CiQUS

Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares

Conferencia:

Chemical Biology and Medicinal Chemistry of Glycosphingolipid Metabolism

Hermen Overkleeft

University of Leiden - Netherlands

17/10/16

Aula de Seminarios do CIQUS

12:15 h

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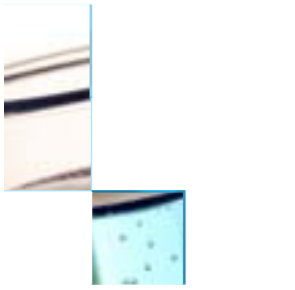

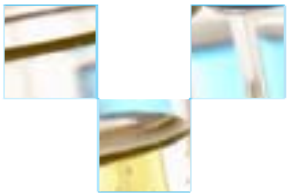

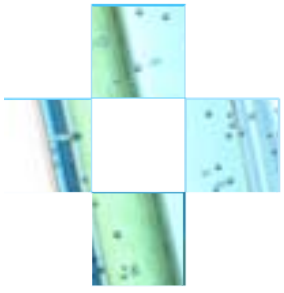

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SHORT CV HERMAN OVERKLEEFT (born 12-04-1969)

Education

Masters Degree:	University of Amsterdam, Faculty of Chemistry, Department of Organic Chemistry, November 1992.
Ph.D. Degree:	University of Amsterdam, Faculty of Chemistry, Department of Organic Chemistry; March 14th, 1997. Promotor: Prof. Dr U. K. Pandit.
Thesis:	Azasugars. Synthesis and evaluation as glycosidase inhibitors.

Research Positions

- July 2001 - present: Full Professor in Bioorganic chemistry at the Leiden Institute of Chemistry, Leiden University.
- July 1999 - June 2001: Post-doctoral fellow in the group of Prof. Dr H. L. Ploegh at the Harvard Medical School, Department of Pathology, Harvard University, Boston, USA.
- March 1997 - June 1999: Post-doctoral fellow in the group of Prof. Dr J. H. van Boom and Dr G. A. van der Marel at the Leiden Institute of Chemistry, Leiden University.

Grants and awards (selection)

2015 Appointed Fellow of the Royal Society of Chemistry (FRSC), United Kingdom.
2015 Jeremy Knowles Award, Royal Society of Chemistry, United Kingdom, awarded to promote interdisciplinary research between chemistry and the life sciences.
2012 Friedrich Wilhelm Bessel Research Award, Alexander von Humboldt Foundation, Germany.
2014 NWO-CW TOPPUNT Grant.
2011 ERC Advanced Grant.
2008 KNCV 'Gouden Medaille' for the best <40-chemist in the Netherlands.
2008 NWO TOP Grant.
2003 NWO CW VICI Grant.

Herman Overkleeft is (co)-author on 401 original publications, reviews and book chapters. He has supervised 33 PhD students who received their PhD degree and currently heads a group composed of 20 PhD students and postdoctoral researchers. Since 2001 he has presented over 30 plenary and invited lectures at international symposia, and over 40 seminars at universities and research institutions.

CHEMICAL BIOLOGY AND MEDICINAL CHEMISTRY OF GLYCOSPHINGOLIPID METABOLISM

HERMAN OVERKLEEFT

Aberrations in glucosylceramide metabolism are at the basis of several human disorders, including the lysosomal storage disorder, Gaucher disease, and type 2 diabetes. Factors involved in glucosylceramide metabolism are therefore valid targets for drug development. In this seminar I will report on the progress we made in the development of inhibitors and activity-based probes of the enzymes involved in glucosylceramide metabolism. Our work analogues of the natural product, deoxynojiorimycin (**1**) as enzyme inhibitors focuses on the evaluation of differently configured and substituted pyrrolidines and piperidines, with the aim to develop selective inhibitors of each of the enzymes involved, namely glucosylceramide synthase (GCS), acid glucosylceramidase (GBA1) and neutral glucosylceramidase (GBA2). In our studies on activity-based glycosidase probes we took the natural product, cyclophellitol, as a basis. Introduction of a fluorophore at C6 (glucose numbering) in cyclophellitol (**2**) yielded an activity-based probe highly specific for GBA1, whereas substitution of the epoxide for a functionalized aziridine yielded an in-class, broad-spectrum acrivity-based retaining beta-glucosidase probe. Moreover, configurational analogues of cyclophellitol/cyclophellitol aziridine yielded activity-based probes able to detect human retaining alpha-galactosidases (involved in Fabry disease) and retaining alpha-glucosidases (involved in Pompe disease).

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2. M. D. Witte, W. W. Kallemeijn, J. Aten, K.-Y. Li, A. Strijland, W. E. Donker-Koopman, B. Blijlevens, G. Kramer, A. M. C. H. van den Nieuwendijk, B. I. Florea, B. Hooibrink, C. E. M. Hollak, R. Ottenhoff, R. G. Boot, G. A. van der Marel, H. S. Overkleeft and J. M. F. G. Aerts, Ultrasensitive *in situ* visualization of active glucocerebrosidase molecules, *Nat. Chem. Biol.* **2010**, *6*, 907.
3. T. Wennekes, A. J. Meijer, A. K. Groen, R. G. Boot, J. E. Groener, M. van Eijk, R. Ottenhoff, N. Bijl, K. Ghauhalari, H. Song, T. J. O'Shea, H. Liu, N. Yew, D. Copeland, R. J. van den Berg, G. A. van der Marel, H. S. Overkleeft and J. M. Aerts, Dual-action lipophilic iminosugar improves glycemic control in obese rodents by reduction of visceral glycosphingolipids and buffering of carbohydrate assimilation, *J. Med. Chem.* **2010**, *53*, 689.
4. A. T. Ghisaidoobe, R. J. B. H. N. van den Berg, S. S. Butt, A. Strijland, W. E. Donker-Koopman, S. Scheij, A. M. C. H. van den Nieuwendijk, G.-J. Koomen, A. van Loevezijn, M. Leemhuis, T. Wennekes, M. van der Stelt, G. A. van der Marel, C. A. A. van Boeckel, J. M. F. G. Aerts and H. S. Overkleeft, Identification and development of biphenyl substituted iminosugars as improved dual glucosylceramide synthase/neutral glucosylceramidase inhibitors, *J. Med. Chem.* **2014**, *57*, 9096-9104.
5. J. Jiang, C.-L. Kuo, L. Wu, C. Franke, W. W. Kallemeijn, B. I. Florea, E. van Meel, G. A. van der Marel, J. D. C. Codée, R. G. Boot, G. J. Davies, H. S. Overkleeft and J. M. F. G. Aerts, Detection of active mammalian GH31 □lpha-glucosidases in health and disease using in-class, broad-spectrum activity-based probes, *ACS Central Science* DOI: 10.1021/acscentsci.6b00057.