PERSONAL INFORMATION

Mario van der Stelt, PhD
Professor and chair of Molecular Physiology, Leiden Institute of Chemistry, Leiden University, The Netherlands
ORCID: 0000-0002-1029-5717
Date of birth: 20-09-1975
Nationality: the Netherlands (NL)
www.universiteitleiden.nl/en/science/chemistry/molphys
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EDUCATION

2002 PhD (with highest distinction *cum laude* - top 5%)
Faculty of Science, Department of Bio-organic chemistry, Utrecht University, NL
1998 Master of Chemistry (with highest distinction *cum laude* - top 5%)
Faculty of Science, Utrecht University, NL

CURRENT POSITIONS

2024 Executive Board Member Institute of Chemical Neuroscience
2023 Member Program Board Oncode Accelerator
2022 Vice-scientific director Leiden Institute of Chemistry
2022 Workstream leader small molecule drug discovery OncodeAccelerator
2019 Principal Investigator Oncode Institute
2018 Professor of Molecular Physiology, Leiden University
2017 Founder and chair of the department of Molecular Physiology, Leiden University

PREVIOUS POSITIONS

2019 - 2024 Member Research Management Committee of Oncode Institute
2012 – 2017 Associate Professor of Medicinal Chemistry, dept. Bio-organic Synthesis, Leiden Institute of Chemistry Leiden University, NL
2004 – 2012 Group- and project Leader, dept. of Medicinal Chemistry, Merck Research Laboratories (former Organon), NL
2002 – 2004 Post-doctoral fellow, Institute of Bio-molecular Chemistry, Pozzuoli, Italy
Advisor: Prof. dr. V. Di Marzo (recognized as 'top scientist of the decade 2000-2010 for pharmacology and toxicology' by Thompson Reuters)

FELLOWSHIPS AND AWARDS

2024 Gravitation Award for Institute of Chemical Neuroscience
2022 Utrecht University Award for Excellence in Pharmaceutical Research
2019 Elected member of Oncode Institute
2018 VICI-award of the Dutch Research Council
2017 Prix Galien Research for best preclinical drug discovery research in the Netherland
2017 Young Investigator Award for best research in the field of (endo)cannabinoids by the International Cannabinoid Research Society (ICRS)
2005 Young Investigator Award for best research in the field cannabinoids by the International Association for Cannabis as Medicine
2003 Young Investigator Award from the European Society for Neuroscience
2001 Coy W. Waller Award, Madrid, Spain

SUPERVISION OF GRADUATE STUDENTS and POST-DOCTORAL FELLOWS

2012-2023 10 post-doctoral fellows, 32 PhD-students, 60 Master students

SELECTION OF TEACHING ACTIVITIES

2017 - present Coordinator and lecturer Chemical Biology (3 ECTS), BSc Life Science & Technology, Leiden University, NL
2014 - present Coordinator and lecturer Medicinal Chemistry & Drug Discovery (6 ECTS), Msc Chemistry, LU, NL
2020 Project coordinator Erasmus Plus International Mobility Credits
2019 Visiting Professor in Medicinal Chemistry, University of Rome, Italy
2016 Basis Certification Education (BKO)
2013 - 2018 Honors lecture (1 ECTS), Faculty of Science, Leiden University, NL
2012 - 2016 Lecturer Chemical Genetics (3 ECTS), Faculty of Science, Leiden University, NL

In total more than 1000 students have followed my courses in chemical biology and/or medicinal chemistry & drug discovery.

ORGANISATION OF SCIENTIFIC MEETINGS

2023 Member International Scientific Committee EFMC-International Symposium on Chemical Biology
2023 Chair of Gordon Research Conference on the Cannabinoid function in the Central Nervous System, Barcelona, Spain (co-chair: Prof. dr. M. Melis). Evaluated as a high performance meeting.
2021 Vice-chair of Gordon Research Conference on the Cannabinoid function in the Central Nervous System, Waterville, USA (chairs: Prof. dr. M. Hill and Prof. dr. S. Patel)
2018 Organizer Symposium of the International Cannabinoid Research Society, Leiden (550 participants; 33 countries)
2016 Member program committee CHAINS, largest chemistry conference NL, 1500 participants

FUNDING

2024 Gravitation Program Institute of Chemical Neuroscience
2023 ROADS Progam II
2022 OncodeAccelerator (National Growth Fund; Architect & coordinator small molecule drug discovery workstream,; Architect artificial intelligence platform)
2022 Oncode Institute Phase 2 (selected as Principal Investigator)
2020 ROADS-program I
2020 ErasmusPlus International Credit Mobility Project with Kiev
2020 Tech Development Fund, Oncode Institute
2020 MAGL in MS, Institute of Chemical Immunology
2019 Oncode Institute (selected as Principal Investigator)
2018 VICI, talent scheme of the Dutch Research Council
2018 NAVISTROKE, Dutch Research Council
2018 NACTAR, Dutch Research Council
2016 ZON-MW MiddelGroot
2015 OncoDrugs, Dutch Research Council
2015 Roche Post-doc Fellowship program
2015 Lipid signaling in immune cells, Institute of Chemical Immunology
2014 ECHO, Dutch Research Council
2014 European Lead Factory, Innovations Medicines Initiative)
2013 ECHO-STIP, Dutch Research Council

PROFESSIONAL MEMBERSHIPS and ACTIVITIES

2021 - present Member working group on Chemical Biology, European Federation Medicinal Chemistry
2021 - present Consulting Editor Medicinal Chemistry, British Journal of Pharmacology
2021 - present Board member section Medicinal Chemistry & Chemical Biology, Royal Dutch Chemistry Society
2018 - present Member Editorial Board Cannabis & Cannabinoid Research
2018 - present Section reviewer Concise guide to pharmacology, British Pharmacology Society
2018 - 2022 Member Chemistry-for-Life council, Dutch Research Council
2016 - present Board member Havinga Foundation
2015 - 2018 Board member study group medicinal chemistry, Dutch Research Council
2014 - present Scientific advisor for Hoffman-LaRoche & Scenic Biotech
2013 - present Reviewer/panel member funding organizations, PhD theses (NL, Belgium, Germany, Finland, Israel, Italy)
2012 - present Reviewer for scientific journals (e.g., ACS, Wiley-VCH, RSC, Elsevier and NPG journals)

FELLOWSHIPS and AWARDS FOR GRADUATE STUDENTS

Alexander Bakker, Best thesis in Medicinal Chemistry in the Netherlands 2021-2022 (2023), Aukje Beers, Unilever Research Prize (2023), Verena Straub, best poster prize ISEV symposium, Rome (2023), Daan van der Vliet, best poster prize Symposium on Lipids in Brain diseases, Leiden (2023); Jeroen Punt, Pfizer Prize 2nd best M.Sc-thesis in life science from KHMW (2022), Jara Bouman, best oral presentation at the ICRS-meeting Galway Ireland, (2022); Dr. E. Mock (Rubicon, 2021); Dr. M. Baggelaar, Best thesis in Medicinal Chemistry in the Netherlands 2017-2018 (2019), Marie Sklodoska-Curie Fellowship (2016); Dr. A. Janssen, public prize Young European Medicinal Chemistry Symposium EFMC, Slovenia (2018); Dr. T. van der Wel, best poster presentation Chemical Biology meeting EMBL, Germany (2018); Dr. Van Esbroeck, best oral presentation at British Pharmacological Society Meeting, London (2017), best oral presentation at the ICRS-meeting Montreal, Canada (2017); F. Janssen, Young European Medicinal Chemist of the Year, EFMC, Manchester (2016).

KEY OUTPUT PARAMETERS: www.universiteitleiden.nl/en/staffmembers/mario-van-der-stelt)

- Total Publications (> 150 in peer-review journals), book chapters (6), patent applications (granted): 10 (3)
- h-index (48); sum of citations (10588); Average citations per item (68) and 27 articles received > 100 citations
- Compounds developed in my lab, which are widely used by scientific community: CB2 receptor agonists (LEI-101, LEI-102); DAGL inhibitors (LEI-105, DH376); MAGL inhibitors (LEI-515), Activity-based probes (MB064, LEI-463 and LEI-945) and NAPE-PLD inhibitor (LEI-401)

RESEARCH PROFILE

Van der Stelt, an expert in the field of medicinal chemistry, is a full professor and chair of Molecular Physiology at Leiden University. By developing and integrating innovative chemical biology tools and concepts in medicinal chemistry, he aims to innovate the drug discovery process with the ultimate goal to efficiently discover clinical candidates for cancer and brain disorders to improve human health. He draws from his experience as a project leader at Merck Research Laboratories (2004-2011), where he led drug discovery programs in various therapeutic areas, including neuroscience and cancer, for several target proteins, such as G Protein-coupled receptors (GPCRs) and kinases.

Approximately only one out of ten clinical candidates currently reaches the market. Most compounds fail due to a lack of efficacy or unexpected off-target toxicity in clinical trials. Information on target engagement at a certain concentration will help to select the best molecule as a drug candidate and may guide the dose selection by providing information on full target engagement, while minimizing the risk for untoward off-target interactions by preventing overexposure. This information is, however, often lacking for many drug discovery programs, due to a dearth of chemical tools and methods to establish target engagement in human cells. At Leiden University Van der Stelt and his team develop chemical probes to interrogate biological systems in (inter)national collaborations. Activity-based proteomic and chemical genetic strategies are used to determine on- and off-target profiles for compounds and to identify drugable targets in a cellular or in vivo context.

A first example of the integration of chemical biology concepts into drug discovery is his work on the fatty acid amide hydrolase (FAAH) inhibitor BIA 10-2474, an experimental drug developed by a Portuguese company, that caused the death of a volunteer in a phase 1 clinical trial in France in 2016. By using activity-based proteomics and targeted lipidomics in human cortical neurons and human brain tissue his lab discovered that BIA 10-2474 was a non-selective compound that interacted with several lipases and disrupted lipid homeostasis [**Key output 1-2**]. These findings were instrumental in the decision-making process to resume clinical trials with other safe FAAH inhibitors, which are currently being tested in major depressive disorder, social anxiety disorder and post-traumatic brain disorders. For this work, Van der Stelt received the prestigious Prix Galien Research Award for best preclinical drug discovery research in the Netherlands (2017). The impact of this technology is also witnessed by several collaborations he has established with small biotech start-up and large pharmaceutical companies to guide their drug optimization programs. This led to successful identification of a clinical candidate, which is currently tested in phase 1 clinical trials.

A second example is the application of activity-based proteomics to guide the discovery of best-in-class ligands to investigate and validate the (patho)physiological function of proteins in lipid signaling [**Key output 3-5**]. He identified LEI-515 as the first orally bioavailable, peripherally restricted monoacylglycerol lipase inhibitor that showed thereapeutic efficacy in chemotherapy-induced neuropathic pain without inducing psychotropic side effects or dependence. LEI-515 represents a novel chemotype that acts as a new class of non-steroidal, anti-inflammatory analgesics without inducing CNS side effects [**Key output 4**]. He also discovered brain active inhibitors of proteins responsible for the biosynthesis and metabolism of the endocannabinoids, thereby establishing the biological role of these lipid neurotransmitters in emotional behavior and neuroinflammation [**Key output 6-9**]. For this work, funded by a VICI-grant from the talent scheme of Dutch Research Council, he received the Young Investigator Award from the International Cannabinoid Research Society (2017) and the Utrecht University Award for Excellence in pharmaceutical research (2022).

A third example is the discovery of the first-in-class bifunctional probes for the profiling of GPCRs, lipid signaling and aldehyde dehydrogenases (ALDHs) [**Key output 10-12**]. An important step that drives the drug discovery process is the determination of the cellular expression profile and engagement of the target protein in humans. This provides a challenge for the study of GPCRs and ALDHs, because they are usually expressed at very low levels in a dynamic manner in cells and tissues. Furthermore, GPCRs lack a catalytically nucleophilic amino acid that can be targeted by activity-based probes, thus rendering them inaccessible for activity-based protein profiling. Van der Stelt addressed this problem by designing and synthesizing a photoreactive probe equipped with a strategically positioned ligation tag for the introduction of reporter groups. In this manner he was the first to monitor the expression and engagement of the cannabinoid CB2 receptor, a promising GPCR to treat tissue injury and inflammatory diseases, upon photoactiviation in primary human immune cells using flow cytometry. The paper was highlighted by the editors and placed on the cover of JACS. Likewise, he developed a photoaffinity-based probe based on an oxidative metabolite of an ω-3 fatty acid and identified prostaglandin reductase-1 as a key metabolic hub in human macrophages [**Key output 10**]. ALDHs constitute a class of 19 enzymes responsible for detoxification of anti-cancer drugs and are upregulated as a resistance mechanism. No biochemical methods are available to detect specific aldehyde dehydrogenase activity in cells. Van der Stelt developed a first-in-class bifunctional, substrate-based probe that allowed to detect individual ALDH activities in breast cancer cells [**Key output 11**]. Furthermore, recently he applied ABPP to discover the antibiotic targets of oxadiazolones in MRSA and discovered a new allosteric antibiotic targeting DNA gyrase [**Key output 12-13**]. Together, these publications demonstrate the power of chemical probes to uncover new biology and serve as tools for target validation.

A fourth example is the development of a chemical genetics strategy to selectively study engagement of endogenously expressed kinases [**Key output 14**]. Kinases belong to a large druggable protein family for the treatment of cancer and autoimmune diseases, but the clinical development of kinase inhibitors is hampered by off-target effects and the difficulty establishing a causal relationship between on-target inhibition and phenotype. By substituting a serine residue into cysteine in the ATP-binding pocket, a kinase was sensitized towards covalent labeling by a complementary fluorescent chemical probe. The mutation was introduced in the genome of human cells by gene editing. Leveraging the temporal and acute control offered by the strategy, a key role for the kinase in neutrophil phagocytosis was uncovered.

Van der Stelt, as a member of the research management committee of Oncode Institute, proposed to apply for a national growth fund to translate the fundamental discoveries of Oncode Institute into clinical solutions for patients. The resulting Oncode Accelerator proposal was awarded by the Dutch government in 2022. Van der Stelt is the architect of the small molecule workstream and the artificial intelligence platform. As coordinator of the small molecule workstream he assembled a public-private consortium that aims to generate clinical candidates for the treatment of cancer. Innovative concepts from the field of chemical biology will be integral part of the workstream to explore new chemical space for traditionally considered undruggable targets.

Finally, Van der Stelt is a co-founder and executive board member of the Institute of Chemical Neuroscience (iCNS), an initiative funded by a Gravitation Award from the Dutch Ministery of Science and Education in 2024. The aim of iCNS is to discover the molecular drivers of psychiatric symptoms in human brain by combining various -OMIC technologies and data science with the innovations in chemical biology, such as advanced probe-development, activity-based proteomics and bio-orthogonal chemistry, in human brain tissue.

KEY OUTPUT – SELECTED PUBLICATIONS

[1] van Esbroeck, A. C. M.; Janssen, A. P. A.; Cognetta, A. B., 3rd; Ogasawara, D.; Shpak, G.; van der Kroeg, M.; Kantae, V.; Baggelaar, M. P.; de Vrij, F. M. S.; Deng, H.; Allara, M.; Fezza, F.; Lin, Z.; van der Wel, T.; Soethoudt, M.; Mock, E. D.; den Dulk, H.; Baak, I. L.; Florea, B. I.; Hendriks, G.; De Petrocellis, L.; Overkleeft, H. S.; Hankemeier, T.; De Zeeuw, C. I.; Di Marzo, V.; Maccarrone, M.; Cravatt, B. F.; Kushner, S. A.; **van der Stelt, M**., Activity-based protein profiling reveals off-target proteins of the FAAH inhibitor BIA 10-2474. *Science* 2017**,** *356* (6342), 1084-1087 DOI: 10.1126/science.aaf7497

[2] van Rooden EJ, Florea BI, Deng H, Baggelaar MP, van Esbroeck ACM, Zhou J, Overkleeft HS, **van der Stelt M**. Mapping in vivo target interaction profiles of covalent inhibitors using chemical proteomics with label-free quantification. *Nature Protoc*. 2018, 13(4):752-767. doi: 10.1038/nprot.2017.159.

[3] Punt JM, van der Vliet D, **van der Stelt M**. Chemical Probes to Control and Visualize Lipid Metabolism in the Brain. *Acc Chem Res.* 2022 Nov 15;55(22):3205-3217. doi: 10.1021/acs.accounts.2c00521.

[4] Jiang M, Huizenga MCW, Wirt JL, Paloczi J, Amedi A, van den Berg RJBHN, Benz J, Collin L, Deng H, Di X, Driever WF, Florea BI, Grether U, Janssen APA, Hankemeier T, Heitman LH, Lam TW, Mohr F, Pavlovic A, Ruf I, van den Hurk H, Stevens AF, van der Vliet D, van der Wel T, Wittwer MB, van Boeckel CAA, Pacher P, Hohmann AG, **van der Stelt M**. A monoacylglycerol lipase inhibitor showing therapeutic efficacy in mice without central side effects or dependence. *Nat Commun*. 2023 Dec 5;14(1):8039. doi: 10.1038/s41467-023-43606-3.

[5] Li X, Chang H, Bouma J, de Paus LV, Mukhopadhyay P, Paloczi J, Mustafa M, van der Horst C, Kumar SS, Wu L, Yu Y, van den Berg RJBHN, Janssen APA, Lichtman A, Liu ZJ, Pacher P, **van der Stelt M**, Heitman LH, Hua T. Structural basis of selective cannabinoid CB2 receptor activation. *Nat Commun*. 2023 Mar 15;14(1):1447. doi: 10.1038/s41467-023-37112-9.

[6] Mock ED, Mustafa M, Gunduz-Cinar O, Cinar R, Petrie GN, Kantae V, Di X, Ogasawara D, Varga ZV, Paloczi J, Miliano C, Donvito G, van Esbroeck ACM, van der Gracht AMF, Kotsogianni I, Park JK, Martella A, van der Wel T, Soethoudt M, Jiang M, Wendel TJ, Janssen APA, Bakker AT, Donovan CM, Castillo LI, Florea BI, Wat J, van den Hurk H, Wittwer M, Grether U, Holmes A, van Boeckel CAA, Hankemeier T, Cravatt BF, Buczynski MW, Hill MN, Pacher P, Lichtman AH, **van der Stelt M**. Discovery of a NAPE-PLD inhibitor that modulates emotional behavior in mice. *Nature Chem Biol.* 2020, 16(6):667-675 DOI: 10.1038/s41589-020-0528-7

[7] Ogasawara D, Deng H, Viader A, Baggelaar MP, Breman A, den Dulk H, van den Nieuwendijk AM, Soethoudt M, van der Wel T, Zhou J, Overkleeft HS, Sanchez-Alavez M, Mori S, Nguyen W, Conti B, Liu X, Chen Y, Liu QS, Cravatt BF, **van der Stelt M**. Rapid and profound rewiring of brain lipid signaling networks by acute diacylglycerol lipase inhibition. *Proc Natl Acad Sci U S A.* 2016, 113(1):26-33. doi: 10.1073/pnas.1522364112.

[8] Baggelaar MP, Chameau PJ, Kantae V, Hummel J, Hsu KL, Janssen F, van der Wel T, Soethoudt M, Deng H, den Dulk H, Allarà M, Florea BI, Di Marzo V, Wadman WJ, Kruse CG, Overkleeft HS, Hankemeier T, Werkman TR, Cravatt BF, **van der Stelt M**. Highly Selective, Reversible Inhibitor Identified by Comparative Chemoproteomics Modulates Diacylglycerol Lipase Activity in Neurons. *J Am Chem Soc*. 2015, 137(27):8851-7. doi: 10.1021/jacs.5b04883.

[9] Soethoudt, M.; Stolze, S. C.; Westphal, M. V.; van Stralen, L.; Martella, A.; van Rooden, E. J.; Guba, W.; Varga, Z. V.; Deng, H.; van Kasteren, S. I.; Grether, U.; AP, I. J.; Pacher, P.; Carreira, E. M.; Overkleeft, H. S.; Ioan-Facsinay, A.; Heitman, L. H.; **van der Stelt M**., Selective Photoaffinity Probe That Enables Assessment of Cannabinoid CB2 Receptor Expression and Ligand Engagement in Human Cells. *J Am Chem Soc* 2018**,** *140* (19), 6067-6075 DOI: 10.1021/jacs.7b11281

[10] Gagestein B, von Hegedus JH, Kwekkeboom JC, Heijink M, Blomberg N, van der Wel T, Florea BI, van den Elst H, Wals K, Overkleeft HS, Giera M, Toes REM, Ioan-Facsinay A, **van der Stelt M**. Comparative Photoaffinity Profiling of Omega-3 Signaling Lipid Probes Reveals Prostaglandin Reductase 1 as a Metabolic Hub in Human Macrophages. *J Am Chem Soc*. 2022, 144(41):18938-18947. doi: 10.1021/jacs.2c06827.

[11] Koenders STA, Wijaya LS, Erkelens MN, Bakker AT, van der Noord VE, van Rooden EJ, Burggraaff L, Putter PC, Botter E, Wals K, van den Elst H, den Dulk H, Florea BI, van de Water B, van Westen GJP, Mebius RE, Overkleeft HS, Le Dévédec SE, **van der Stelt M**. Development of a Retinal-Based Probe for the Profiling of Retinaldehyde Dehydrogenases in Cancer Cells. *ACS Cent Sci*. 2019, 5(12):1965-1974. doi: 10.1021/acscentsci.9b01022.

[12] Bakker AT, Kotsogianni I, Mirenda L, Straub VM, Avalos M, van den Berg RJBHN, Florea BI, van Wezel GP, Janssen APA, Martin NI, **van der Stelt M**. Chemical Proteomics Reveals Antibiotic Targets of Oxadiazolones in MRSA. *J Am Chem Soc*. 2023 Jan 18;145(2):1136-1143. doi: 10.1021/jacs.2c10819.

[13] Bakker AT, Kotsogianni I, Avalos M, Punt JM, Liu B, Piermarini D, Gagestein B, Slingerland CJ, Zhang L, Willemse JJ, Ghimire L, van den Berg RJHBN, Janssen APA, Ottenhoff THM, Van Boeckel CAA, Van Wezel GP, Ghilarov D, Martin NI and **Van der Stelt M**. Discovery of isoquinoline sulfonamides as allosteric gyrase inhibitors active against fluoroquinolone-resistant bacteria, *Nature Chem*., 2024, *in press*

[14] van der Wel T, Hilhorst R, den Dulk H, van den Hooven T, Prins NM, Wijnakker JAPM, Florea BI, Lenselink EB, van Westen GJP, Ruijtenbeek R, Overkleeft HS, Kaptein A, Barf T, **van der Stelt M**. Chemical genetics strategy to profile kinase target engagement reveals role of FES in neutrophil phagocytosis. *Nat Commun*. 2020 Jun 25;11(1):3216. doi: 10.1038/s41467-020-17027-5.