

# Polishing Medical Rough Diamonds

The Max Planck Society has established a new center in Dortmund to make better use of the enormous potential of basic research in the area of drug discovery, and to bridge the gap between basic research and industrial product development. In this way, it aims to ensure that innovative ideas don't fall by the wayside before being given an opportunity to come to fruition.

TEXT **MARCUS ANHÄUSER**

Analytical challenges: Poured into specimen jars, potential drug candidates are subjected to elaborate testing.



**T**he location is the outskirts of the German city of Dortmund. The days of coal mining and shaft towers are long gone here in the southwest. A number of research institutes, the Technical University, and the University of Applied Sciences have all cropped up on a campus called the “Technology Center.” Since the mid-1980s, around 280 small and large companies involved in the electronics, microtechnology and nanotechnology sectors have also found a home on the campus near the academies – visible proof of the structural change that has been driving the region for decades. Similar to the companies that can often be found in the technology parks of any major city, 26 of these operations generate their revenues in the life sciences: bio-IT, analysis technology and medical technology.

In November 2008, however, a new company unlike any other anywhere in Germany opened its doors on the first and second floors of the Biomedicine Center: the Lead Discovery Center, or LDC. It was founded by Max Planck Innovation, the Max Planck Society’s technology transfer company. Any assumption that this is likely just another Max Planck Institute is mistaken: “It is an independent company,” explains Matthias Stein-Gerlach, Patent and Licensing Manager at Max Planck Innovation.

The clue to the objective of the limited liability company lies in its name: “lead” is a term used in the drug discovery field. It does not, however, refer to the leading position in a class of drugs

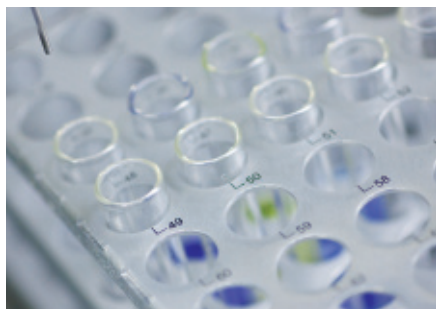
or medications. A lead is a well-characterized representative of a defined substance class that emerges in the early initial phase of drug discovery research. It is the core around which everything else revolves – the molecular diamond in the rough that needs refining and polishing to become a potent agent. “The Lead Discovery Center does not develop drugs – it discovers new substances using ideas from basic research. The pharmaceutical industry then eventually develops new drugs from these substances,” says Stein-Gerlach, describing the concept behind the LDC.

#### **POTENT SUBSTANCES FROM BASIC RESEARCH**

Drug discovery is a quintessential industry field. Although elements of this activity are carried out at the Max Planck Institutes and other academic research facilities, “they are basically only minor components of the overall process,” says Stein-Gerlach. It was clear that setting up an institution like the LDC would require the help of industry experts who had several years of experience in drug discovery and who would also be able to manage the process. “And we wanted to create a center that would inspire such people, where they could establish their own business model, and where we are not tied to public-service salary structures,” says Stein-Gerlach. That it why the decision was made to set up a private enterprise.

The scientific manager is one of the initiators and heads a project called the “Drug Discovery & Development

» The early phase of drug discovery is filled with imponderables. A lot of established firms get cold feet. “They immediately respond that it is too risky for them,” says LDC Managing Director Bert Klebl.



No job for the impatient: Fractionated samples are repeatedly collected, cleaned, analyzed and tested again.

Center” (DDC). The LDC is the first module of the overall DDC concept and has already been implemented. The second module has only a working title for now – Development Company (DevCo) – and is in the process of being set up. That is where the rough diamonds from the LDC will undergo their initial polishing before being licensed to pharmaceutical companies, which will then refine them further to produce potent drugs. While the LDC retains some financial ties to the Max Planck Society, the DevCo will be financed completely through private funding. “The Development Company is a playground for all of the business models found in the biotechnology sector: co-development, co-financing and cooperation,” explains Stein-Gerlach.

The aim of the general concept is to close a gap by enabling the LDC to build a bridge between basic research and industrial drug development. The

problem to be solved: there are many good ideas for innovative therapeutic approaches, particularly in the Max Planck Institutes, but far too few of them make it to the industrial development stage. “Some of these approaches are developed for the market by spin-off companies, or are licensed to third parties as patents through Max Planck Innovation,” says Stein-Gerlach. The cancer drug Sutent is a successful example of this approach. This drug, which is based on a novel mechanism of action against renal cell cancer, was developed in the 1990s by Max Planck scientists working with Axel Ullrich. It received regulatory approval in the US and the EU in 2006.

Yet, according to Stein-Gerlach, most of the treatment-relevant discoveries made by Max Planck researchers are at too early a stage in their development. For this reason, they are often dismissed as being of insufficient interest to the pharmaceutical industry or private investors. Established companies get cold feet if the cellular target behind the discovery is not precisely identifiable, or if an entirely new approach is adopted: “They immediately respond that it is too risky for them,” says Bert Klebl, who, together with chemist Peter Nussbaumer, is Managing Director of the LDC.

The imponderabilities of the early phase of drug discovery probably also explain why major pharmaceutical companies are withdrawing more and more from this sector. Many believed that small gung-ho biotech companies would step into the breach, but this hope has remained largely unfulfilled.

“Apart from a few exceptions, hardly any biotechnology companies in Germany today are involved in substantial research activities. The majority of them have retreated into the service business,” says Klebl, who is also Chief Scientific Officer (CSO) of the Max Planck startup.

He and Nussbaumer themselves worked in the pharmaceutical and biotech sectors for several years. Now they and their 30-plus employees want to forge a link between two worlds that have drifted apart: academic and industrial research. “We want to bring the participants together to the table again and act as their interpreters,” says Klebl. The problem, however, is that the two worlds pursue different goals. Scientists engaged in basic research are constantly on a quest for something new and off the beaten track. This furthers their careers and enables them to publish. This is of no interest whatsoever to industrial researchers: “Industry only works on projects with clearly defined work packages and milestones,” says Klebl. Those who stray from the beaten track run the risk of getting lost. There is no time for flights of fancy in the creative sense, for following one’s curiosity: “That simply costs too much,” says Klebl.

### **COSTLY DEVELOPMENT, HIGH RISK**

The development of a drug is time-consuming, expensive and risky. As a rule, a period of 10 to 15 years passes from the initial idea to the appearance of the end product on pharmacy shelves. Ac-



cording to the German Association of Research-Based Pharmaceutical Companies (VFA), the cost of developing a drug is around EUR 600 million; other sources put it at EUR 100 million. The rule of thumb is that for every successful project, 99 fail to come to fruition. The high attrition rate is due to not only scientific factors, but also structural ones within the pharmaceutical concerns and biotech companies. This problem will not exist at the LDC: "While we must also expect that some projects may not work, we are spared the risk of making rushed strategic decisions that have implications for company politics and survival," says Stein-Gerlach.

In the biotech sector, for example, "people cling desperately to one or two projects and do everything possible to drive them forward. Otherwise, they face the threat of bankruptcy," says Stein-Gerlach. Indeed, financial bonuses in the pharmaceutical sector are often dependent on reaching the next phase in a project. As a result, repeated attempts are made to progress to the next round with – scientifically – unpromising candidates. Not so in the

LDC: "Scientific quality is the only criterion here," says Stein-Gerlach. The business model does not provide extra rewards for keeping projects going. There is no fear of dropping a project for a new one, as the next one is already on the starting blocks anyway. "It's a bit like a biotech company with a never-ending pipeline supplied by the research carried out at some 30 life science institutes of the Max Planck Society," he adds. The supply of potential projects is guaranteed.

### **AN EYE ON THE SHARE PRICE AT ALL TIMES**

The conflict between science and capital in the pharma industry, and to a much greater extent in biotech companies, poses another problem: "The scientists there struggle with very short investment cycles of just two or three years, which they must coordinate with the long development periods," says Bert Klebl. Situations often arise between the financial backers and company employees in which the focus is less on scientific objectives than financial ones. In other words, shareholder

They filter potential drug candidates by their scientific quality: The Lead Discovery Center's Managing Directors Bert Klebl (left) and Peter Nussbaumer.



top	Birgit Ammermann from the Pharmacology Department loads a mass spectrometer with a view to determining the properties and the stability of a substance.
bottom	Still life from the lab: The reservoir bottles contain buffer solutions, which supply the analyzers through tubes.

value and investor satisfaction dictate how scientific results are presented. The LDC operates independently of such short investment cycles and of individuals whose only concern is to capitalize on science as quickly as possible.

That doesn't mean, however, that the LDC isn't interested in making money. On the contrary – it is, after all, a private enterprise. One long-term source of income will be the returns from licenses for substances developed at the LDC. An additional fund has been established that invests in the DevCo's projects with the hope of eventually making a profit from these. Irrespective of the capital market's playing rules, everyday activity is initially financed by different sources, such as private investments, donations and public subsidies. Then there are funds for projects of the Max Planck Society and other institutes that form development partnerships with the LDC for the implementation of their projects.

There was also a fortuitous windfall right at the beginning, in the form of prize money: the DDC concept won the German Federal Ministry of Education and Research's BioPharma Strategy Competition in September 2008, for which it received a sum of EUR 20 million. After three years and successful evaluation, these winnings can be increased by an additional several million.

Using funding from public and private sources, the LDC's 30-plus employees are currently working on six projects. These include a project that may produce a drug for the treatment of cancer or Alzheimer's disease. Mat-

tias Baumann, an expert in pharmacokinetics, heads this project, which operates internally under the name PP2A and combines many of the typical elements of an LDC project: The idea originates from a Max Planck Institute, has solid scientific foundations, and is based on an original approach that probably would not be pursued by a pharmaceutical company.

### THE GREAT HOPE FOR CANCER AND ALZHEIMER'S TREATMENT

The project was initiated by a group of researchers working with human geneticist Susann Schweiger, who now works at the University of Dundee in Great Britain. Before moving to Scotland, she was a researcher at the Max Planck Institute of Molecular Genetics in Berlin, in a department headed by Hans-Hilger Roper, with whom she still maintains close ties. The team is supported by Rainer Scheider's team at the Institute of Biochemistry at the University of Innsbruck.

The starting point of the project is the protein phosphatase 2A molecule (thus the abbreviation PP2A), an enzyme that removes a phosphate moiety attached to a molecule's amino acid residue. Scientists call this process dephosphorylation. "PP2A plays a role in a significant number of the body's cellular signal pathways," says Baumann. The molecule is of particular interest to medicine because it is a very powerful tumor suppressant. "If an agent can activate PP2A, or even prevent its blockage, you have a good chance of impeding the growth of cancer cells," says

Baumann. And that's not all: because PP2A also plays an important role in regulating the proteins associated with a cell's cytoskeleton, it also plays a role in Alzheimer's disease.

The roots of this project lie far in the past. In the 1960s, American geneticist John Opitz described a genetic disorder characterized by abnormalities of the midline, or central axis, of the human body. The condition was named after him. Patients who suffer from this disorder are born with a cleft jaw or palate and have wide-set eyes and a deformed urethra. It wasn't until the 1990s that the genetic cause of the disease, in at least some of those affected by the condition, was identified: the mutation of a gene called MIDLINE 1, abbreviated MID1. If this gene fails to function to its full capacity, the embryo doesn't develop properly.

### NOT AN EXCLUSIVE CLUB

In 2001, the Berlin-based research group working with Schweiger, Ropers and Schneider discovered a crucial correlation in the emergence of Opitz syndrome: the protein MID1, which is coded by the MID1 gene, connects to PP2A via a regulatory subunit and causes the degradation of the PP2A. This is normally how things work and is precisely what fails to occur in people with Opitz syndrome. They have an elevated PP2A level, the very state that would be advantageous to cancer and Alzheimer's patients, as it would prevent the growth of cancer cells in the former and the accumulation of the tau proteins that gives rise to Alzheimer's in the latter. >

»» Until a molecular structure emerges that has what it takes to become an active agent, they work on the principle that “the proof of the pudding is in the eating.” Only then is the molecular equivalent of a rough diamond polished and tested further.

### THE LONG ROAD TO THE PHARMACY SHELF

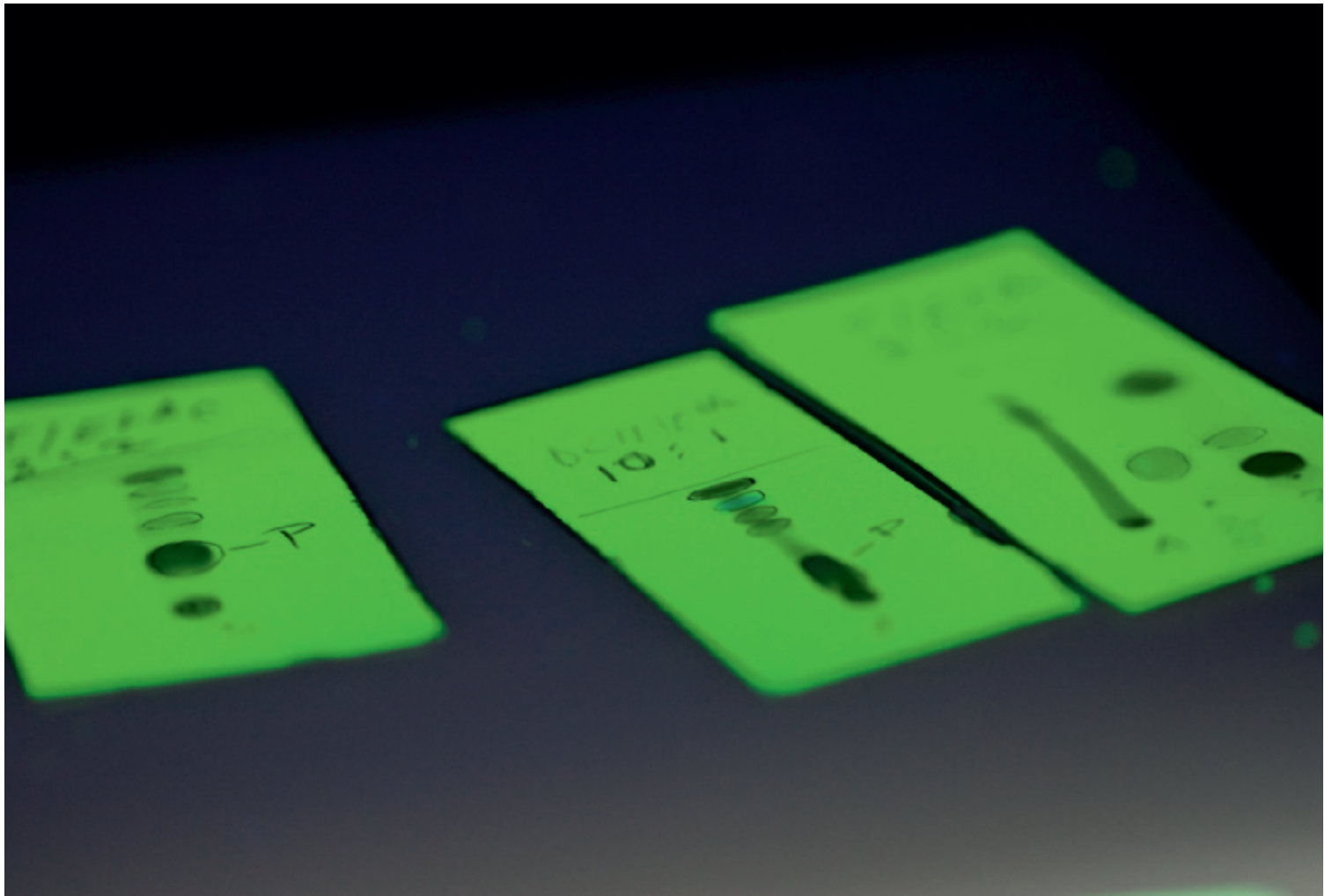
Any substance that hopes to become the active agent in a potent drug undergoes a selection process similar to those used in the “Next Top Model” or “Idols” TV talent contests. There are three major phases leading to regulatory approval of a drug, a process that can take up to 15 years. The starting point is often a target – a target structure in the body that is associated with a disease and that can provide clues as to a possible active agent that could hinder the course of the illness or influence it positively. One example is a receptor that provides a docking site for a signal molecule that is part of an inflammatory process.

Once the researchers have discovered this target structure, they then try to find a substance that attaches to it and activates or blocks it. At this stage, they generally work on the principle that “the proof of the pudding is in the eating.” Therefore, thousands of substances, referred to as compounds, in substance libraries are tested in automated processes until a molecular structure emerges that has what it takes to become an active agent. This is the first “hit.” If it can be further optimized, it becomes the “lead.” Once this rough diamond has been discovered, a selected representative of this lead structure series is developed. “You start with a framework, the scaffold, which can be decorated in different ways to see whether the molecule becomes more potent, soluble, or perhaps even more toxic,” says Matthias Baumann, biologist and pharmacokinetics expert at the LDC.

A framework of this kind can be a chemical structure, such as an aminopyrimidine, a ring consisting of two carbon atoms, two nitrogen atoms and an amino group. Various other chemical groups are then attached to these in hopes of improving the active agent. The X-ray crystal structure of the target together with the substance in question is helpful here: “Then you know, for example, how a compound docks into the active pocket of an enzyme. You can see where space remains at which you can link other interactions with the enzyme, for example via hydrogen bonds,” explains Baumann. The key gradually achieves a better fit with the lock – the substance gains in potency and selectivity. The lead is then tested in increasingly complex situations, first in solutions, then in cells and, finally, in live animals. If it passes this hurdle, this is considered the “proof of concept.” The LDC offers its services up to this point.

In the pre-clinical phase, the active agent is scrutinized in greater detail, mainly in tests on animals ranging from mice to monkeys, to establish how it progresses through the metabolism and what kind of side effects it triggers. The clinical phase takes place at the end of the “contest” to find the active agent. The latter then undergoes tests for utility, safety and potency as compared with a placebo in the course of three stages (phase 1 study, phase 2 study, phase 3 study). During these stages, the tests become ever more complex and are carried out on increasing numbers of people. Only when the substance has overcome these hurdles does the selection process come to an end. Then the drug can finally be approved for use in patients.





The laboratory tests carried out by the research group with which Baumann and his colleagues collaborate confirmed that this is how things could work. "If we could induce a situation similar to that found in the bodies of Opitz patients, we would have a possible opening or starting point for the treatment of Alzheimer's and cancer," says Baumann. The researchers are thus looking for a substance with which they can prevent MID1 from connecting to the regulatory subunit and neutralizing PP2A.

The PP2A project is an example of the form a project must take if it wants to survive the review process. Simply having an idea is not enough. "The project should also have already been thoroughly validated by tests," says Baumann. At the very least, initial tests that confirm and validate the hypothesis must be available.

The PP2A project is just one of three projects that aim to discover a treatment for cancer and, perhaps, eventually follow in the footsteps of Sutent. In the other two projects, the scientists

have set their sights on treatments for autoimmune diseases and inflammation. All six projects involve basic research from Max Planck Institutes. And this is just the beginning.

It is also intended to make the LDC available to other research institutes, universities and companies throughout Europe. "It shouldn't remain an exclusive club for the Max Planck Society," stresses Stein-Gerlach. Good scientists with interesting ideas can also be found at other institutes, and the LDC wants to help them to make the leap into industry as well. The LDC will generate income every time such a project succeeds. Thus, research projects that have received public funding would have an opportunity to give something back to the public. Space is already at a premium in the offices and laboratories of the Biomedicine Center in Dortmund; a move to new premises a few blocks away is planned in the near future. The new premises will provide more than double the amount of workspace currently available, thus creating the space needed to test lots of new ideas. ◀

Thin-layer chromatography spectra under UV light: Scientists can use this technique to quickly demonstrate the purity of newly synthesized substances or follow the progression of the syntheses.