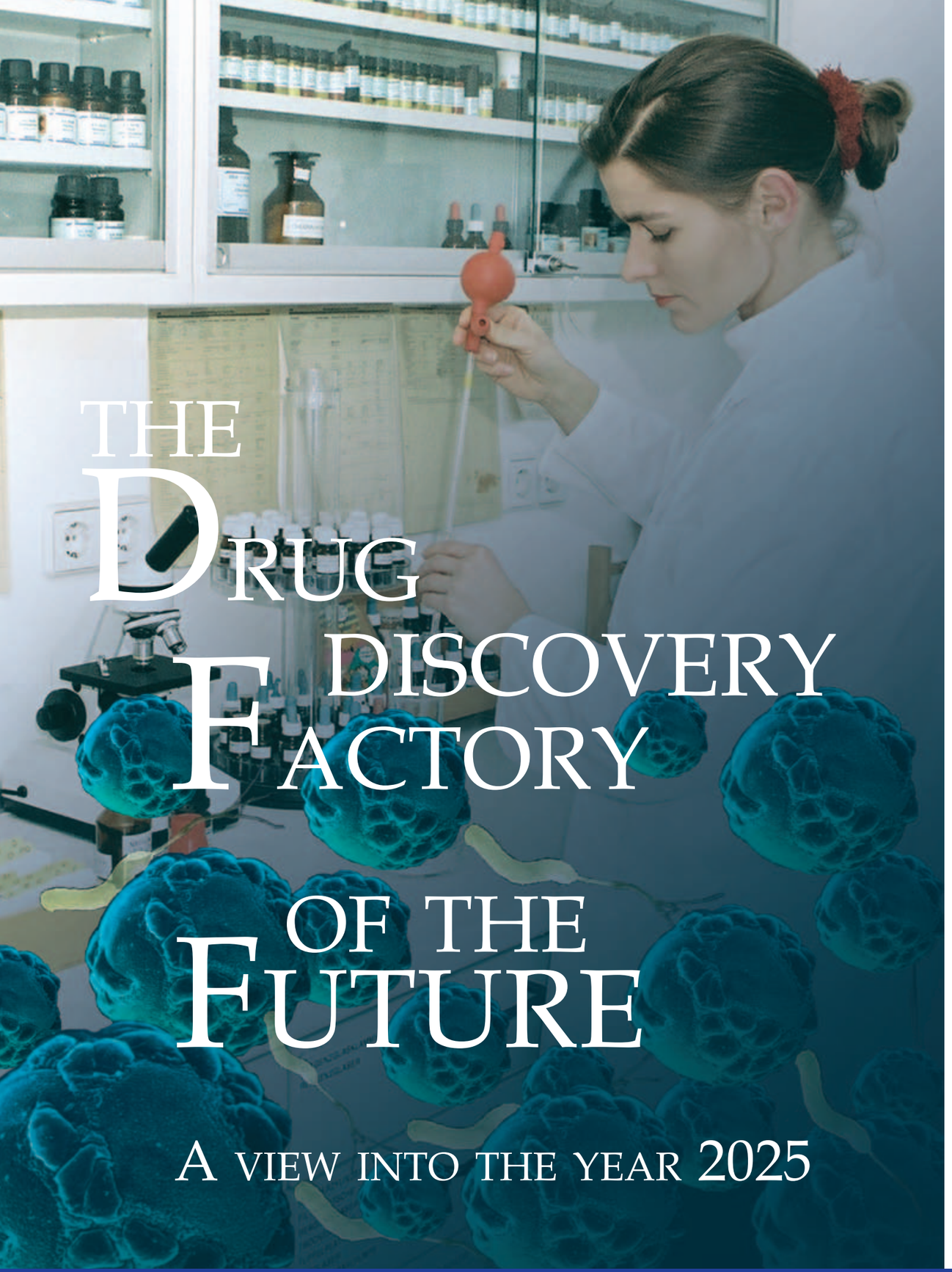


THE DRUG DISCOVERY FACTORY OF THE FUTURE

A VIEW INTO THE YEAR 2025

The evolution of novel viruses and bacteria has always been a fundamental threat to mankind. Known pathogens, regarded as finally being treatable by established drugs, may mutate and regain their deadly power. All these pathogens burden the budget of health care systems, hamper global trade and traffic and even cause health care systems of certain countries to collapse. Diseases of the Middle Ages – forgotten or still unknown – spread at great speed, especially in developing countries. The poorest seem to have abandoned hope, forsaken by the rest of the world. Which pharmaceuticals may be able to help here? Where can new drug candidates be found and how can therapeutic solutions be brought up rapidly after new diseases have evolved?

About ten years ago this was the scenario we all expected for the year 2025. The media were full of reports on epidemics unstoppable spreading all over the globe and the apocalyptic circumstances that were certain to follow. Today, this all plays a much less pronounced role in public reception. What happened? Have we become ignorant, do we not realize the problem anymore – or is there something that has revolutionized the treatment of infectious diseases?

Indeed, invisible for the public, a unique technological development has taken place. New or improved drugs are now rapidly accessible whenever variants of known infectious diseases develop. In fact, there is again a choice of 'last resort' medication against multi-resistant pathogens. NATFACT, the 'Natural Product Factory', is an example of a young company in the field of medicinal chemistry. NATFACT successfully manufactures drugs on the basis of natural products, employing new methodologies for synthesis. The key to success was the combined use of microfluid polycomponent reactor systems for chemical and enzymatic natural product synthesis and nano technology. We talked to Dr. Fischer, head of research and development at NATFACT, about NATFACTS's strategies and the technological background of their success.

DR. FISCHER, HAVE WE ALREADY WON THE FIGHT AGAINST MICROBES AND VIRUSES, EMPLOYING TECHNOLOGIES AND PROCEDURES LARGELY DEVELOPED BY NATFACT?

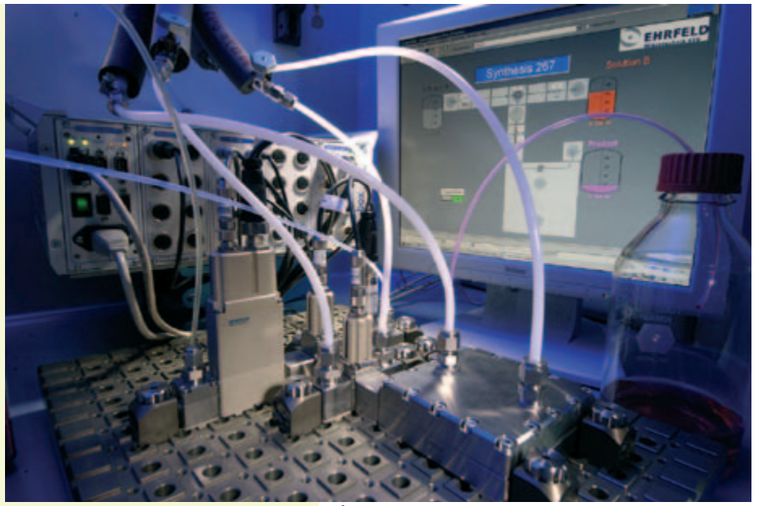
First of all, I have to straighten out that the fear of epidemics and plagues of biblical dimensions as well as deadly threats from the insight of earth or space have always accompanied mankind. People then usually react by turning to spirituality or religion. Today, innovation in technology and science has become the answer but the fight still reminds us of the race between the tortoise and the hare. What remains is "angst" and feelings of helplessness in the face of upcoming doom. That has never changed and despite of our great technological progress, we have yet failed to banish epidemics from earth. Microorganisms will always react with new strategies. It would be fatal and careless not to be prepared.

WHAT DISTINGUISHES CHEMISTS AT NATFACT FROM FORMER GENERATIONS OF CHEMISTS?

The origin of our innovation reaches back to the middle of the last century. Scientists realized that microorganisms are not only the cause for epidemics but also a source for medication against them - something that had long been known before for plants and their active ingredients. This paved the way for natural products to be widely used in the treatment of infectious diseases caused by bacteria and fungi, cancer and to some extent viral infections. The success caused us to become phlegmatic and overconfident, failing to continue research on natural products to an extent, necessary in light of emerging multiresistance. In fact, regarding natural products as too complex, too difficult to handle and too expensive in pre-commercial development had become a widespread

Nanotechnology
According to the generally accepted definition, nanotechnology is the study of structures exhibiting novel properties due to their small size (less than 100 nanometers in at least one spatial direction).

How will search for and synthesis of new drugs develop in the future?



The "Drug Discovery Factory" utilizes small microreactor flow elements.

attitude. Thus, simple automation technologies, i.e. robots, designed to copy and replace the classical synthetic chemist, infiltrated our laboratories. In medicinal chemistry, large libraries of fully synthetic compounds were generated and screened, disregarding the large potential of natural products – compounds already receptor-optimized during evolution. The consequence was disastrous: although large in number but without significant structural variety, these libraries were incapable of generating enough new lead compounds suitable as drug candidates. The result of this approach, known as "***Combinatorial Chemistry***", is well known: From the end of the 20th century on, pharmaceutical companies started to conduct numerous hostile takeovers in order to cover the large costs for little success in drug development. In many cases, the resulting humongous pharma-conglomerates could only survive by re-merchandising established pharmaceuticals of their former competitors.

THEN, OBVIOUSLY AUTOMATION AND HIGH-THROUGHPUT-TECHNOLOGY WAS NOT THE RIGHT STRATEGY?

The idea of automation was not wrong in principal, but any technology must focus on the principal question to be answered. In this case it was not just producing thousands of analogues but rapidly finding the counterpart to a biological target, i.e. the key to the lock. Natural products, being evolutionary validated ligands, provide excellent chances to fulfill the structural requirements of the receptor. During biological evolution, nature has only tested and developed a fraction of possible proteinic receptors. Due to statistical considerations, a full evaluation of all possible structures is not even feasible for nature. Small ligands, i.e. natural products, are the adaptors to these macromolecular structures, being especially developed for this world of receptors. Of equal importance is their ability to pass biological phase layers like ***membranes*** – a huge advantage for drug development. With the development of ***micro-reaction technology***, the application of immobilization strategies for chemical reagents, enzymes, antigens and whole cells, and the advent of nano-technology, the doors to a new sphere could be opened: the microfluid synthesis methodology, which is especially valuable for the provision of natural products and the synthesis of natural product analogues.

DR. FISCHER, PLEASE EXPLAIN TO OUR READERS WHAT IS THE BACKGROUND FOR THE TECHNOLOGIES DEVELOPED BY NATFACT!

We had taken into account the basics and known applications of nanotechnology and developed complex micro structures. These consist of fine micro channels, agitators, pumps, valves and electrodes in a glass matrix. It is possible to immobilize catalysts, reagents, enzymes and antigens at defined positions on the surface of these channels. Thus, chemical transformations can be conducted step by step or in parallel. A fluid, containing the reactants, is channeled through an entanglement of various devices, driven by small pumps or by electro-osmotic power and accordingly electrophoretic control units. We employ natural products or building blocks, which are transferred to natural products and derivatives or analogues, while passing reactive surfaces. Integrating sensors allow for online control of synthetic transformations. The flow is controlled by valves which may also direct intermediates in separate chambers, where they rest until their reaction partner from another part of the system is assembled. This concept, known as "Lab on a Chip", represents a drug discovery factory or, in our case, a natural product factory. Its design is extraordinarily flexible and allows for the assembly of complex products "just on time" – just like nature does it.

YOU HAVE JUST MENTIONED NATURE AS A GUIDE – WHERE IS THE CONNECTION TO MICROFLUID REACTION FACTORIES?

We should not only take nature as a guide for structures, i.e. the product side, but also for the manufacturing process, i.e. the bioengineering. Nature produces in micro factories, namely in cells, which contain volume in the range of a few microliters. Dividing the cell in compartments, and channeling reactants across functionalized surfaces are major principles. Membranes and cytoskeleton surfaces, mostly covered with enzymes, act as functionalized surfaces. Why then, should we not abandon the idea of a closed reaction vessel which does not allow exchange of matter with its environment? Several years ago, we asked ourselves: Why not follow nature's way and create microfluidic systems with functionalized surfaces? The volume transported through our factories are only marginally larger than those in cells. It is possible to show that diffusion only plays an insignificant role in these systems, allowing for an excellent exchange of matter and energy. Our modulated synthesis system enables a rapid and defined assembly of natural products and derivatives of outstanding structural complexity and variety. Subsequent biological screening assures optimal exhaustion of the pharmacological potential of natural products. By now, this method of micro-manufacture is also applied to provide flavors in food industry. Whenever we are to produce larger amounts of a natural product or a derivative, we can imitate nature again: nature does not use mega-cells but hundreds of thousands of cells in parallel.

Dr. Fischer, we thank you for this interview.

Richard Dehn & Andreas Kirschning

Small and beautiful: The "Drug Discovery Factory" in operation.

Combinatorial chemistry
Chemical-synthetic processes allowing for the rapid assembly of huge substance libraries within few synthetic transformations.

Lead structure
Molecular template of a compound serving as model system for structures with similar properties.

Membrane
Separating layer between compartments of a cell or between a cell and its environment (cell membrane). A biological membrane is not only a passive separating layer but also plays an active role for the transport of molecules and information from one side to the other.

Micro-reaction technology
Development and application of chemical reactors on a micrometer scale.

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Links on the Web

Ehrfeld Mikrotechnik BTS
www.ehrfeld-shop.biz/shop/catalog/index.php

ThalesNano Nanotechnology Inc
www.thalesnano.com

What will our destiny be, if current antibiotics and antiviral drugs have lost their potency due to resistancy?