Curriculum Vitae

Prof. dr. Mario van der Stelt

Chair of the Department of Molecular Physiology, Leiden Institute of Chemistry, Leiden University
Einsteinweg 55, 2333 CC Leiden, The Netherlands
Phone: +71 527 4768
E-mail: m.van.der.stelt@chem.leidenuniv.nl
URL: www.universiteitleiden.nl/en/science/chemistry/molphys

Personal details

Date and place of birth: 20-09-1975, Nieuwendijk, The Netherlands
Nationality: Dutch

Academic positions

2017 – present	Full Professor of Molecular Physiology, Leiden University
2016 – present	Chair and founder of the department of Molecular Physiology, Leiden Institute of Chemistry, Leiden University
2012 – 2017	Associate Professor & Principal Investigator Medicinal Chemistry, Leiden Institute of Chemistry, Tenured (permanent position) since 2017
2004 – 2011	Group & Project leader Medicinal Chemistry, Merck Research Laboratories (former Organon), Oss, The Netherlands
2002 – 2004	Post-doctoral researcher, Institute of Biomolecular Chemistry, Pozzuoli, Italy Endocannabinoid Research Group, Prof. dr. V. Di Marzo, one of the world's leading endocannabinoid scientists with > 460 publications and recognised by Thompson Reuters as 'top scientist of the decade' for pharmacology and toxicology (2010).
1998-2002	PhD-student, Bio-organic Chemistry, Utrecht University, The Netherlands

Education

12 April 2002	PhD in Chemistry, Utrecht University, The Netherlands Distinction: *Cum Laude* (top 5%) Thesis title: The Endocannabinoid Anandamide: metabolism & neuroprotection Advisors: Prof. dr. J.F.G. Vliegenthart & Prof. dr. G.A. Veldink
31 May 1998	Master of Science in Chemistry, Utrecht University, The Netherlands Distinction: *Cum Laude*

Distinctions and awards

2018	VICI-award (€1.5M), personal grant for excellent senior researchers, part of the innovational research incentive scheme of the Netherlands Organisation for Scientific Research (NWO)
2017	Prix Galien Research (Galenus Research Award) for best preclinical drug discovery research in the Netherlands
2017	Young Investigator Award of the International Cannabinoid Research Society
2005	Young Investigator Award of the International Cannabis Association for Medicine
2003	ESN Young Scientist Award from the European Society for Neuroscience

Funding

Personal grants

2018 - 2022	VICI-award (€ 1.5M) from NWO

Netherlands Organisation for Scientific Research (NWO) grants

2018 - 2022	Future Medicine Initiative, TopSector Chemistry & Life Sciences & Health, co- PI with Prof. dr. A. Heck (UU) and others
2018 - 2022	TTW – Navistroke, co-PI with Prof. dr. W. Mulder (AMC) and others
2018 - 2022	TTW- NACTAR, co-PI with Prof. dr. T. Ottenhof (LUMC) and others
2016	ZonMW, middelgroot, co-PI with Dr. R. Pannu (UL) and others
2015 - 2019	OncoDrugs, New Chemical Innovations, Topsector Chemistry, lead PI
2014 - 2019	ECHO (NWO-Chemical Sciences)
2013 - 2018	ECHO-STIP (NWO-Chemical Sciences)

Industrial & other (inter)national collaborations

2018 - 2019	Dutch Arthritis Foundation, co-PI with Prof. dr. R. Toes (LUMC)
2016 - present	Roche
2015 - 2017	Roche Post-doc Fellowship Programme, co-PI with Prof. dr. IJzerman (UL)
2015 - 2019	Institute of Chemical Immunology, Gravitation Program, participant
2013 - 2018	Innovative Medicines Initiative - European Lead Factory, co-founder & participant

Summary of research over past five years:

My lab is worldwide recognized for the design, synthesis and application of small molecules as chemical tools to control and visualize proteins of the endocannabinoid system in physiological and disease processes. In multidisciplinary research lines organic and medicinal chemistry are combined with innovative chemical biology techniques, such as chemical proteomics, and gene editing to optimize and profile compounds as drug candidates. My current research interests are focused on the detection and modulation of endocannabinoid biosynthesis/metabolism and kinase signaling. Recently, I have coordinated an (inter)national team that discovered the off-targets of the experimental drug BIA 10-2474, a fatty acid amide hydrolase inhibitor, which caused severe neurological symptoms and killed a patient in a first-into-human study in France *(Science, 2017*). I also led a multinational joint venture that reported an extensive cannabinoid CB2 receptor ligand profiling (*Nature Commun*, *2017; JACS, 2018*). Furthermore, my group discovered the first inhibitors of endocannabinoid biosynthesis in the brain (*PNAS, 2016*). Key to the discovery of these compounds was the development of tailored activity-based probes that could be used to determine the activity and selectivity of the compounds in complex brain proteomes using chemical proteomics (*Nature Prot., 2018; JACS, 2015; ACS Chem. Biol., 2017; ACIE, 2013; J. Med. Chem., 2014, 2015, 2017*). Previously, I was the first to report on the role of the endocannabinoid system in neurodegeneration and discovered that anandamide can act as an intracellular messenger (*EMBO J. 2005; Science 2003; J. Neurosci, 2003, 2001a,b*).

Research output:

Peer-reviewed international publications: **70**
Book chapters: **3**
Patents: **6**
Citations: **4580** (an average of **65** citations/article; 15 articles with > 100 citations)
H-index: **27** (Google Scholar)
Invited lectures: **> 30**
Chemical tools used by the research community: DAGL inhibitors & probe (**LEI105, DH376** & **MB064**), peripherally, restricted CB2 receptor agonist (**LEI101**) and allosteric RoRyT inhibitors (**MRK871**).

Top-10 key publications (chronological order)

The following publications, in which I am last and corresponding author, have been selected, because they represent important breakthroughs in the field of drug discovery, chemical biology, neuroscience and/or endocannabinoid biology.
Full publication list: https://www.universiteitleiden.nl/en/science/chemistry/molphys/publications

1. Soethoudt M, Stolze SC, Westphal MV, van Stralen L, Martella A, van Rooden EJ, Guba W, Varga ZV, Deng H, van Kasteren SI, Grether U, IJzerman AP, Pacher P, Carreira EM, Overkleeft HS, Ioan-Facsinay A, Heitman LH, **van der Stelt M.** Selective Photoaffinity Probe That Enables Assessment of Cannabinoid CB_2 Receptor Expression and Ligand Engagement in Human Cells. *J. Am. Chem. Soc.* **2018**, doi: 10.1021/jacs.7b11281

This paper describes the first bifunctional, photoreactive GPCR-probe that visualizes the cannabinoid CB2 receptor on primary human immune cells. The paper was selected by the JACS editors to feature in the "Spotlights".

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, 752

This paper describes a detailed method for label-free quantification of inhibitor-protein interaction landscapes in tissues using chemical proteomics.

3. van Esbroeck, A.C.M., Janssen, A.P.A., Cognetta, A.B., Ogasawara, D., Shpak, G., Van der Kroeg, M., Kantae, V., Baggelaar, M.P., de Vrij, F.M.S., Deng, H., Allarà, M., Fezza, F., Lin, Z., Van der Wel, T., Soethoudt, M., Mock, E.D., Den Dulk, H., Baak, I.L., Florea, B.F., 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 Fatty Acid Amide Hydrolase inhibitor BIA 10-2474. *Science*, **2017,** 356, *1084* [IF =37.2]

This paper is the first to show the off-target profile of the fatal FAAH inhibitor BIA 10-2474 that may potentially explain the molecular causes of the adverse neurological effects observed in human volunteers during a phase 1 clinical trial, which led to the death of one volunteer and hospitalization of four others in Rennes (France) in 2016. The paper generated comments in other journals and (social) media attention, including comments in Science, Nature Reviews Drug Discovery, Nature Chemical Biology, F1000, C&EN, Chemistry World, BioWorld, Le Figaro, NRC Handelsblad and Nemokennislink.nl; Altmetric attention score: 144 (top 5% of all research output scored by altmetric.com).

4. Soethoudt, M., Grether, U., Fingerle, J., Grim, T.W., Fezza, F., De Petrocellis, L., Ullmer, C., Rothenhäusler, B., Perret, C., Can Gils, N., Finlay, D., MacDonald, C., Chicca, C., Dalghi Gens, M., Stuart, J., De Vries, H., Mastrangelo, N., Xia, L., Alachouzos, G., Baggelaar, M.P., Martella, A., Mock, E.D., Deng, H., Heitman, L.H., Connor, M., Di Marzo, V., Gertsch, J., Lichtman, A., Maccarrone, M., Pacher, P., Glass, M. **Van der Stelt,** M., Cannabinoid CB_2 Receptor Ligand Profiling Reveals Biased Signaling and Off-target Activity. *Nature Commun.*, **2017**, Jan 3. 13958, [IF = 12.1]

In this paper the results are reported of a multinational collaboration that I coordinated with 13 academic and industry laboratories worldwide in which the most extended molecular pharmacology, off-target and pharmacokinetic profile of a set of 19 reference ligands of the cannabinoid CB2 and CB1 receptor have been determined. The paper reaches consensus on the best three selective CB2 ligands to be used in preclinical target validation studies. The paper generated (social) media attention, including an animation made by the Netherlands public broadcasting organisation (NOSop3) published on Twitter (https://t.co/VmPAsorn2d?ssr=true) and an article on newscientist.nl. Altmetric attention score: 88 (top 5% of all research output scored by altmetric.com).

5. Ogasawara, D.; Deng, H.; Viader, A.; Baggelaar, M. P.; Breman, A.; den Dulk, H.; van den Nieuwendijk, A. M.; Soethoudt, M.; van der Wel, T.; Zhou, J.; Overkleeft, H. S.; Sanchez-Alavez, M.; Mo, S.; Nguyen, W.; Conti, B.; Liu, X.; Chen, Y.; Liu, Q. S.; Cravatt, B. F.; **van der Stelt, M**., Rapid and profound rewiring of brain lipid signalling networks by acute diacylglycerol lipase inhibition. *Proc. Natl. Acad. Sci. USA,* **2016,** *113* (1), 26-33 [IF = 9.7]

This paper describes the first CNS-active DAGL inhibitors that can be used to block endocannabionid biosynthesis in the brain. Using these inhibitors it was also found that arachidonic acid and pro-inflammatory prostaglandins pools are derived from diacylglycerol and dependent on DAGL activity. DAGL was found to have a short half life (< 4h). The inhibitors described in this paper are currently used by the scientific community to investigate the role of DAGL in food intake and various neurological and neuroinflammatory conditions (e.g. Bluett et al., Nature Comm., 2017; Deng et al., J. Med. Chem, 2017).

6. Baggelaar, M. P.; Chameau, P. J.; Kantae, V.; Hummel, J.; Hsu, K. L.; Janssen, F.; van der Wel, T.; Soethoudt, M.; Deng, H.; den Dulk, H.; Allara, M.; Florea, B. I.; Di Marzo, V.; Wadman, W. J.; Kruse, C. G.; Overkleeft, H. S.; Hankemeier, T.; Werkman, T. R.; Cravatt, B. F.; **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; [IF = 13.9]

This paper describes a chemical proteomics method that led to the discovery of the most selective, reversible DAGL inhibitor to date. The paper was selected by the JACS editors to feature in the "Spotlights"

7. Baggelaar, M. P.; Janssen, F. J.; van Esbroeck, A. C.; den Dulk, H.; Allara, M.; Hoogendoorn, S.; McGuire, R.; Florea, B. I.; Meeuwenoord, N.; van den Elst, H.; van der Marel, G. A.; Brouwer, J.; Di Marzo, V.; Overkleeft, H. S.; **van der Stelt, M**., Development of an activity-based probe and in silico design reveal highly selective inhibitors for diacylglycerol lipase-alpha in brain. *Angew. Chem. Int. Ed.* **2013,** *52* (46), 12081-5; [IF = 12.0]

This paper describes the first activity-based probe to visualize DAGL activity in the brain, which resulted in new avenues for inhibitor identification. The paper was designed as a hot paper by the editors and selected to feature as a cover picture. A commentary was also written in Nature/Science business exchange.

8. **Van der Stelt, M**. *et al.* Anandamide acts as an intracellular messenger amplifying Ca2+ influx via TRPV1 channels. *The EMBO J.* **24**, 3026-3037 (2005). [cited: 214; IF = 9.8]

This paper describes for the first time the action of the endocannabinoid anandamide as an intracellular messenger in sensory neurons.

9. **Van der Stelt, M**. & Di Marzo, V. Endovanilloids. Putative endogenous ligands of transient receptor potential vanilloid 1 channels. *Eur. J. Biochem.* **271**, 1827-1834, (2004). [cited: 382; IF = 3.6]

This paper provides a definition and criteria to qualify endogenous metabolites that activate the ion channel TRPV1 as "endovanilloids".

10. **Van der Stelt, M**. *et al.* Exogenous anandamide protects rat brain against acute neuronal injury in vivo. *J. Neurosci.* **21**, 8765-8771 (2001). [cited: 194; IF = 5.9]

This paper describes for the first time the neuroprotective properties of the endocannabinoid anandamide in an animal model.

Top-5 invited presentations (chronological order)

1. Young Investigator Award Lecture ICRS, Leiden, The Netherlands, 2018
2. International Singapore Lipid Symposium, Singapore, 2018
3. Gordon Research Conference on Cannabinoids, Waterville, USA, 2015 & 2017
4. European Federation of Medicinal Chemistry, Manchester, UK, 2016
5. Gratama Workshop, Tokyo, Japan, 2013

Memberships of (inter)national committees and boards

2018	**Local organizer Conference of the International Cannabinoid Research Society (ICRS)**
2017 – present	**Co-founder of Future Medicine Initiative** - In close collaboration with the Dutch TopSector Chemistry and Lifes Sciences and Health, we have established the Future Medicine Initiative, which is a public private partnership of several Dutch universities and medical centers, patient charity organisations, biotech companies.
2016 – present	**Board member of Cell Observatory** - The Cell Observatory is an interdisciplinary facility of the Faculty of Science to foster multidisciplinary science between the different Institutes by combining all the high-end microscopy infrastructure for bio-imaging.
2016 – present	**Board member of the Havinga Foundation** – This foundation awards the Havinga-medal to internationally renowned eminent scientists who are leaders in groundbreaking fundamental or applied molecular research. Laureates include several scientists who won thereafter the Nobel Prize.

2016 **Member Program Committee CHAINS** – CHAINS brings together all chemists from all chemical subdisciplines, to share the state-of-the-art and the breakthroughs in the chemical and molecular sciences. With as much as 1500 participants, CHAINS is the largest scientific chemistry congress in the Netherlands. http://www.nwochains.nl

2015 – present **Board member of the Netherlands Research Council – Chemical Sciences - Study group Pharmacochemistry** This study group oversees the funding schemes for academic medicinal chemistry research and also helps to stimulate public-private partnerships.

2015 – present **Member of Local Animal Welfare Body** – This body oversees all experimental animal research of the Faculty of Science, Leiden University. It advises scientists and staff dealing with animals on matters related to animal welfare. (I have got an Article 9 license.)

2014 – present **Chairmen of Cancer Drug Discovery Initiative**. This is a public private collaboration of Leiden University with the Netherlands Cancer Institute and the Pivot Park Screening Centre and three small medium enterprises (Covalution Pharma, Lead Pharma and NTRC). The goal is to screen 6 different targets (estimated value 1.2 M Euros) and to develop two lead series for the treatment of cancer. A Netherlands Research Council (NWO)- New Chemical Innovations Grant was obtained and five PhD-students have been appointed. http://cddi.nl

2013 – 2018 **Coordinator Faculty Profiling Program Endocannabinoids,** Leiden University. The Faculty of Science has funded a 750.000 Euro program to investigate the role of the endocannabinoid system in health and disease. In this multidisciplinary project researchers from the Leiden Institute of Chemistry (LIC), Leiden Academic Center for Drug Research (LACDR) and Institute for Biology Leiden (IBL) and Leiden University Medical Center will collaborate to address fundamental questions regarding the endocannabinoid system. http://endocannabinoids.leidenuniv.nl

2013 – 2018 **Co-founder of the European Lead Factory, the largest public private partnership in Europe in the area of drug discovery.** The ELF is funded with a 196 million euro grant from the Innovative Medicines Initiative (a collaboration of the European Union and EFPIA partners). Leiden University is the managing entity of the consortium consisting of 13 academic partners and 7 major pharmaceutical companies as well as 5 small medium enterprises. It consists of two parts: the Joint European Compound Collection (JECCL) and the European Screening Centre and I am involved in both parts. The JECLL will contain 500.000 compounds, which will have different physico-chemical properties and unique structures, compared to the contemporary pharmaceutical libraries. In close collaboration with the European Screening Centre, my lab has developed multiple high-throughput assays and successfully screened the JECCL. The resulting hits are currently being optimized in house. https://www.europeanleadfactory.eu

2002 – present regularly reviewer for top-tier journals, including Nat. Chem. Biol, J. Am. Chem. Soc., Proc. Natl. Acad. Sci., and J. Med. Chem.

Supervision:

Currently I supervise 15 PhD students & 2 post-docs. Previously, 4 PhDs have been awarded (of which one cum laude).

Teaching & Educational activities

2017-	Member Examination Board: BSc Life Science & Technology, Leiden University
2017-	Coordinator & Lecturer Chemical Biology, BSc Life Science & Technology, Leiden
2015-	BKO certificate
2014−	Coordinator and Lecturer: Advanced Medicinal Chemistry, MSc Chemistry
2013−2017	Lecturer: Honours Class, Leiden University
2013	Coordinator and Lecturer: Design and Synthesis, BSc BioPharmaceutical Sciences,
2012−2017	Lecturer Modern Drug Discovery, MSc Chemistry, Leiden University
2012−2015	Lecturer Chemical Genetics, MSc Chemistry, Leiden University