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â??We specialise in producing DNA of extraordinarily high purity for gene therapy and genetic vaccine researchâ?•

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The PlasmidFactory GmbH was founded in 2000 in Bielefeld/Germany, with four employees. In the meantime, under the leadership of the Founder and Managing Director , Dr Martin Schleef, the company has become a well-known contract manufacturer (CDMO) for plasmid and minicircle DNA. Today, PlasmidFactory has 50 highly qualified employees. For more than four years now, the company has been working at full speed and on an extraordinary scale - in addition to scientific research and optimisation of production â??especially for production of mRNA vaccines. Dr Schleef shares his insights about PlasmidFactory and his rich experience in developing life-saving products.



You have been working in plasmid research and production for more than 30 years and have played a crucial part in contributing to the development of the COVID-19 mRNA vaccine. How did this come about?

PlasmidFactory specialises in producing DNA of extraordinarily high purity for gene therapy and genetic vaccine research. We are an established supplier to biotechnology and pharmaceutical companies as well as to universities and research institutes worldwide. We are well-known within the industry. All manufacturing, research and development is concentrated at the Bielefeld site in Germany. Our manufacturing processes for plasmid DNA are ideally suited for producing mRNA vaccines based on it.

Was the rapid growth in demand for mRNA for vaccines surprising?

Not really. Plasmids have been used as starting materials for manufacturing viral vectors (AAV, Lenti, etc.), and for producing RNA for quite some time. In particular, the production of plasmid DNA as a starting material to produce RNA cancer therapeutics and vaccines has become very important, especially against the background of the COVID-19. RNA is considered a promising vaccine candidate for the prevention of certain viral infections. It has the advantage of neither integrating into the genome of the cell nor remaining in the long term as a potentially effective active molecule in a patient's body. Besides protection against COVID-19, recently developed mRNA-based vaccines have been tested for their protection against influenza virus, Zika virus, cytomegalovirus, and many others. In addition, various mRNA vaccines are currently being tested for their tolerability when used as combination vaccination. So, as you can see, the current applications for mRNA are not yet exhaustive, and we look forward to continuing to play an essential role in the value chain.

Large-scale manufacturing and production in the highest purity grades of plasmid and minicircle DNA as a starting material for RNA vaccines has gained importance. How did you ensure that PlasmidFactory can handle both parameters simultaneously?

We have been working in this area for several years and are constantly optimising it. Even before COVID-19, 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 the laboratory expansion was finalised. We received funding from the NRW state government and have been able to produce on a multi-gram scale in High Quality Grade to support the COVID-19 vaccine industry.

Moreover, investments have been made to implement the manufacturing of DNA in full GMP Grade. The newly built GMP facility is also located in Bielefeld and will be up and running by the end of summer 2024. This will enable us to provide our global customers not only with High Quality Grade but also with GMP Grade plasmid and minicircle DNA on a large scale.

You mentioned the term "High Quality Grade". Is it your creation, and what exactly does it mean? How does it differ from GMP Grade?

Yes, initially, it is, but it denotes "high quality", so the term is now also used by other manufacturers.

Our "High Quality Grade" plasmid DNA was established over 15 years ago based on the EMA guidelines CHMP/BWP/2458/03, CPMP/BWP/3088/99, and, since 2021, on EMA/246400/2021 for highest quality requirements. For product safety reasons, the manufacturing process avoids using substances of animal origin throughout the entire production chain. It 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 (HQ) Grade plasmids; no parallel plasmid productions occur 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.

Actually, HQ Grade products are already being used in clinical trials studies. However, GMP Grade goes one step further by exclusively using single-use equipment and complying with applicable GMP guidelines, and it is, of course, GMP certified. This is a stand-alone trait and signifies another important step in PlasmidFactory’s goal to further extend the lead over the competition.

What unique expertise do you have in this field?

The proprietary, unique purification process is one of our unrivalled advantages. It results in a high grade of pure, supercoiled (ccc) plasmid monomers that meet regulatory requirements to form a defined, homogeneous product, which undergoes a series of cell bank and plasmid DNA product quality control checks before release.

High-quality Grade Plasmid DNA is produced based on a cell bank (RCB) created at PlasmidFactory and the uniquely 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 a product is ultimately created that is tailor-made for the respective application or as per 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 precisely optimised and, if necessary, further developed because we want to be uncompromising in quality and competence.

HQ and GMP Grade DNA are required not only for vaccine production but also in the field of cancer research. Could you elaborate?

That's right, with our national and international customer base, we at PlasmidFactory are also well positioned in other research areas.

Exciting and no less important is the so-called CAR-T cell development. Ongoing research and advancements in CAR-T-cell technology currently unlock new possibilities for personalised and targeted cancer treatments. This groundbreaking approach has demonstrated remarkable success.

PlasmidFactory has developed and patented a method for producing CAR-T cells. 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 (MC) technology contributed to the success of CAR-T cell therapy?

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 and highly effective vector system is the result. It already meets the future regulatory requirements for gene therapy and vaccination.

We also produce customised minicircles using our unique, patented method: the plasmid containing 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 GOI.

The minicircle DNA, produced with our proprietary technology, is patented for use in CAR-T cells worldwide and is exclusively available at PlasmidFactory.

What kind of R&D activities do you have at PlasmidFactory?

The R&D activities of the PlasmidFactory are carried out in our laboratories, as well as in close cooperation with national and international partners.

For example, in the fields of:

- Optimisation of vectors to produce viral vectors (AAV or LV) or for efficient antibody or RNA production

- Development of resistance gene-free vector systems (e.g., minicircles)

- 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

- High cell density cultivation

- Single use technology in process technology

- Linear DNA vectors with loops at their ends (MIDGE)

- Vector development and gene transfer

Besides these scientific collaborations, we are also implementing strategic partnerships. In 2022, we partnered with ARCHIMED, a leading investment firm focused exclusively on healthcare industries. With ARCHIMED at our side, we are strengthened in expanding our business globally.

In addition, we have also found a more specific partner to support us in entering the Indian market.

Does this mean you have a new strategy to meet the increasing demand for highest quality DNA in the Indian market?

Yes, we do. After the success in handling COVID-19 in India, a large number of biotechnology and pharmaceutical firms are investing heavily in mRNA R&D. We are pleased to introduce Dr Nagaraj Rao, RRR Labs, Navi Mumbai, as our new partner in India. Dr Rao is well-known in the Indian pharma industry and among Indian biopharmaceutical and vaccine manufacturers for providing customers with state-of-the-art media and feeds for mammalian cell culture in recent years. Having lived in Germany for a decade earlier, his strong support and his role in bridging communication gaps between Indian and German companies play a crucial role in the success of such technology-driven businesses.

Being a biologist, how are you able to balance the business and research activities?

I am a biologist and researcher who manages the PlasmidFactory family. PlasmidFactory's products are manufactured by an energetic team of motivated colleagues.

Our 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 unique techniques, we want to advance biotechnology together - a simple part of my DNA.