Doctoral College
Metabolic & Cardiovascular Disease

SAME MECHANISM ... VERY DIFFERENT DISEASE?

(MIS)REGULATION OF NUCLEAR IMPORT IN NEURODEGENERATIVE DISEASES AND CANCER

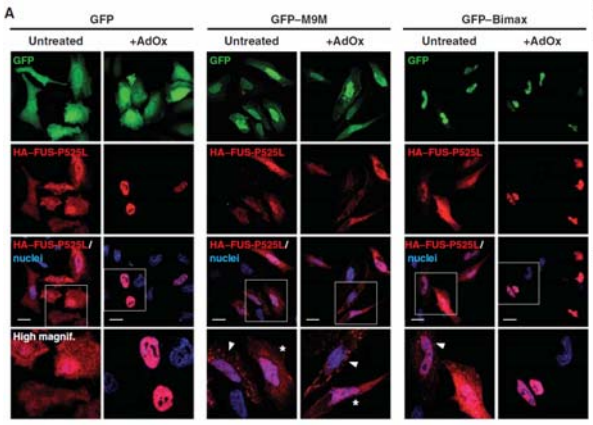
GUEST LECTURE by

Dr. Tobias Madl

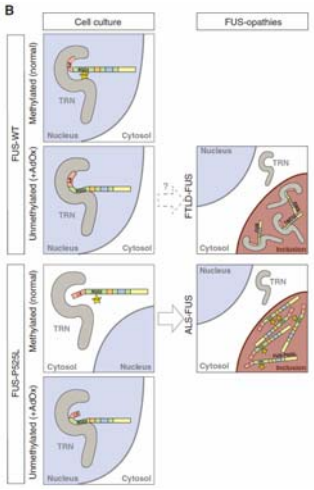
Department of Chemistry,
Technical University of Munich, Germany

Friday, 05.09.2014
14:00

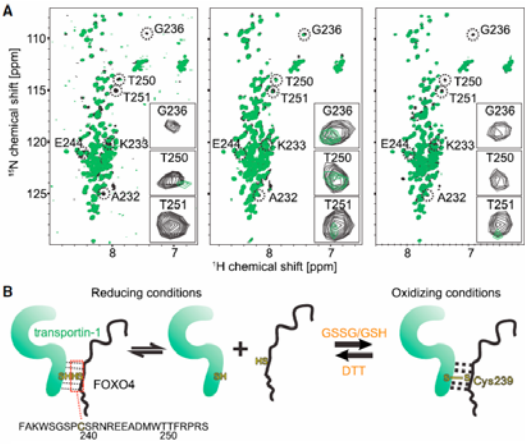
SR 07.11, Preclinics
Harrachgasse 21, MUG



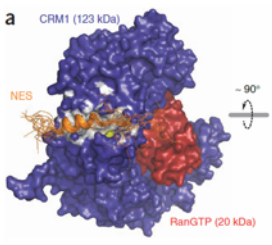
Nuclear import of FFUS-P525L upon AdOx treatment is dependent on TRN.
Arginine methylation next to the PY-NLS modulates Transportin binding and nuclear import of FUS. Dorman et al. (2012) EMBO J 31:4258-75

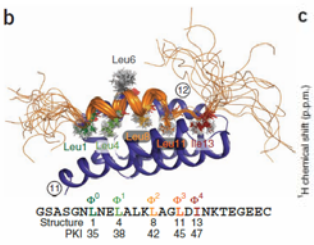


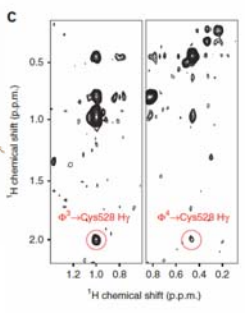
Modulation of the FUS-TRN interaction in cellular models and human FUSopathies.

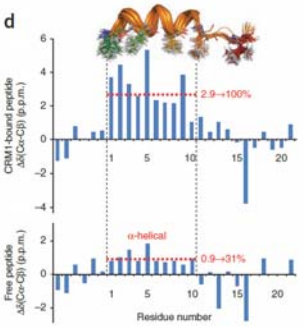


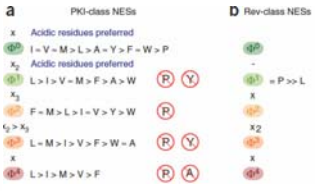
NMR analysis of the redox-dependent interaction of FOXO4 with TNPO1.
Redox-dependent control of FOXO/DAF 16 by Transportin-1. Putker et al. (2013) Mol Cell 49:730-42











Redefinition of the NES consensus.

Solution NMR structures of the CRM1-bound PKI Φ^0Leu NES.

NES consensus redefined by structures of PKI-type and Rev-type nuclear export signals bound to CRM1. Güttler et al. (2010) Nat Struct Mol Biol 17:1367-77

CURRICULUM VITAE

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Technische Universität München

Mag.Dr. Tobias Madl

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Personal data

Date of Birth:	July 1, 1980
Place of Birth:	Graz, Austria
Family status:	Married, 1 son (born May 2010)
Nationality:	Austrian

Short CV

Date of PhD	**24.09.2007**
02/2013-	Member of the Junior Scientist Program (Tenure Track position), Helmholtz Zentrum Munich (HMGU), Germany
09/2012-	Emmy Noether research group leader, Helmholtz Zentrum Munich, Germany
07/2012-	BioSysNet research group leader & TUM Junior Fellow, Technical University Munich, Germany
2012	APART fellow at Utrecht University, The Netherlands and University Graz, Austria
2010-2011	PostDoc with Prof. Rolf Boelens, Utrecht University, The Netherlands
2007-2010	PostDoc with Prof. Michael Sattler, Technical University and Helmholtz Zentrum Munich, Germany
2007	PostDoc with Prof. Klaus Zangger, University Graz, Austria
2004-2007	PhD thesis with Prof. Dr. Klaus Zangger, University Graz, Austria

Group members

Benjamin Bourgeois (PD, since 2013)	Regulation of nuclear import by arginine-glyicine-glycine repeats
Christoph Göbl (PD, since 2012)	Redox-regulated nuclear import
Henry Hocking (PD, since 2012)	Regulation of FOXO transcription factor activity
Sandra Scanu (PD, since 2013)	Detection and modeling of residual structure in disordered proteins
Christoph Hartlmüller (PhD, since 2012)	Integrated approaches for bio-molecular structure calculation
Martin Viertler (PhD, since 2013)	Molecular mechanisms of Wnt signaling
Hannah Adebar (Technician, since 2013)	Technical assistance
Moritz Resch (HiWi, since 2013)	Regulation of nuclear import by arginine-glyicine-glycine repeats

FULL CV

Work Experience

2013-	Member of the Junior Scientist Program (Tenure-Track position), Helmholtz Zentrum Munich
2012-	**Emmy Noether research group leader**, Helmholtz Zentrum Munich
2012-	**BioSysNet research group leader & TUM Junior Fellow**, TU Munich
2012	**APART fellow** at Utrecht University, The Netherlands and University Graz, Austria
2010-2011	**PostDoc** with Prof. Rolf Boelens at Utrecht University, The Netherlands
2009-	**Visiting scientist** at the synchrotrons ESRF Grenoble/France & DESY Hamburg/Germany
2006-	**Visiting scientist** at Bruker Biospin, Karlsruhe, Germany
2007-2010	**PostDoc** with Prof. Michael Sattler, Helmholtz Zentrum and TU Munich
2007	**PostDoc** with Prof. Klaus Zangger, University Graz, Austria
2006-2007	**Industrial research** for Sanochemia Pharmazeutika AG, Graz, Austria.
2003-2007	**(Grant funded) industrial research** for Biodiesel International Ltd., Graz, Austria.
2001-2005	**Research assistant** with Prof. Martin Mittelbach, University of Graz
1999-2000	**Laboratory assistant**, "Blocklabor II", Landeskrankenhaus Graz (hospital), Austria

Education

2004-2007	**PhD thesis** with Prof. Klaus Zangger at the Institute of Chemistry, University of Graz, Austria. *Thesis title: Structural and Dynamic Investigations on the bacterial ccd killing system.*
2003-2004	**Diploma thesis** with Prof. Dr. Martin Mittelbach.at the Institute of Chemistry, University of Graz, Austria. *Thesis title: Mass Spectrometric and NMR Studies on the Triterpene Saponins of Chenopodium quinoa Willd.*
2002,2004	**First Diplomas** within the enrolled programs (comparable to Bachelor of Science).
1999-2000	Interruption of the studies due to the **alternative civilian service** at the laboratory of the Landeskrankenhaus Graz (hospital), Austria
1998-2004	**Diploma Studies** in Chemistry, Physics and History (teachership) at the University Graz, Austria
1998	**Matura (final High School Exam)**, Graz, Austria

Scholarships, Prizes, awards (selection)

2012	**Science Award** of the Austrian Chemical Society
	APART fellowship of the Austrian Academy of Sciences (ÖAW)
2008	**PhD Prize** of the Austrian Chemical Society
	EMBO Long Term Fellowship (LTF)
	Schrödinger Fellowship of the Austrian Science Fund (FWF)
2007	**PhD finished with highest distinction** ("Mit Auszeichnung bestanden", average grade 1.0)
2005	**DOC scholarship** of the Austrian Academy of Sciences (ÖAW).
1998	**Final high school exam** passed with highest distinction ("Ausgezeichnetem Erfolg")

Invited Talks (selection, last 5 years)

2014	From Functional Genomics to Systems Biology (Munich, Germany)
	BIT's 7th Annual World Protein & Peptide Conference (Dalian, China)
	8th NMR Winter Retreat Parpan (Parpan, Switzerland)
2013	15th Austrian Chemistry Days (Graz, Austria)
	EUROMAR 2013 Conference (Hersonissos, Greece)
	Ringberg meeting (Ringberg, Germany)
2012	XXVth ICMRBS (Lyon, France)
2011	CHAINS Conference (Maarssen, The Netherlands)
	EMBO Fellows Meeting (Heidelberg, Germany)
	Elite Network of Bavaria (Munich, Germany)
	Bio-NMR and EAST-NMR Annual User Meeting (Brno, Czech Republic)
2010	2nd CCPN/Extend-NMR conference (Joachimsthal, Germany)
	Joint EUROMAR 2010 and 17th ISMAR Conference (Florence, Italy)
	4th EU-NMR Annual User Meeting (Egmond, The Netherlands)

Current collaborations & International activities (Selection)

Prof. J. Buchner	Biotechnology, TU München, Germany on large chaperone complexes
Prof. S. Sieber	Organic Chemistry II, TU München, Germany on the regulation of large bacterial proteases
Prof. M. Zacharias	Biomolecular Dynamics, TU München, Germany: molecular modeling of disordered proteins and protein folding
Prof. C. Haass	Medical Faculty, LMU Munich, Germany, on nuclear import of proteins involved in neurodegenerative diseases
Prof. B. Burgering	Molecular Cancer Research, University Medical Center Utrecht, The Netherlands, on signal
Prof. T.Dansen	transduction (FOXO, TCF/LEF, oxidative stress)
Prof. M. Maurice	Cell Biology, University Medical Center Utrecht, The Netherlands, on the biology of the Wnt signaling pathway (Axin, APC, ß-catenin, GSK3ß, Dvl).
Prof. S. Rüdiger	Bijvoet Center, Utrecht University, The Netherlands, on the Wnt signaling pathway (APC) and molecular chaperones (Hsp90).
Marie Curie ITN	Innovative Doctoral Programme - 2012-2016 - Manipulating folding, assembly and disassembly of protein complexes - "ManiFold" Manifold (Associated Partner)
Founding member	of the Young BioNMR Group

Teaching and academic activities

2014- **Invited speaker** at the EMBO Practical Course "The structural characterization of macromolecular complexes"

TU & Helmholtz Zentrum Munich

- *Lecturer at the "Vortragsseminar Biochemie" (Biochemistry seminar)*

2013- **TU & Helmholtz Zentrum Munich**

- *Lecturer at the HELENA graduate school*

Thesis committee member

- David Minde (Rüdiger group, Utrecht University), Marrit Putker (Burgering/Dansen groups, University Medical Center Utrecht), Gabriel Wagner (Zangger group, University Graz), Janine Weber (Niessing group, Helmholtz Zentrum München), Dzana Pasalic (Buchner group, TUM), Zaiyong Zhang (Lange group, TUM)

2012- **TU & Helmholtz Zentrum Munich**

- *Supervisor Student's, PhD's, PostDoc's Research Projects* (Kristin Hirschberger (S), Moritz Resch (S), Deniz Kobell (S), Christoph Hartlmüller (PhD), Martin Viertler (PhD), Christoph Göbl (PD), Henry Hocking (PD), Sandra Scanu (PD), Gabriel Wagner, Benjamin Bourgeois (PD))
- *Lecturer at the NMR seminar*

EMBO lab management course

2011 **Utrecht University**

- *Lecturer at the Molecular and Cellular Life-Sciences masters course – Biophysics*
- *Supervisor Master's Research Project* (Robbert Kim, Mohamed Kaplan)
- *Supervisor Exchange Student's Research Project* (Christoph Hartlmüller, 3 months, funded by the Studienstiftung des Deutschen Volkes)

2010 **Utrecht University**

- *Lecturer at the Molecular and Cellular Life-Sciences masters courses - Structural Biology & Molecular Recognition*

TU & Helmholtz Zentrum Munich

- *Instructor at EMBO Practical Course* "Structure, dynamics and function of biomacromolecules by solution NMR"

Since 2007 **TU & Helmholtz Zentrum Munich**

- *Organizer and lecturer of the advanced NMR seminar course at the TU Munich*
- *Lecturer at the TU Munich in NMR and Structural Biology*
- *Co-supervisor PhD's and PostDoc's Research Projects in the Sattler group* (Kostas Tripsianes, Irina Anosova, Alex Beribisky, Divita Garg, Hamed Kooshapur, Helge Meyer, Ulrike Schütz, Yun Zhang)

Funding (since 2008, ongoing projects are shown bold)

BayIntAn, Bayerisches Staats-ministerium für Wissenschaft, Forschung und Kunst	Dissecting the complex mechanisms of transcription factor activation	Jan 2013-Dec 2013	2 k€
Emmy Noether MA 5703/1-1	**Deciphering the regulatory code of transcription**	**Sep 2012-Aug 2017**	**992 k€**
BioSysNet, Bayerisches Staats-ministerium für Wissenschaft, Forschung und Kunst	**Order to Protein Disorder**	**Jul 2012 – Jun 2017**	**1.485 k€**
APART (ÖAW)	Exploring the molecular basis for FOXO's tumor suppressive potential	Jan 2012 – Aug 2012	273 k€
EMBO long-term fellowship	Quaternary structure of 3' splice site recognition	Aug 2008– Jul 2012	92 k€
Schrödinger fellowship of the Austrian Science Fund	Quaternary structure of 3' splice site recognition during spliceosome assembly	Apr 2008– Jul 2008	85k€

Miscellaneous

Reviewer for Angewandte Chemie, Journal of the American Chemical Society, Biochemistry, FEBS Letters, Fonds Wetenschappelijk Onderzoek (FWO), etc.

Co-organization of International conferences

- 35th FGMR Discussion Meeting and Joint Conference, Frauenchiemsee, Germany, September 2013

References

Prof. Michael Sattler
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PUBLICATIONS

Journal Articles (peer-reviewed; h-factor: 13, citations: 482 *according to ISI web of knowledge, 05.05.2014*)

1. Huang J.R., Warner L.R., Sanchez C., Gabel F., **Madl T.**, Mackereth C.D., Sattler M., Blackledge M., Transient electrostatic interactions dominate the conformational equilibrium sampled by multi-domain splicing factor U2AF65: A combined NMR and SAXS study, ***Journal of the American Chemical Society*** (2014) **in press**
2. Lorenz O., Freiburger F., Rutz D., Krause M., Zierer B., Alvira A., Cuéllar J., Valpuesta J.M., **Madl T. (co-corresponding author)**, Sattler M., Buchner J., Modulation of the Hsp90 chaperone cycle by a stringent client protein, ***Molecular Cell*** 53 (2014) 941-953
3. Karagöz G.E., Duarte A.M.S., Akoury E., Ippel H., Biernat J., Luengo T.M., Radli M., Didenko T., Nordhues B.A., Veprintsev D.P., Dickey C., Mandelkow E., Zweckstetter M., Boelens R., **Madl T. (co-corresponding author)**, Rüdiger S.G.D., Hsp90-Tau complex reveals molecular basis for specificity in chaperone action, ***Cell*** 156 (2014) 963-974
4. Neuhaus A., Kooshapur H., Wolf J., Meyer H.N., **Madl T.**, Saidowsky J., Hambruch E., Lassam A., Jung M., Sattler M., Schliebs W., Erdmann R., A novel Pex14 interacting site of human Pex5 is critical for matrix protein import into peroxisomes. ***Journal of Biological Chemistry*** 289 (2014) 437-448
5. Müller R., Gräwert M.A., Kern T, **Madl T.**, Peschek J., Sattler M., Groll M., Buchner J., High Resolution Structures of the IgM Fc Domains Reveal Principles of its Hexamer Formation, ***Proceedings of the National Academy of Sciences U.S.A.*** 110 (2013), 10183- 10188
6. Hocking H.G., Zangger K., **Madl T. (corresponding author, COVER ARTICLE)**, Studying structure and dynamics of biomolecules using soluble paramagnetic probes, ***ChemPhysChem*** 14 (2013), 3082-3094
7. Putker M., **Madl T.**, Vos H.R., de Ruiter H., Visscher M., van den Berg M.C.W., Kaplan M., Korswagen H.C., Boelens R., Vermeulen M., Burgering B.M.T., Dansen T.B., Redox-dependent control of FOXO/DAF-16 by transportin-1, ***Molecular Cell*** 49 (2013), 730-742
8. Zhang Y., **Madl T. (shared first author, co-corresponding author)**, Bagdiul I., Kern T. Kang H.-S., Zou P., Mäusbacher N., Sieber S.A., Krämer A., Sattler M., Structure, phosphorylation and U2AF65 binding of the N-terminal domain of splicing factor 1 during 3' splice site recognition, ***Nucleic Acids Research*** 41 (2012), 1343-1354
9. Dormann D., **Madl T.**, Valori C.F., Bentmann E., Tahirovic S., Abou-Ajram C., Kremmer E., Ansorge O., Mackenzie I.R.A., Neumann M., Haass C., Arginine methylation next to the PY-NLS modulates Transportin binding and nuclear import of FUS, ***EMBO Journal*** 12 (2012), 4258-4275
10. Tavanez J.P., **Madl T.**, Kooshapur H., Sattler M., Valcárcel J., hnRNP A1 proofreads 3' splice site recognition by U2AF, ***Molecular Cell*** 45 (2012), 314-329
11. Tripsianes K., **Madl T.**, Machyna M., Fessas D., Englbrecht C., Fischer U., Neugebauer K.M., Sattler M., Structural basis for dimethyl-arginine recognition by the Tudor domains of SMN and SPF30, ***Nature Structural and Molecular Biology*** 18 (2011), 1414-1420
12. Mackereth C.D., **Madl T.**, Bonnal S., Simon B., Zanier K., Gasch A., Rybin V., Valcárcel J. and Sattler M., Multi-domain conformational selection underlies polypyrimidine recognition by U2AF and pre-mRNA splicing, ***Nature*** 475 (2011), 408-411
13. **Madl T.**, Güttler T., Görlich D., Sattler M., Structural Analysis of Large Protein Complexes using Solvent Paramagnetic Relaxation Enhancements, ***Angewandte Chemie*** 50 (2011), 3993-3997
14. **Madl T.**, Gabel F., Sattler M., NMR and Small Angle Scattering-based structural analysis of protein complexes in solution, ***Journal of Structural Biology*** 173 (2011), 472-482
15. Güttler T., **Madl T. (shared first author)**, Neumann P., Deichsel D., Corsini L., Monecke T., Ficner R., Sattler M., Görlich D., Structural basis for the recognition of diverse nuclear export signals by the exportin CRM1, ***Nature Structural and Molecular Biology*** 17 (2010), 1367-1376
16. Meyer H., Tripsianes K., Vincendeau M., **Madl T.**, Kateb F., Brack-Werner R., Sattler M., Structural basis for homodimerization of the Src-associated during mitosis, 68 kD protein (Sam68) Qua1 domain, ***Journal of Biological Chemistry*** 285 (2010), 28893-28901
17. **Madl T.**, Felli I.C., Bertini I., Sattler M., Structural analysis of protein interfaces from ^{13}C direct-detected paramagnetic relaxation enhancements, ***Journal of the American Chemical Society*** 132 (2010), 7285-7287
18. Simon B., **Madl T.**, Mackereth C.D., Nilges M., Sattler M., An Efficient Protocol for NMR-Spectroscopy-Based Structure Determination of Protein Complexes in Solution, ***Angewandte Chemie*** 49 (2010), 1967-1970
19. Spirk S., Belaj F., **Madl T.**, Pietschnig R., A Radical Approach to Hydroxylaminotrichlorosilanes: Synthesis, Reactivity, and Crystal Structure of TEMPO-SiCl3 (TEMPO = 2,2,6,6-Tetramethylpiperidine-N-oxyl), ***European Journal of Inorganic Chemistry*** 2 (2010), 289-297
20. **Madl T.**, Bermel W., Zangger K.: Use of Relaxation Enhancements in a Paramagnetic Environment for the Structure Determination of Proteins Using NMR Spectroscopy, ***Angewandte Chemie*** 48 (2009), 8259-8262
21. **Madl T.**, Sattler M.: Adhesion dance with raver, ***Structure*** 17 (2009), 781-783

22. Zangger K., Respondek M., Göbl C., Hohlweg W., Rasmussen K., Grampp G., **Madl T.**: Positioning of micelle-bound peptides by paramagnetic relaxation enhancements, ***Journal of Physical Chemistry B*** 113 (2009) 4400-4406
23. Traar P., Rumpler A., **Madl T.**, Saischek G., Francesconi KA.: Synthesis of Naturally Occurring Arsenic-Containing Carbohydrates, ***Australian Journal of Chemistry*** 6 (2009), 538-545
24. Neufeld C., Filipp FV., Simon B., Neuhaus A., Schüller N., David C., Kooshapur H., **Madl T.**, Erdmann R., Schliebs W., Wilmanns M., Sattler M..: Structural basis for competitive interactions of Pex14 with the import receptors Pex5 and Pex19, ***EMBO Journal*** 28 (2009) 745-754
25. Spirk S.**, Madl T.**, Pietschnigg R., Relax with TEMPO: A Paramagnetic Relaxation Agent Useful also for Silicon-29 NMR Spectroscopy, ***Organometallics*** 27 (2009), 500-502
26. Respondek M., **Madl T.**, Gobl C., Golser R., Zangger K., Mapping the Orientation of Helices in Micelle-Bound Peptides by Paramagnetic Relaxation Waves, ***Journal of the American Chemical Society*** 129 (2007), 5228-5234
27. **Madl T**., Van Melderen L., Mine N., Respondek M., Oberer M., Keller W., Khatai L., Zangger K., Structural basis for nucleic acid and toxin recognition of the bacterial antitoxin CcdA, ***Journal of Molecular Biology*** 364 (2006), 170-185 (**COVER ARTICLE**)
28. **Madl T. (corresponding author)**, Sterk H., Rechberger G.N., Mittelbach M., Tandem mass spectrometric analysis of a complex triterpene saponin mixture of Chenopodium quinoa, ***Journal of the American Society for Mass Spectrometry*** 17 (2006), 795-806
29. **Madl T. (corresponding author)**, Mittelbach M., Quantification of primary fatty acid amides in commercial tallow and tallow fatty acid methyl esters by HPLC-APCI-MS, ***The Analyst*** 130 (2005), 565-570

Book Chapters

1. **Madl T.**, Sattler M., NMR tools and the analysis of protein-protein interactions, in: NMR of Biomolecules: Towards Mechanistic Systems Biology, Wiley-VCH Verlag GmbH & Co, 2012

Journal Articles (not peer-reviewed)

1. **Madl T.**, Integration von NMR und SAXS/SANS in der Strukturbiologie**,** ***BIOspektrum*** *19* (2013) 386-389
2. Markley J.L., Akutsu H., Asakura T., Baldus M., Boelens R., Bonvin A., Kaptein R., Bax A., Bezsonova I., Gryk M.R., Hoch J.C., Korzhnev D.M., Maciejewski M.W., Case D., Chazin W.J., Cross T.A., Dames S., Kessler H., Lange O., **Madl T.**, Reif B., Sattler M., Eliezer D., Fersht A., Forman-Kay J., Kay L.E., Fraser J., Gross J., Kortemme T., Sali A., Fujiwara T., Gardner K., Luo X., Rizo-Rey J., Rosen M., Gil R.R., Ho C., Rule G., Gronenborn A.M., Ishima R., Klein-Seetharaman J., Tang P., van der Wel P., Xu Y., Grzesiek S., Hiller S., Seelig J., Laue E.D., Mott H., Nietlispach D., Barsukov I., Lian L.Y., Middleton D., Blumenschein T., Moore G., Campbell I., Schnell J., Vakonakis I.J., Watts A., Conte M.R., Mason J., Pfuhl M., Sanderson M.R., Craven J., Williamson M., Dominguez C., Roberts G., Günther U., Overduin M., Werner J., Williamson P., Blindauer C., Crump M., Driscoll P., Frenkiel T., Golovanov A., Matthews S., Parkinson J., Uhrin D., Williams M., Neuhaus D., Oschkinat H., Ramos A., Shaw D.E., Steinbeck C., Vendruscolo M., Vuister G.W., Walters K.J., Weinstein H., Wüthrich K., Yokoyama S., In support of the BMRB, ***Nature Structural and Molecular Biology*** 19 (2012), 854-860
3. **Madl T.**, Sattler M., Strukturaufklärung von Proteinkomplexen in Lösung, ***Laborpraxis*** (2010)