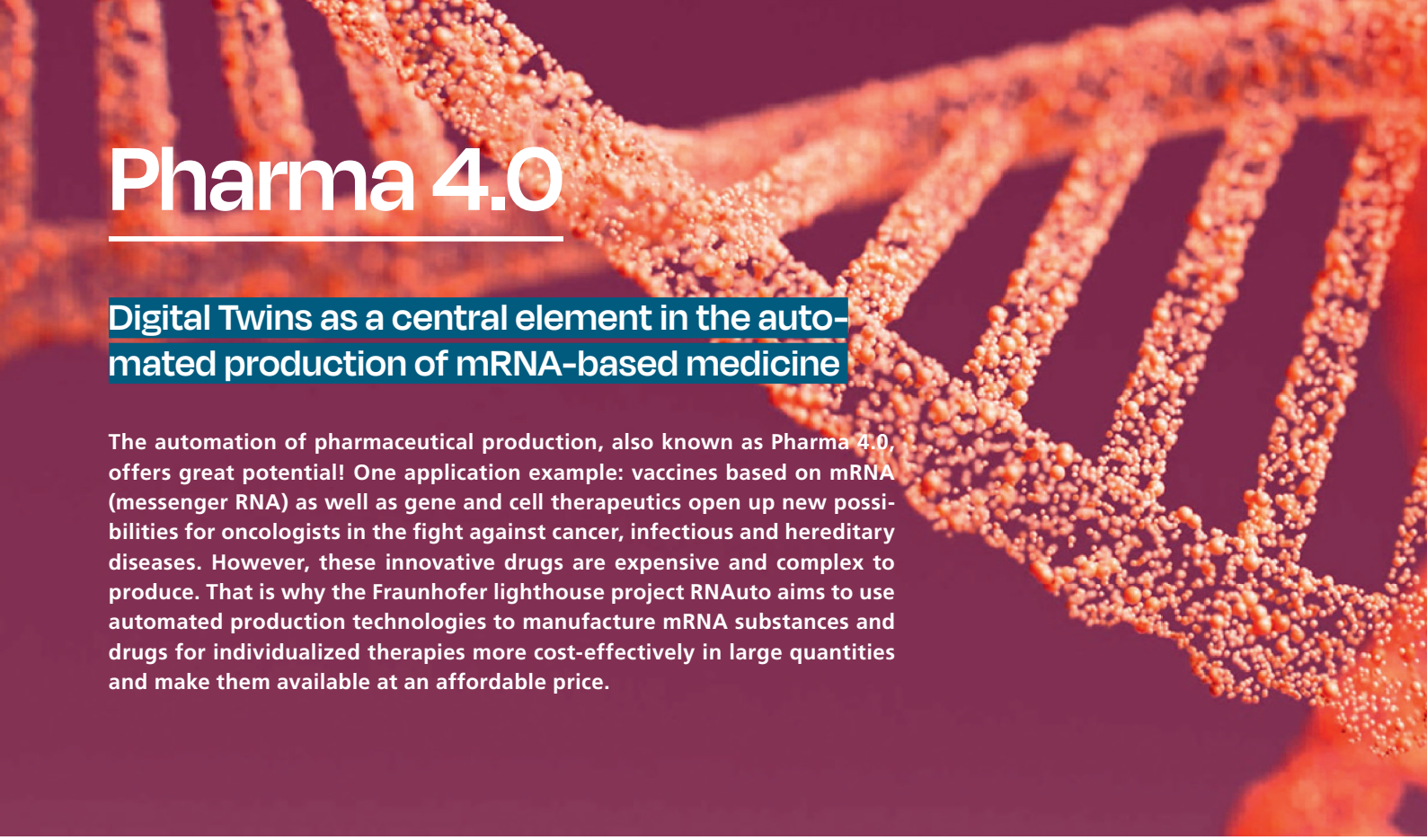


Pharma 4.0

Digital Twins as a central element in the automated production of mRNA-based medicine

The automation of pharmaceutical production, also known as Pharma 4.0, offers great potential! One application example: vaccines based on mRNA (messenger RNA) as well as gene and cell therapeutics open up new possibilities for oncologists in the fight against cancer, infectious and hereditary diseases. However, these innovative drugs are expensive and complex to produce. That is why the Fraunhofer lighthouse project RNAuto aims to use automated production technologies to manufacture mRNA substances and drugs for individualized therapies more cost-effectively in large quantities and make them available at an affordable price.

In order to offer tailored, personalized therapies to as many patients as possible, fully digitalized, automated production processes are required. In the lead project RNAuto, seven Fraunhofer Institutes have been pooling their expertise in the fields of medicine, biology and engineering since the beginning of 2022 in order to produce mRNA vaccines and gene and cell therapeutics that use mRNA as a starting material automatically, quickly and cost-effectively in large quantities.

Modular screening system for the production of mRNA substances

One focus of the research work is the development of a screening platform that is scalable up to industrial scale with digital process control and data-driven online quality control, with which mRNA can be encapsulated in lipid nanotransporters. The project team is initially aiming for mRNA drug production on a laboratory scale of up to 20 ml. In cooperation with the Fraunhofer Institutes for Microsystems and Microtechnology IMM, for Production Technology IPT and for Cell Therapy and Immunology IZI, the Fraunhofer Institute for Experimental Software Engineering IESE is coordinating the design and construction of the automated, component-based screening system. The system, measuring 1.4 m x 0.8 m x 1.6 m, consists of scalable, flexible and manufacturer-independent production modules that can be easily replaced in the event of a defect.

Use of Digital Twins in quality control and process control

In order to produce a dependable mRNA drug, consistent product quality must be guaranteed, including, for example, quantification of the amount of encapsulated mRNA in the nanotransporters. The uneven ratio of encapsulated mRNA at the start of the mixing process and high flow rates in the production process pose challenges for continuous quality control. Due to the resulting fluctuations in the viscosities of the mixture, refractive indices, conductivities, temperatures and pH values and the corresponding influence on product quality, not only process optimisation but also comprehensive quality control and documentation of the fractions is crucial.

Quality assurance and process control, i.e. the control of pumps, mixers and further devices, are fully digitally mapped – via Digital Twins and AI-supported software tools – a novelty in the production of mRNA active ingredients. To this end, the researchers are using their experience from Industry 4.0 and are utilizing software such as the Industry 4.0 middleware Eclipse BaSyx from Fraunhofer IESE and the process control software COPE from Fraunhofer IPT. Digital information for process monitoring and quality assurance is recorded via the Digital Twins of the individual components. One example is the DLS (Dynamic Light Scattering) detector, a messurement technique for characterizing particle sizes in emulsions. Further data is recorded via temperature and pressure sensors, flow sensors, viscosity sensors and pH sensors. Each component is represented by its own Digital Twin.

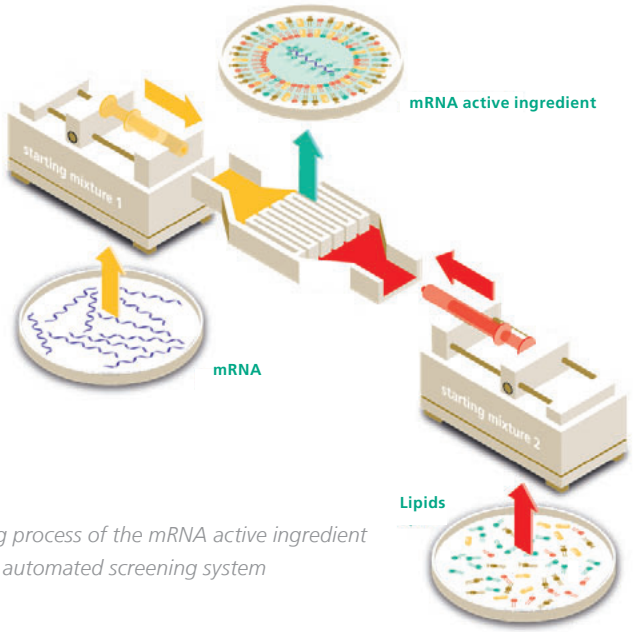
Digital Twin enables online analytics and digital documentation

With the screening system, the project partners can determine the optimal combination of mRNA and lipids and the best degree of packaging. Each individual test with changed parameters can be recorded digitally using the Digital Twin of product quality. Any errors, such as temperatures that are too low, are documented

in this way and the associated information is made available digitally.

In the final expansion stage, the Digital Twin will be able to initiate appropriate corrective measures in such a situation. With the integrated online analytics, the quality can be automatically measured during the manufacturing process and the optimum active ingredient composition and production parameters can be determined. The system will enable automated, component-based, flexible and validatable production, bringing the vision of Pharma 4.0 production closer step by step. Upon completion, the team of researchers will be able to produce 20 ml of mRNA active ingredient in a quality-assured manner within a few seconds.

Once the screening platform has been completed, a mRNA vaccine against West Nile fever will be produced as part of the research project. The vaccine will be tested for its effectiveness at the Fraunhofer IZI in Leipzig. By the end of 2025, it should be fully developed at the Fraunhofer IMM in Mainz and also made available to industrial partners.



Mixing process of the mRNA active ingredient in the automated screening system

Further information:
https://www.iese.fraunhofer.de/de/referenz/rnauto.html