Lew BG, Boyle JM, Harland R, and **Rape M**. (2018). Dimerization quality control ensures neuronal development and survival. Science 12;362(6411). pii: eaap8236. doi: 10.1126/science.aap8236.
5. Yau R, Doerner K, Castellanos ER, Werner A, Haakonsen D, Wang N, Yang WX, Matsumoto M, Dixit V, and **Rape M**. (2017). Assembly and function of heterotypic ubiquitin chains in cell cycle and protein quality control, Cell 171, 918-933.

B. Positions and Honors

Positions and Employment

2014-present	Dr. K. Peter Hirth Chair in Cancer Biology, UC Berkeley
2013-present	Investigator, Howard Hughes Medical Institute
2013-present	Professor of Cell and Developmental Biology University of California, Berkeley, USA
2011-2013	Associate Professor with tenure, University of California at Berkeley
2006-2011	Assistant Professor of Cell and Developmental Biology University of California at Berkeley

2003-2006	Postdoctoral Fellow, Harvard Medical School, Boston; Laboratory of Dr. Marc W. Kirschner
1999-2002	Graduate Student, Max-Planck Institute of Biochemistry, Munich, Germany

Honors

2018	Pew Innovation Award
2016	National Blavatnik Laureate in the Life Sciences
2016-2018	Chair, NIGMS study section CSRS
2015-present	Co-organizer, Cold Spring Harbor Meeting “The Ubiquitin Family”
2015	Organizer, Keystone Ubiquitin Meeting
2015	Board of Reviewing Editors, eLife
2015	President’s Lecture, Sanford Burnham Prebys Medical Discovery Institute
2014, 2015	Finalist, National Blavatnik Award
2014-present	Member, NIGMS study section CSRS
2014	Dr. K. Peter Hirth Chair in Cancer Biology, UC Berkeley
2014	Editorial Board, Molecular Cell
2013	Member, NCI site visit group, Frederick
2013	Investigator, Howard Hughes Medical Institute
2013	Curci Foundation Award
2013	Vilcek Prize for Creative Promise
2012	NIH PO1 review panel
2012	Bakar Fellow, University of California at Berkeley
2012	Editorial Board, EMBO Reports
2011	Editorial Board, Journal of Cell Science
2010-2014	ad hoc member NIGMS study section CSRS
2010	Board of Reviewing Editors, Molecular Biology of the Cell
2009	Member, Faculty of 1000
2007	NIH Director’s New Innovator Award
2007	Pew Scholar Award
2007	Kimmel Scholar Award (declined)
2004	Long-Term Fellowship of the Human Frontier Science Program
2003	Long-Term Fellowship of the European Molecular Biology Organization
2002	Dissertation “summa cum laude”
2002	Otto-Hahn Medal of the Max Planck Society
2001	Max Planck Institute Junior Research Award
1999	Diploma “with highest honors”
1996	Fellowship of the German National Scholarship Foundation
1994	Bavarian Fellowship for very talented students

Keynote and Named Lectures

2018	UT Southwestern University Lecture
2018	Keynote Lecture, 2nd Frankfurt Conference on Quality Control (Germany)
2018	Tony Pawson Memorial Lecture, Banff (Canada)
2017	Danny Thomas Lecture, St. Jude Children’s Research Hospital
2016	Distinguished Lecture, Max Planck Institute of Biochemistry (Germany)
2015	Keynote Lecture, ETH Zurich
2014	Keynote Lecture, Boehringer Ingelheim Foundation Meeting, Woods Hole
2014	Keynote Lecture, Ubiquitin and Drug Discovery, San Diego
2011	3rd SCILLS lecture, Dundee, UK
2011	George Connell Lecture, University of Toronto, Canada

C. Contributions to science

a. Discovering mechanisms of ubiquitin-dependent control of cell fate decisions

The substrate specificity of ubiquitylation is determined by more than 600 E3 ligases. However, despite their frequent mutation in cancer or neurodegenerative diseases, the function of most E3 ligases remain poorly understood. Starting with genetic screens, we have discovered essential functions of E3 ligases and their substrates in human development and thereby revealed molecular mechanisms of mitotic bookmarking, ribosome specification, or control of vesicle size. Our work documented essential roles of ubiquitylation in ensuring stem cell pluripotency, driving neural crest specification, or controlling neuronal differentiation and hence contributed significantly to our understanding of how tissue formation and maintenance can be accomplished in dynamic environments.

1. Oh E, Mark KG, Mocciaro A, Watson ER, Prabu JR, Cha DD, Kampmann M, Gamarra N, Zhou CY, and **Rape M.** (2020). APC/C-dependent control of gene expression and cell identity. Nature 579(7797):136-140.
2. McGourty CA, Akopian D, Walsh C, Gorur A, Schekman R, Bautista D, and **Rape M.** (2016). Regulation of the CUL3 ubiquitin ligase by a calcium-dependent co-adaptor. Cell 167(2):525-538.
3. Werner A., Iwasaki S., McGourty C., Medina-Ruiz S., Teerikorpi N., Fedrigo I., Ingolia N. , and **Rape M.** (2015). Cell fate determination by ubiquitin-dependent regulation of translation. Nature 525, 523-37.
4. Jin L, Bajai K, Wickliffe K, Gorur A, Schekman R, and **Rape M.** (2012). Ubiquitin-dependent regulation of COPII coat size and function. Nature 482(7386):495-500.

b. Discovering novel quality control networks

Cells possess multiple signaling systems that can detect and alleviate adverse conditions, and inactivation of such stress responses is a frequent cause of neurodegenerative disease. We have recently discovered three stress responses that protect cells from protein aggregation, formation of aberrant protein complexes, or mitochondrial dysregulation. Mutation in components of these stress responses cause Amyotrophic Lateral Sclerosis, accelerate progression of Huntington's Disease, or trigger cardiomyopathy and diabetes. The central E3 ligases of these stress responses are of high interest for the development of small molecules triggering degradation of pathological proteins. Thus, our work revealed principles of eukaryotic stress signaling with high relevance for drug discovery.

1. Manford AG, Rodríguez-Pérez F, Shih KY, Shi Z, Berdan CA, Choe M, Titov DV, Nomura DK, and **Rape M**. (2020). A cellular mechanism to detect and alleviate reductive stress. Cell *in press*
2. Mena E, Jevtic P. et al., and **Rape M.** (2020). Structural basis for dimerization quality control. Nature *in press*
3. Mena El, Kjolby RAS, Saxton R, Werner A, Lew BG, Boyle JM, Harland R, and **Rape M**. (2018). Dimerization quality control ensures neuronal development and survival. Science 12;362(6411). pii: eaap8236. doi: 10.1126/science.aap8236.
4. **Rape, M.,** Hoppe, T., Gorr, I., Kalocay, M., Richly, H., and Jentsch, S. (2001). Mobilization of processed, membrane-tethered SPT23 transcription factor by CDC48. Cell 107, 667-677.

c. Identification of essential ubiquitin chain types

Ubiquitylation controls many processes in a highly specific manner, as it comes in different flavors: monoubiquitylation often functions in a non-proteolytic manner to alter protein interactions or localization, whereas ubiquitin chains drive protein degradation, transcription factor regulation, or DNA repair. We have identified the first atypical ubiquitin chain, linked through Lys11 of ubiquitin. Moreover, we recently discovered the first function of branched ubiquitin chains as proteasomal priority signaling. We have integrated our findings in the "ubiquitin code" hypothesis, which proposes that distinct ubiquitin chain types encode unique information and hence serve specific functions in cellular regulation.

1. Yau R, Doerner K, Castellanos ER, Werner A, Haakonsen D, Wang N, Yang WX, Matsumoto M, Dixit V, and **Rape M**. (2017). Assembly and function of heterotypic ubiquitin chains in cell cycle and protein quality control, Cell 171, 918-933.
2. Meyer, HJ., and **Rape M.** (2014). Enhanced protein degradation by branched ubiquitin chains. Cell 157 (4): 910-921
3. Matsumoto M*, **Wickliffe KE***, et al. (2010). K11-Linked Polyubiquitination in Cell Cycle Control Revealed by a K11 Linkage-Specific Antibody. Mol. Cell 39(3):477-84
4. Jin, L.*, Williamson, A.*, Banerjee, S., Phillip, I., and **Rape M.** (2008). Mechanism of ubiquitin chain formation by the human Anaphase-Promoting Complex. Cell, 133, 653-665.

d. Understanding mechanisms of ubiquitin chain formation

Ubiquitin contains eight residues that can function as acceptor sites for the next ubiquitin during chain assembly. How proper acceptor residues are selected for chain formation has been unclear, and so, the biochemical basis underlying the function of ubiquitin chain topologies has been understood incompletely. Using the APC/C and its E2 enzymes Ube2C and Ube2S, we unraveled the mechanism of linkage specific chain formation, thereby laying the foundation to targeting specific signaling through the ubiquitin pathway.

1. Kelly, A, Wickliffe, KE, Song, L, Federigo, I., and **Rape M.** (2014). Ubiquitin chain formation requires E3-dependent tracking of the emerging conjugate. Mol. Cell 56(2): 232-45.
2. Williamson A*, Banerjee S*, Zhu X, Philipp I, Iavarone AT, and **Rape M**. (2011). Regulation of ubiquitin chain initiation to control the timing of substrate degradation. Mol Cell 42, 744-57.
3. Wickliffe KE*, Lorenz S*, Wemmer D, Kuriyan J, and **Rape M.** (2011) The mechanism of ubiquitin chain formation by a single-subunit E2. Cell 144, 769-781
4. **Rape, M.,** Reddy, S.K., and Kirschner, M.W. (2006). The anaphase-promoting complex controls substrate ordering by an intrinsic process akin to kinetic proofreading. Cell 124, 89-103.

d. Developing induced protein degradation as a novel therapeutic modality

Ubiquitylation was traditionally thought to be “undruggable”, as E3 ligases do not possess obvious binding pockets for small molecules. Starting in my lab, we have developed a robust strategy to isolate small molecules that can activate E3 ligases to trigger degradation of disease-causing proteins. In the course of these studies, we have isolated the first prospective molecular glue for ubiquitin ligases. Moreover, our work has led to formation of a public biomedical company, Nurix Therapeutics, which is located in San Francisco and has ~125 in-house employees.

1. Simonetta K.R., et al. (2019). Prospective discovery of small molecule enhancers of an E3 ligase-substrate interaction. (2019). Nature Commun. 10(1):1402. doi: 10.1038/s41467-019-09358-9