H. Waldmann

*H. Waldmann has recently published his **50th article** since 2000 in Angewandte Chemie:*
"Synthesis of the Rheb and K-Ras4B GTPases": Y.-X. Chen, S. Koch, K. Uhlenbrock, K. Weise, D. Das, L. Gremer, L. Brunsveld, A. Wittinghofer, R. Winter, G. Triola, H. Waldmann, *Angew. Chem.* **2010**, *122*, 6226–6231; *Angew. Chem. Int. Ed.* **2010**, *49*, 6090–6095.

Herbert Waldmann

Date of birth:	June 11, 1957
Position:	Director at the Max-Planck-Institut für Molekulare Physiologie, Dortmund and Professor of Biochemistry at the Technische Universität Dortmund (Germany)
E-mail address:	herbert.waldmann@mpi-dortmund.mpg.de
Homepage:	www.mpi-dortmund.mpg.de/ueberInstitut/Struktur/Direktoren/Waldmann/index.html
Education:	1976–1985 Studies of Chemistry and PhD in Organic Chemistry under the guidance of Horst Kunz at the Johannes-Gutenberg-Universität Mainz (Germany) 1985–1986 Postdoctoral fellow with George Whitesides at Harvard University, Cambridge, Massachusetts (USA) 1986–1991 Habilitation at the Johannes-Gutenberg-Universität Mainz (Germany)
Awards since 2000:	2001: Otto Bayer Award; 2003: Max Bergmann Medal; 2004: F. C. Donders Professorship, Utrecht; 2004: President of the Bürgenstock Conference; 2004: Member of the "Deutsche Akademie der Naturforscher Leopoldina, Halle/Saale"; 2005: Fellow of the Royal Society of Chemistry; 2006: GlaxoSmithKline Award for Outstanding Achievement in the field of Chemical Biology; 2009: Member of the NRW Akademie der Wissenschaften und der Künste; 2009: Member of the Akademie der Wissenschaften und der Literatur, Mainz; 2010: Hans-Herloff Inhoffen Medal
Current research interests:	We work in three major fields at the chemistry–biology interface. We develop a logic to chart chemical space and to identify biologically relevant compound classes. This logic leads to synthesis programs, in which novel methods are developed that are used to synthesize natural-product-inspired compound collections, which are investigated in biochemical and cell-based assays. We identify and validate the cellular targets of active molecules. My research group develops novel methodologies for the synthesis of lipid-modified peptides and proteins, in particular GTPases like Ras, Rabs, and RheB. These proteins are utilized to gain new insight into signal transduction and vesicular transport. Finally, we develop novel methodologies for protein ligation and immobilization and apply them to the preparation of protein biochips and microarrays.
Hobbies:	I like to read crime stories and to watch science fiction movies.

The biggest problem that scientists face is … to repeatedly come up with good ideas in the course of their entire career.

The greatest scientific advance in the next decade will be … the development of personalized medicine.

Looking back over my career I would change … the research topics I worked on during my Habilitation; I would choose much riskier topics.

My greatest achievement has been … the systematic analysis of all natural products known and the use of this analysis to guide organic synthesis for biological research; these results are door openers.

My most exciting discovery to date has been … the regulation of the dynamic Ras cycle (in cooperation with Philippe Bastiaens), because it gave truly novel insights and marked the culmination of a 20-year research program on Ras proteins.

The secret of being a successful scientist is … to be rich in creative ideas, to boldly tackle them, to differentiate the doable from the unreachable, and to consistently work at 95% of your personal capacity. In other words: inspiration, motivation, transpiration.

The best advice I have ever been given is … to search and meet major challenges and unsolved problems and not to focus on one asymmetric synthesis after the other.

What I enjoy the most about my job are … the singular moments of discovery and first insight.

My favorite dishes are … many—too many to be listed. I like to eat and to drink (who doesn't?), and my wife is an excellent cook. A choice would be: appetizer: half a dozen of oysters Fine de Claire; 2nd course: risotto with truffles from Piemonte; main course: dry aged filet Mignon, rare or bistecca Fiorentina; finally: well-aged Munster cheese with overripe Gewürztraminer grapes. The wines suggest themselves, but Cloudy Bay, Cà dei Frati Lugana, Montes Alpha, and an Alsacian Gewürztraminer Grand Cru would do well.

My favorite song is … "Jump" by Van Halen, which I like to listen to at full volume and at 200 km/h in my red roadster.

How is chemistry research different now than it was at the beginning of your career?

Analytical techniques like high-field NMR spectroscopy and modern mass spectrometry, as well as powerful separation techniques have changed the way we carry out research. When I was graduating in glycopeptide chemistry with Horst Kunz, we initially had chromatography columns with a length of 2 m, and a single run would take all night or even the entire weekend. The initial NMR instruments were a 60 MHz continuous wave Jeol or a 90 MHz FT Bruker, and getting a ^{1}H or ^{13}C NMR spectrum would frequently last several days. Today separations are done within hours, NMR spectra are available within hours or at most a day, and hands-on mass spectrometers are standard lab equipment. This development has made chemistry research much faster and more competitive, which does not mean, however, that it is harder today than it was 25 years ago to conduct good research.

Has your approach to chemistry research changed since the start of your career?

I always have been and always will be a preparative organic chemist, a "molecule maker". Our synthetic endeavors have always been related to biological problems or have had a biological background. However, our research programs have evolved significantly, and today truly integrate biochemistry and biology. Being a chemist used to precise analytical techniques, I needed to learn and appreciate that biological results often are more approximative and uncertain in character.

Has your approach to publishing your results changed since the start of your career?

No, in principle it hasn't changed. We try to conduct good research and to publish it in top journals. Today I keep much calmer when we obtain negative reviews and I always take a positive attitude towards them. In my experience the reviewers often (although not always) are not "enemies", and their advice has helped me in many cases to improve the quality of our papers. Caused by the evolution of my group's research programs, we publish more in interdisciplinary journals.

What do you think the future holds for your field of research?

Science is always a wide and open field if one is willing and able to accept and be inspired by its everchanging face and to venture into new areas. Those who get stuck, remain rigid, and believe that their current research will and must prevail for the coming decades, will fall behind. The utilization of chemistry to gain insight into biological phenomena is not new, but the preconditions to carry out such interdisciplinary work have changed during the last decades. We now have full access to advanced synthesis methodologies as well as proteomics, molecular biology, imaging technology, biophysics, and notably hard- and software to analyze the results. Among others it is for these reasons that the field has gained major interest since the mid-nineties. The future will be bright and open; most importantly, there is no reason why chemists should not play the leading role (!) in chemical biology research.

Have you changed the main focus of your research throughout your career and if so why?

The fundamental approach became clear after my Habilitation. Since then the major thrust has remained constant but has been split up in very different directions. By and large the reserach group has evolved from a strictly chemical research group to a truly interdisciplinary team that develops and employs small-molecule chemistry, cheminformatics, protein chemistry, biochemistry, proteomics, and cell biology.

What has been your biggest influence/motivation?

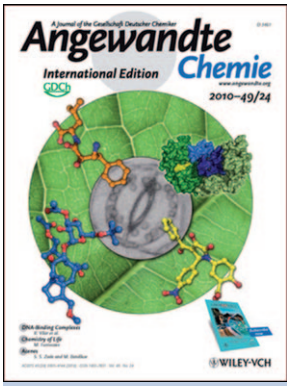
The scientific daringness, the demand, and scientific rigor of my mentor Horst Kunz and his mentor Leopold Horner, the wide-ranging interests and scientific openness of George Whitesides, and the enthusiasm of Helmut Ringsdorf set examples that influence me to this very day. They are fearless researchers asking big questions. Their examples combined with the "lightheartedness", the easy way of living in Rheinland, where I grew up, shaped my approach to science and how to combine the preciseness of chemical methodology with the approximating character of biological methods. Later Stuart Schreiber's work on the chemistry and biology of FK506 and Rapamycin was a source of inspiration to me.

What advice would you give to up-and-coming scientists?

Be fearless and don't be shy to attack major problems and challenges, even if they lie outside your current expertise. Remain true to yourself, good science will be recognized and rewarded.

What is the secret to publishing so many high-quality papers?

Good science will lead to good papers that will be published in good journals. For good science one needs: 1) good ideas, 2) good students and postdocs, 3) good money. Whoever reverses this order is doomed to fail. Even the best money will not guarantee good science if it isn't used for research based on good ideas carried out by good scientists. For publishing papers it is additionally important to communicate well. A good paper (like a good lecture) tells an interesting story. Don't be discour-



H. Waldmann has been featured on the cover of Angewandte Chemie
"Identification and Structure of Small-Molecule Stabilizers of 14–3–3 Protein–Protein Interactions": R. Rose, S. Erdmann, S. Bovens, A. Wolf, M. Rose, S. Hennig, H. Waldmann, C. Ottmann, *Angew. Chem.* **2010**, *122*, 4223–4226; *Angew. Chem. Int. Ed.* **2010**, *49*, 4129–4132.

aged by negative reviewers and try to have a positive attitude toward their comments. Usually, they will be helpful. Don't give up readily if you have good arguments, they are worth a fight, even if you finally may loose it. I recall at least one case in which I initially had recommended "reject" to the Angewandte Editor, and upon having read the rebuttal and the revised manuscript I admitted having made a mistake and recommended acceptance.

My 5 top papers:

1. "Natural Products are Biologically Validated Starting Points in Structural Space for Compound Library Development: Solid-Phase Synthesis of Dysidiolide-Derived Phosphatase Inhibitors": D. Brohm, S. Metzger, A. Bhargava, O. Müller, F. Lieb, H. Waldmann, *Angew. Chem.* **2002**, *114*, 319–323; *Angew. Chem. Int. Ed.* **2002**, *41*, 307–311.
   This paper was one of the first publications to demonstrate that natural products and compounds of similar structural complexity ("natural product inspired" we termed them later) can be synthesized in the format of compound library synthesis, including asymmetric transformations. I consider the paper important because it proved that compound library development and natural product synthesis are not contradictions. The paper argues against one of the major decisions in the pharmaceutical industry at the time, namely to abandon natural products in medicinal chemistry because they are too complex for drug discovery.
2. "Oriented Immobilization of Farnesylated Proteins by the Thiol-Ene Reaction": D. Weinrich, P.-C. Lin, P. Jonkheijm, U. T. T. Nguyen, H. Schröder, C. M. Niemeyer, K. Alexandrov, R. Goody, H. Waldmann, *Angew. Chem.* **2010**, *122*, 1274–1279; *Angew. Chem. Int. Ed.* **2010**, *49*, 1252–1257.
   This paper demonstrates the oriented, chemoselective, and site-specific immobilization of proteins equipped with a genetically encoded farnesylation tag directly from cell lysate without any isolation or purification. The publication is based on more than a decade of work in Dortmund (with Christof Niemeyer and Roger Goody) on prenylated proteins and on surface immobilization and ligation of proteins. It paves the way to conveniently generate protein biochips.
3. "Small-molecule inhibition of APT1 affects Ras localization and signaling ": F. J. Dekker, O. Rocks, N. Vartak, S. Menninger, C. Hedberg, R. Balamurugan, S. Wetzel, S. Renner, M. Gerauer, B. Schölermann, M. Rusch, J. W. Kramer, D. Rauh, G. W. Coates, L. Brunsveld, P. I. H. Bastiaens, H. Waldmann, *Nat. Chem. Biol.* **2010**, *6*, 449–456.
4. "The Palmitoylation Machinery Is a Spatially Organizing System for Peripheral Membrane Proteins ": O. Rocks, M. Gerauer, N. Vartak, S. Koch, Z.-P. Huang, M. Pechlivanis, J. Kuhlmann L. Brunsveld, A. Chandra, B. Ellinger, H. Waldmann, P. I. H. Bastiaens, *Cell* **2010**, *141*, 458–471.
   The latter two papers together demonstrate the dynamic regulation of the Ras cycle by means of reversible S-palmitoylation. They give entirely novel insight into one of the most important biological signal transduction processes and its regulation in space and time. The two papers represent the culmination of approximately two decades of research, which was initially focused on the chemistry of Ras peptides and proteins and then on the use of these proteins in biological research. They mark intense collaborations initially with Jürgen Kuhlmann and Fred Wittinghofer (see *Nature* **2000**, *403*, 223–226) and later with Philippe Bastiaens (see *Science* **2005**, *307*, 1746–1752). This insight was gained by combination of numerous experimental approaches, including inhibitor development by "BIOS" (see 5.). Similarly I could mention papers coauthored with Roger Goody and Kirill Alexandrov on the chemical biology of the Rab proteins, which tell an equally exciting story (see *Nat. Chem. Biol.* **2010**, *6*, 534–540 and *Science* **2003**, *302*, 646–650).
5. "Charting Biologically Relevant Chemical Space: A Structural Classification of Natural Products (SCONP)": M. A. Koch, A. Schuffenhauer, M. Scheck, M. Casaulta, A. Odermatt, P. Ertl, H. Waldmann, *Proc. Natl. Acad. Sci.* **2005**, *102*, 17272–17277.
   This paper introduces "The Natural Product Tree" or "The Periodic System of Natural Products" as Frankfurter Allgemeine Zeitung called it. It provides a systematic analysis of the structural diversity generated by evolution and ultimately led to the development of "biology-oriented synthesis" delineated for the first time in *Proc. Natl. Acad. Sci.* **2006**, *103*, 10606–10611. I regard these papers as important because they provide a construct of ideas to identify biologically relevant regions in vast chemical space, how to use this knowledge to guide synthesis and how to prospectively assign bioactivity to particular compound classes (see *Nat. Chem. Biol.* **2009**, *5*, 581–583, *Nat. Chem. Biol.* **2009**, *5*, 585–592 and *Angew. Chem.* **2010**, 122, 3748–3752; *Angew. Chem. Int. Ed.* **2010**, *49*, 3666).

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