WACKER OUR SOLUTIONS MAKE A BETTER WORLD FOR GENERATIONS

Innovative Technologies Enable Highly Efficient Development and Manufacturing of Nucleic Acid Based Therapeutics

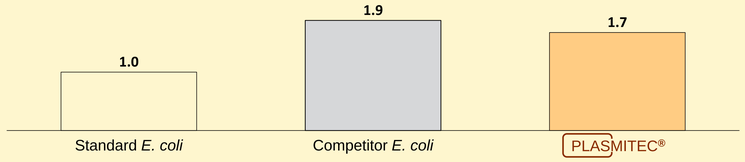
Philipp Schmid[1], Ralph Krafczyk[1], Michael Daume[1], Christian Bosch[1], Vanessa Koch[1], Christian Dubiella[1], Elisabeth Kuffner[1], Christian Hundshammer[1], Hagen Richter[1]

[1]Wacker Chemie AG, Zielstattstrasse 20, 81379 Munich, Germany - Corresponding author: hagen.richter@wacker.com

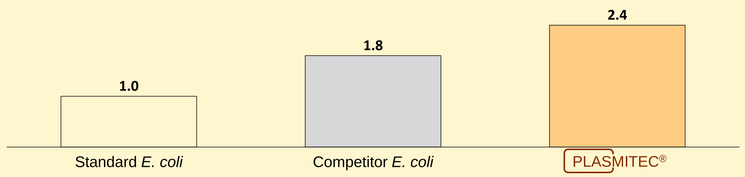
Post-SARS-CoV2, GMP production space for RNA therapeutics is no longer a bottleneck. Reducing costs, while increasing clinical success, needs a focus on optimized production process, including template DNA manufacturing, *in vitro* transcription (*iv*T) and RNA formulation. Supporting this endeavor, we set out to innovate at different steps of the value chain. While meeting regulatory standards and halving the production time of plasmid DNA, our strain design, novel plasmid sequence and cutting-edge fermentation have improved quality and yield. CRISPR-Cas9 enables sequence-independent linearization of plasmid DNA, producing blunt-end template DNA for mRNA manufacturing. These templates support optimized *in vitro* transcription, yielding high-quality RNA with a homopolymeric poly A tail. Machine learning approaches are followed to design novel lipids for RNA-specific LNP formulations.

Optimized *E. coli* Strains and Plasmid Designs Yield High quality pDNA

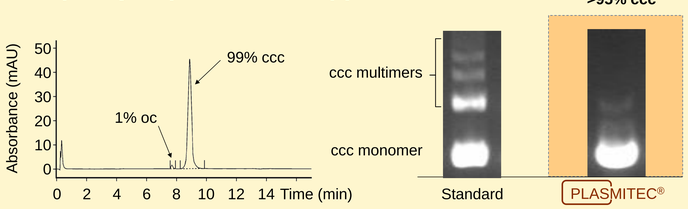
High yielding production strains for pDNA



Fastest production rate of pDNA

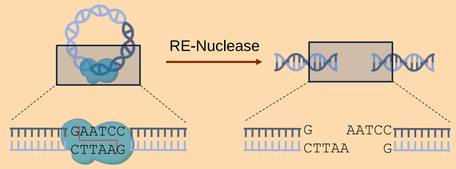


Best quality of pDNA for all applications



Using CRISPR-Cas9, Optimal Template DNA for *iv*T Is Generated

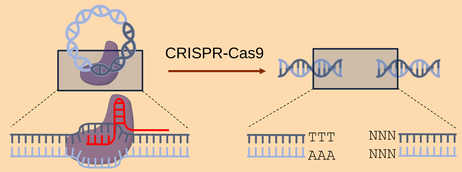
Conventional pDNA linearization



Characteristics

- 3' or 5' overhangs
- hetero-polyT in template
- sequence limitations

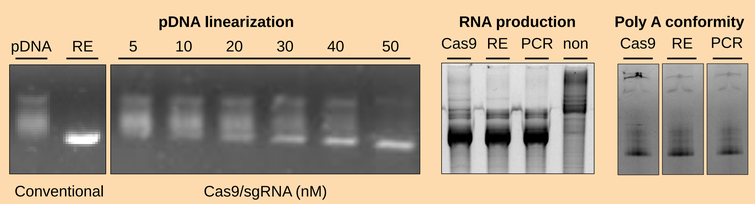
CRISPR-Cas9 based pDNA linearization



Characteristics

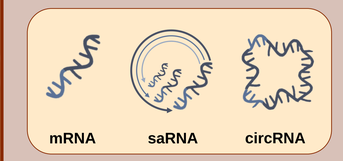
- blunt end
- free polyT in template
- no sequence limitations

CRISPR-Cas9 & conventional approaches perform equally

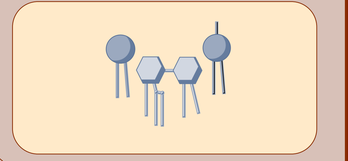


AI-Supported Factorial Design of RNA Lipid Nanocarriers[2]

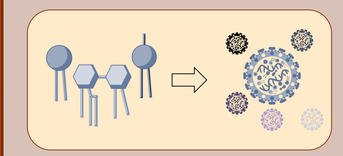
Production of various RNAs



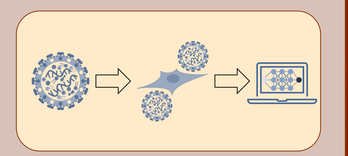
Novel lipid synthesis



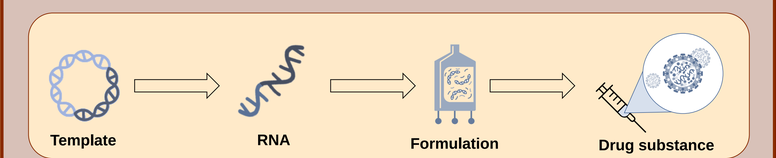
Lipid screening



ML algorithm training



AI- Optimized lipids and formulation compositions



[2] In collaboration with the teams of Prof. Dr. Olivia Merkel (LMU), Prof. Dr. Christoph Arenz (HUB) and CordenPharma