Challenges during scale-up HPLC purification of therapeutic oligonucleotides

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During the last two decades oligonucleotides have become an important tool in basic research and a potent technology for drug development. Especially silencing oligonucleotides such as siRNA and antisense DNA stepped into clinical development and the first oligonucleotide drugs have been approved by the FDA (e.g. Patisiran) in the last years. These oligonucleotide-based drugs proved their therapeutic potency and showed a fantastic toxicology profile.
A major challenge during drug development is the production of GMP material, scale-up and process development. One aspect in the manufacturing process is the purification of the API and its separation from unwanted side products. Ion exchange chromatography is widely used since it is an efficient method regarding loading and separation. Furthermore, ion exchange chromatography can be scaled up and transferred from method development- to pilot- as well as commercial production equipment. Some modification that are commonly used in oligonucleotide drug development also limit the potency of that technology. Here, we present recent chromatographic developments, regarding also new resins and eluents, which enable this technology to be used for a broad spectrum of highly modified oligonucleotides.

Prof. Dr- Tobias Pöhlmann is biologist by training with PhD in obstetrics/gynaecology/oncology; as a postdoc he invented cell specific peptid-siRNA and developed this technology into late preclinic; he founded BianoScience, which further develops this technology for mammary cancer treatment and he is a co-founder of BianoGMP, a Germany based CMO for therapeutic oligonucleotides focused on medium-scale projects. The company is GMP certified by the German authorities and in the last years the typical GMP projects were in the range of 10-250 g, which is especially required for initial clinical trials.