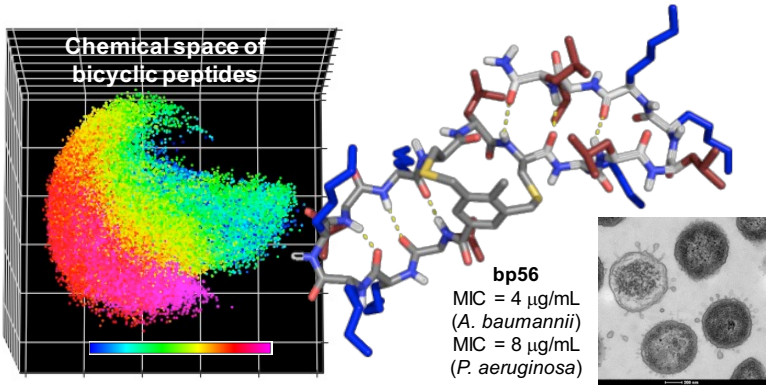
The Peptide Chemical Space as Tool for Discovery and Optimization

Jean-Louis Reymond

University of Bern, Department of Chemistry and Biochemistry, Freiestrasse 3 3012 Bern, Switzerland
http://gdb.unibe.ch; jean-louis.reymond@dcb.unibe.ch

By investigating peptide dendrimers as simply mimics for proteins and enzymes, we discovered that these usual multi-branched peptides can be optimized for inhibiting bacterial biofilms,[1] killing multidrug resistant bacteria,[2–4] and for delivering drugs and oligonucleotides into cells.[5,6] We then developed a chemical space approach to discover and optimize these compounds in the absence of well-defined structures based on molecular fingerprints borrowed from small molecule cheminformatics and adapted for large molecules. We have used this approach to visualize the chemical space of large molecules[7,8] and to discover and optimize antimicrobial bicyclic peptides[9,10] and peptide dendrimers[11] as antimicrobial agents against multidrug resistant (MDR) bacteria, with focus on Gram-negative MDR strains of *Pseudomonas aeruginosa, Acinetobacter baumannii, Escherichia coli* and *Klebsiella pneumoniae*, which are particularly problematic. In this lecture, I will discuss the experiments that led us from our initial studies with antimicrobial and cell penetrating dendrimers that used combinatorial chemistry and targeted design,[12,13] to our latest methods to explore and visualize the peptide chemical space.[14–16]



(1) Michaud, G.; Visini, R.; Bergmann, M.; Salerno, G.; Bosco, R.; Gillon, E.; Richichi, B.; Nativi, C.; Imberty, A.; Stocker, A.; Darbre, T.; Reymond, J.-L. Overcoming Antibiotic Resistance in Pseudomonas Aeruginosa Biofilms Using Glycopeptide Dendrimers. *Chem. Sci.* **2015**, *7* (1), 166–182. https://doi.org/10.1039/C5SC03635F.

(2) Stach, M.; Siriwardena, T. N.; Kohler, T.; van Delden, C.; Darbre, T.; Reymond, J. L. Combining Topology and Sequence Design for the Discovery of Potent Antimicrobial Peptide Dendrimers against Multidrug-Resistant Pseudomonas Aeruginosa. *Angew. Chem., Int. Ed. Engl.* **2014**, *53* (47), 12827–12831. https://doi.org/10.1002/anie.201409270.

(3) Siriwardena, T. N.; Stach, M.; He, R.; Gan, B.-H.; Javor, S.; Heitz, M.; Ma, L.; Cai, X.; Chen, P.; Wei, D.; Li, H.; Ma, J.; Köhler, T.; van Delden, C.; Darbre, T.; Reymond, J.-L. Lipidated Peptide Dendrimers Killing Multidrug-Resistant Bacteria. *J. Am. Chem. Soc.* **2018**, *140* (1), 423–432. https://doi.org/10.1021/jacs.7b11037.

(4) Siriwardena, T. N.; Lüscher, A.; Köhler, T.; van Delden, C.; Javor, S.; Reymond, J.-L. Antimicrobial Peptide Dendrimer Chimera. *Helv. Chim. Acta* **2019**, *102* (4), e1900034. https://doi.org/10.1002/hlca.201900034.

(5) Heitz, M.; Javor, S.; Darbre, T.; Reymond, J.-L. Stereoselective PH Responsive Peptide Dendrimers for SiRNA Transfection. *Bioconjugate Chem.* **2019**, *30* (8), 2165–2182. https://doi.org/10.1021/acs.bioconjchem.9b00403.
(6) Heitz, M.; Zamolo, S.; Javor, S.; Reymond, J.-L. Fluorescent Peptide Dendrimers for SiRNA Transfection: Tracking PH Responsive Aggregation, SiRNA Binding, and Cell Penetration. *Bioconjugate Chem.* **2020**. https://doi.org/10.1021/acs.bioconjchem.0c00231.
(7) Jin, X.; Awale, M.; Zasso, M.; Kostro, D.; Patiny, L.; Reymond, J. L. PDB-Explorer: A Web-Based Interactive Map of the Protein Data Bank in Shape Space. *BMC bioinformatics* **2015**, *16*, 339. https://doi.org/10.1186/s12859-015-0776-9.
(8) Capecchi, A.; Awale, M.; Probst, D.; Reymond, J. L. PubChem and ChEMBL beyond Lipinski. *Mol. Inf.* **2019**, *38*, 1900016. https://doi.org/10.1002/minf.201900016.
(9) Di Bonaventura, I.; Jin, X.; Visini, R.; Probst, D.; Javor, S.; Gan, B. H.; Michaud, G.; Natalello, A.; Doglia, S. M.; Kohler, T.; van Delden, C.; Stocker, A.; Darbre, T.; Reymond, J. L. Chemical Space Guided Discovery of Antimicrobial Bridged Bicyclic Peptides against Pseudomonas Aeruginosa and Its Biofilms. *Chem. Sci.* **2017**, *8* (10), 6784–6798. https://doi.org/10.1039/c7sc01314k.
(10) Di Bonaventura, I.; Baeriswyl, S.; Capecchi, A.; Gan, B.-H.; Jin, X.; Siriwardena, T. N.; He, R.; Kohler, T.; Pompilio, A.; Di Bonaventura, G.; van Delden, C.; Javor, S.; Reymond, J.-L. An Antimicrobial Bicyclic Peptide from Chemical Space Against Multidrug Resistant Gram-Negative Bacteria. *Chem. Commun.* **2018**, *54*, 5130–5133. https://doi.org/10.1039/c8cc02412j.
(11) Siriwardena, T. N.; Capecchi, A.; Gan, B. H.; Jin, X.; He, R.; Wei, D.; Ma, L.; Kohler, T.; van Delden, C.; Javor, S.; Reymond, J. L. Optimizing Antimicrobial Peptide Dendrimers in Chemical Space. *Angew. Chem., Int. Ed. Engl.* **2018**, *57* (28), 8483–8487. https://doi.org/10.1002/anie.201802837.
(12) Stach, M.; Maillard, N.; Kadam, R. U.; Kalbermatter, D.; Meury, M.; Page, M. G. P.; Fotiadis, D.; Darbre, T.; Reymond, J.-L. Membrane Disrupting Antimicrobial Peptide Dendrimers with Multiple Amino Termini. *MedChemComm* **2012**, *3* (1), 86–89. https://doi.org/10.1039/c1md00272d.
(13) Eggimann, G. A.; Blattes, E.; Buschor, S.; Biswas, R.; Kammer, S. M.; Darbre, T.; Reymond, J. L. Designed Cell Penetrating Peptide Dendrimers Efficiently Internalize Cargo into Cells. *Chem. Commun.* **2014**, *50*, 7254–7257. https://doi.org/10.1039/c4cc02780a.
(14) Probst, D.; Reymond, J.-L. Visualization of Very Large High-Dimensional Data Sets as Minimum Spanning Trees. *J. Cheminf.* **2020**, *12* (1), 12. https://doi.org/10.1186/s13321-020-0416-x.
(15) Capecchi, A.; Zhang, A.; Reymond, J.-L. Populating Chemical Space with Peptides Using a Genetic Algorithm. *J. Chem. Inf. Model.* **2020**, *60* (1), 121–132. https://doi.org/10.1021/acs.jcim.9b01014.
(16) Capecchi, A.; Probst, D.; Reymond, J.-L. One Molecular Fingerprint to Rule Them All: Drugs, Biomolecules, and the Metabolome. *J. Cheminf.* **2020**, *12* (1), 43. https://doi.org/10.1186/s13321-020-00445-4.