

New developments in the field of nucleoside and oligonucleotide therapeutics

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Nucleosides are a well-established group of therapeutics. Oligonucleotides establish themselves currently as a novel class of pharmaceuticals. The latter allow the precise binding to cellular nucleic acids to interfere with splicing or to degrade specific mRNAs. mRNA in turn has started to create a new class of vaccines.

In the lecture I am addressing new aspects in all three areas i) nucleosides, ii) oligonucleotides and iii) mRNA vaccines. I will present a new nucleoside that efficiently reduces the levels of epigenetic m⁵C in the genome to trigger an epigenetic anti-cancer response. I will present mouse PDX models that show that efficient demethylation can have a profound anticancer effect.[1] In the second part of my lecture, I will present data that allow to deliver oligonucleoside therapeutics efficiently into different cell types.[2,3] The chemistry involves the development of click-adaptor molecules that enable an efficient and cost effective one-pot multiple click linkage of oligonucleotides to different targeting ligands with flexible multiplicity. Finally, I am presenting data that explain why pseudouridine (Y) and 1-methylpseudouridine (1MeY) containing mRNA can escape immune detection.[4,5] Immune silencing of mRNA is a prerequisite for the development of mRNA vaccines and potentially new chemical modifications in RNA are needed to create immune silent RNA therapeutics.[6]

References:

- [1] F. R. Traube, N. F. Brás, W. P. Roos, C. C. Sommermann, T. Diehl, R. J. Mayer, A. R. Ofial, M. Müller, H. Zipse, T. Carell *Chem. Eur. J.* **2022**, 10.1002/chem.202200640.
- [2] A. J. Tölke, J. F. Gaisbauer, Y. V. Gärtner, B. Steigenberger, A. Holovan, F. Streshnev, S. Schneider, M. Müller, T. Carell *Angew. Chem. Int. Ed.* **2024**, 10.1002/anie.202405161.
- [3] E.S. Schönegger, A. Crisp, M. Radukic, J. Burmester, T. Frischmuth, T. Carell *ChemBioChem* **2023**, 10.1002/cbic.202300701.
- [4] W. Greulich, M. Wagner, M.M. Gaidt, C. Stafford, Y. Cheng, A. Linder, T. Carell, V. Hornung *Cell* **2019**, doi: 10.1016/j.cell.2019.11.001.
- [5] M. Bérouti, M. Wagner, W. Greulich, I. Piseddu, J. Gärtig, L. Hansbauer, C. Müller-Hermes, M. Heiss, A. Pichler, A.J. Tölke, G. Witte, K.-P. Hopfner, D. Anz, M. Sattler, T. Carell, V. Hornung *Cell* **2025**, 10.1016/j.cell.2025.05.032.
- [6] V. R. Graziano, J. Porat, M. D. Ah Kioon, I. Mejdrová, A.J. Matz, C. G. Lebedenko, P. Chai, J. V. Pluinage, R. Ricci-Azevedo, A. G. Harrison, S. S. Wright, X. Wang, M. S. Strine, P. Wang, M. R. Wilson, S. K. Vanaja, B. Zhou, F. J. Barrat, T. Carell, R. A. Flynn & V.A. Rathinam *Nature* **2025**, 10.1038/s41586-025-09310-6.