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ASIA EDITION

# Plasmid DNA as a starting material for large-scale mRNA vaccines from the PlasmidFactory

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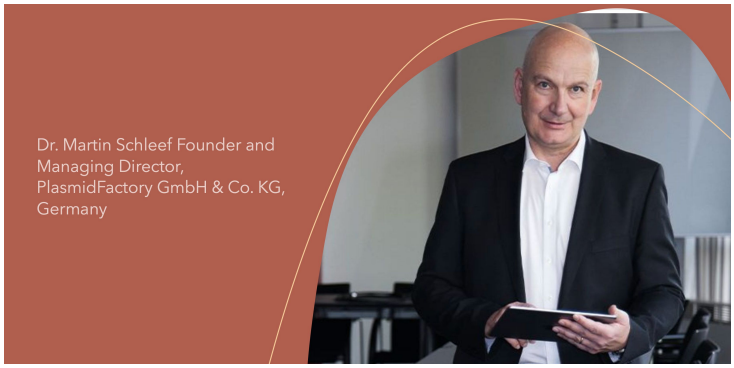
**The PlasmidFactory GmbH & Co. KG was founded in 2000 in Bielefeld/Germany with 4 employees. In the meantime, under the founder and managing director Dr. Martin Schleef, the company has become a well-known contract manufacturer (CMO) for plasmid and minicircle DNA. Today, PlasmidFactory has 30 highly qualified employees, and for more than a year, the company has been working at full speed and on an extraordinary scale - in addition to scientific investigations and optimization of production - for vaccine productions.**




**You have been working in plasmid research and production for 20 years and were immediately available with your company when it came to contributing to the development of the Covid vaccine last year. How did this come about?**

Dr. Martin Schleef: PlasmidFactory specializes in producing DNA of extraordinarily high purity for
gene therapy and genetic vaccine research and works both scientifically and as a supplier with universities, biotechnology and pharmaceutical companies worldwide. We are well known in the industry. All manufacturing as well as research and development is concentrated at the Bielefeld site. Our manufacturing processes for plasmid DNA are ideally suited for the production of mRNA vaccines based on it.

**Was the production of mRNA vaccines a surprise for you?**

Dr. Martin Schleef: Not really.Plasmids have been used as starting material for the production of viral vectors (AAV, Lenti, etc.) and for the production of RNA for quite some time. In particular, the production of plasmid DNA as a starting material for the production of RNA vaccines has become very important, especially against the background of the COVID-19 pandemic situation, since RNA is considered a promising vaccine candidate for the prevention of certain viral infections and has the advantage of neither integrating into the genome of the cell nor remaining in the long term as a potentially effective molecule in the body of a patient.

**Did you have the capacity to jump in right away?**

Dr. Martin Schleef: We have been working in this area for several years and are constantly optimizing it: Even before the pandemic, we significantly expanded our capacity in 2020 to meet the orders of our national and international customers. In the summer of 2020, the concept for expanding the laboratories was finalized. We received funding from the NRW state government and have been able to produce on a multi-gram scale since December. In contrast to previously available processes, which were qualitatively and quantitatively sufficient for the production of plasmid DNA for research, a process has now been created through which plasmids can be produced in high quality grade and sufficient quantities. Due to the high quality requirements, this represents a considerable challenge, which currently needs to be solved both in the area of cultivation and with regard to the chromatographic processing of the DNA product. Due to the given expertise, PlasmidFactory has a pioneering role here - we are happy to accept this challenge.

**Is the expression “high quality grade” yours and what exactly is it?**

Dr. Martin Schleef: Yes, originally it is, but it denotes “high quality”, so it is now also used by other manufacturers.

High Quality Grade plasmid DNA has been established based on the EMEA guidelines CHMP/ BWP/2458/03 and CPMP/BWP/3088/99 for highest quality requirements. For reasons of product safety, the manufacturing process avoids the use of substances of animal origin throughout the entire process and guarantees the highest possible product purity through reliable separation of impurities, e.g. bacterial chromosomal DNA or damaged plasmids. To prevent further contamination, only one plasmid is produced at a time in the facility used exclusively for High Quality Grade Plasmids; no parallel plasmid productions take place in the same facility.

The HQ fermentation is physically separated from the purification (chromatography) to ensure that downstream processing of the sensitive DNA is not affected by live contaminants.

**What expertise do you have in this field?**

Dr. Martin Schleef: The proprietary special purification process results in a high grade of pure, supercoiled (ccc) plasmid monomers that meet regulatory requirements to form a defined, homogeneous product that undergoes a series of cell bank and plasmid DNA product quality controls prior to release.

The High Quality Grade Plasmid DNA is produced based on a cell bank (RCB) created at PlasmidFactory and the particularly effective proprietary ccc Grade DNA technology. For both the cell bank and the plasmid DNA product, PlasmidFactory offers a wide range of quality controls, so that ultimately a product is created that is tailor-made for the respective application or the corresponding regulatory requirements.

For example, our High Quality Grade Plasmid DNA is used in the GMP-compliant production of recombinant viruses, antibodies and RNA for clinical trials.

Our products and processes are continuously and specifically optimized and, if necessary, newly developed, because we want to be uncompromising in quality and competence.

**PlasmidFactory is now benefiting from the Covid wave. What are your plans for the future?**

Dr. Martin Schleef: Of course, we are benefiting ike the entire biotech industry and are doing everything possible, but we also had some exhausting months to get this up and running under the challenging conditions.

Due to the difficult availability of excipients and starting materials worldwide - and especially of the key substance DNA for the pharmaceutical production of the vaccine - there is an extraordinary and still very long-lasting demand for it, which therefore has to be met not only in Germany or the European Community, but worldwide. We ensure an independent

supply of the currently most important raw material for mRNA production and its deliverability in Germany and Europe. mRNA vaccines are gradually replacing viral ones. This means that - just as before - there will be demand for our products even after the pandemic.

**You work not only in vaccine production, but also in the field of cancer research. What exactly do you do there?**

Dr. Martin Schleef: That's right, with our national and international customer base, we are also well positioned in other areas with the PlasmidFactory.

Exciting and no less important is the CAR-T cell development: PlasmidFactory has developed and patented a method with which so-called CAR-T cells can be produced. In contrast to conventional methods, no viral vectors are used here, but PlasmidFactory's proprietary minicircle technology. Corresponding products are currently undergoing clinical trials.

**Has the proprietary minicircle technology contributed to the success in CAR-T cell therapy?**

Dr. Martin Schleef: Yes, without "MC" it does not work: Minicircle DNA contains practically only the "Gene of Interest" (GOI). Unnecessary sequences used only for the plasmid production process are completely removed. A safe, highly effective vector system is the result. It already meets the regulatory requirements of the future for gene therapy and vaccination.

We also produce customized minicircles using our unique, patented method: the plasmid containing the gene of interest (GOI) is the starting material. This is inserted into the so-called "parental plasmid". From this, the minicircle DNA molecule is produced by recombination, which consists almost exclusively of the Gene of Interest.

The Minicircle DNA, produced with our technology, is patented worldwide and exclusively available at PlasmidFactory.

**In the press, you read about R&D activities and other business areas besides those already mentioned. Can you manage that alone?**

Dr. Martin Schleef: The R&D activities of the PlasmidFactory are carried out in our laboratories, partly in close cooperation with national and international partners, e.g. in the fields of
- Optimization of vectors for the production of viral vectors (AAV or LV) or for efficient antibody or RNA production
- Development of resistance gene-free vector systems

(e.g. minicircle)
- Investigation of the influence of various factors on the

long-term stability of plasmid DNA (e.g. plasmid size, DNA concentration, storage medium, freezing and thawing conditions)

- DNA vaccines
- Production of dimeric plasmids - Vector development
- Gene transfer

**As CEO in your company, you have now become an entrepreneur? What part does science still play?**

Dr. Martin Schleef: Actually, I am a biologist and researcher who also manages the company. The products of PlasmidFactory are manufactured jointly by an energetic team of motivated colleagues.

Our and my work here is in the service of science, but of course science also meets entrepreneurship in our company. We remain researchers for researchers!

With new convincing ideas and extraordinary techniques, we want to advance biotechnology together - a simple part of my DNA, too.

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