To:	Merus N.V. (jlclark@woodphillips.com)
Subject:	U.S. TRADEMARK APPLICATION NO. 79225691 - DOCK & BLOCK - 11137T00050U - Request for Reconsideration Denied - Return to TTAB
Sent:	4/16/2019 4:49:32 PM
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Attachments:	Attachment - 1 Attachment - 2 Attachment - 3 Attachment - 4 Attachment - 5 Attachment - 6

UNITED STATES PATENT AND TRADEMARK OFFICE (USPTO)
OFFICE ACTION (OFFICIAL LETTER) ABOUT APPLICANT'S TRADEMARK APPLICATION

U.S. APPLICATION SERIAL NO. 79225691

MARK: DOCK & BLOCK

79225691

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APPLICANT: Merus N.V.

CORRESPONDENT'S REFERENCE/DOCKET NO:
11137T00050U
CORRESPONDENT E-MAIL ADDRESS:

jlclark@woodphillips.com

REQUEST FOR RECONSIDERATION DENIED

ISSUE/MAILING DATE: 4/16/2019

INTERNATIONAL REGISTRATION NO. 1386289

The trademark examining attorney has carefully reviewed applicant's request for reconsideration and is denying the request for the reason stated below. *See* 37 C.F.R. §2.63(b)(3); TMEP §§715.03(a)(ii)(B), 715.04(a). The following refusal made final in the Office action dated October 2, 2018, is maintained and continues to be final: SECTION 2(e)(1) PARTIAL REFUSAL. *See* TMEP §§715.03(a)(ii)(B), 715.04(a). The following requirement made final in the Office action is satisfied: INDEFINITE IDENTIFICATION OF GOODS. *See* TMEP §§715.03(a)(ii)(B), 715.04(a).

In the present case, applicant's request has not resolved all the outstanding issues, nor does it raise a new issue or provide any new or compelling evidence with regard to the outstanding issue in the final Office action. In addition, applicant's analysis and arguments are not persuasive nor do they shed new light on the issues. Accordingly, the request is denied.

If applicant has already filed a timely notice of appeal with the Trademark Trial and Appeal Board, the Board will be notified to resume the appeal. *See* TMEP §715.04(a).

If no appeal has been filed and time remains in the six-month response period to the final Office action, applicant has the remainder of the response period to (1) comply with and/or overcome any outstanding final requirement(s) and/or refusal(s), and/or (2) file a notice of appeal to the Board. TMEP §715.03(a)(ii)(B); *see* 37 C.F.R. §2.63(b)(1)-(3). The filing of a request for reconsideration does not stay or extend the time for filing an appeal. 37 C.F.R. §2.63(b)(3); *see* TMEP §§715.03, 715.03(a)(ii)(B), (c).

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CANCER DISCOVERY

Research Watch

A Bispecific Antibody Targeting HER2 and HER3 Suppresses Tumor Growth

DOI: 10.1158/2159-8290.CD-RW2018-087 Published July 2018 Check for updates

Article | Info & Metrics

- **Major finding:** Unbiased phenotypic combinatorial screening uncovers a bispecific antibody (bAb) targeting HER2 and HER3.
- **Mechanism:** The HER2/HER3-targeted bAb blocks HRG/HER3 signaling through a "dock and block" mechanism.
- **Impact:** This bAb design may allow therapeutic targeting in tumors resistant to monoclonal antibody therapies.

HER2 dimerizes with HER3 to activate PI3K/AKT signaling and promote tumor growth and survival. Resistance to HER2-targeted therapies can occur via upregulation of HER3 or its ligand HRG. These findings support therapeutic approaches aimed at inhibiting HER3 pathway activation, but these strategies have failed to provide meaningful clinical benefit. Geuijen and colleagues sought to identify bispecific antibodies (bAb) that can potently block PI3K/AKT signaling via HER3. An unbiased phenotypic combinatorial screen of 545 bAbs targeting both HER2 and HER3 identified bAbs that potently inhibited tumor growth. Subsequent humanization and optimization of the top hit yielded PB4188, a bispecific immunoglobulin G1 (IgG1) antibody against HER2 and HER3. PB4188 potently inhibited tumor cell growth, even under high levels of HRG where monoclonal antibodies (mAb) targeting HER2 and HER3 failed to suppress growth. Further, PB4188 inhibited HRG-mediated HER2–HER3 heterodimerization and downstream signaling. *In vivo*, PB4188 inhibited HRG-driven tumor growth in a dose-dependent manner in an *ERBB2* (encoding HER2)-amplified breast cancer xenograft model, whereas the tumors were resistant to the HER2-targeted monoclonal antibody trastuzumab. Similar results were observed in other tumor xenograft and patient-derived xenograft models. PB4188 acted through a "dock and block" mechanism, with the HER2 antigen binding fragment (Fab) of PB4188 docking and saturating HER2 binding sites on tumor cells, thereby increasing the local concentration of HER3 Fab to block HRG binding to HER3 and abolish downstream signaling. These findings indicate that a IgG1-based bAb targeting HER2 and HER3 may be effective in tumors with hyperactive HRG/HER3 signaling even when mAb therapies have failed. Further, bAbs designed with this "dock and block" mode of action may allow for therapeutic targeting of a broad range of targets where clinical activity cannot be achieved using mAbs.

Geuijen CA, De Nardis C, Maussang D, Rovers E, Gallenne T, Hendriks LJ, et al. Unbiased combinatorial screening identifies a bispecific IgG1 that potently inhibits HER3 signaling via HER2-guided ligand blockade. Cancer Cell 2018;33:922–36.

Notes

Note: *Research Watch* is written by *Cancer Discovery* editorial staff. Readers are encouraged to consult the original articles for full details. For more Research Watch, visit *Cancer Discovery* online at http://cancerdiscovery.aacrjournals.org/CDNews.

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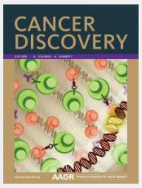

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Cancer Discovery
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NEWS

Dock and Block: Scientists Develop Technique That Makes Cells Resistant to HIV

From amfAR, The Foundation for AIDS Research

April 18, 2017

Scientists at The Scripps Research Institute (TSRI) have discovered a way of creating HIV- resistant cells by using antibodies to block HIV directly on the cell surface. Interestingly, in lab experiments, the resistant cells largely replaced the susceptible cells, potentially leading to long-term HIV protection.

The new technique, which researchers referred to as "a form of cellular vaccination," has an advantage over other therapies in that the antibodies are expressed by the cell and dock on the cell surface rather than float freely throughout the bloodstream. This allows the antibodies to block the specific interaction between HIV and CD4, the primary cell receptor for entry of the virus. However, the antibodies do not block CD4 from performing normal cellular activities.

Scientists initially used the rhinovirus as a model, which is responsible for many cases of the common cold. They used a lentiviral vector to deliver a new gene to cultured human cells. The new gene instructed cells to synthesize antibodies that bind with the human cell receptor that rhinovirus needs.

Study senior author Dr. Richard Lerner (Credit: Kevin Fung, courtesy of amfAR)

In a Darwinian "survival of the fittest" lab dish, cells without antibody protection died off, leaving protected cells to survive and multiply, passing on the protective gene to new cells.

Researchers then tried the technique against HIV. The scientists aimed to protect immune cells normally killed by HIV. Using the same technique to discover antibodies that would specifically block the HIV-CD4 interaction, scientists engineered immune cells to express the antibody gene. The researchers found that even after attempted infections in a petri dish, the cells were resistant to HIV.

The researchers, led by study senior author Dr. Richard Lerner, Lita Annenberg Hazen Professor of Immunochemistry at TSRI, plan to collaborate with investigators at City of Hope's Center for Gene Therapy in Los Angeles to evaluate the new therapy before testing in patients. City of Hope currently has active clinical trials of using gene therapy and blood stem cell transplantation to cure HIV.

"The ultimate goal will be the control of HIV in patients with AIDS without the need for other medications," said Dr. John Zaia, director of the Center for Gene Therapy in the Hematological Malignancy and Stem Cell Transplantation Institute at City of Hope.

The ultimate goal will be the control of HIV in patients with AIDS without the need for other medications.

Commenting on the study for the *San Diego Union-Tribune*, amfAR's associate director of research Dr. Marcella Flores said the "dock and block" technique described by these researchers holds promise as an alternative to stem cell transplantation. But she said more study is required before patient trials can commence.

The findings were published April 12 in *Proceedings of the National Academy of Sciences*.

Read the full press release here.

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Farewell to chemotherapy?

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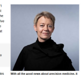

With all the good news about precision medicine, it can be difficult to explain why many patients are still being treated with expensive and toxic drugs that do not benefit them. Pia Heinemann, science editor for the German newspaper Die Welt, won the 2016 Cancer World Best Reporter prize for an article, republished here, that helped readers make sense of the complex reality.

Chemotherapy. That's the word Jana Hermann doesn't want to hear under any circumstances. She has breast cancer; she received the diagnosis four weeks ago. She underwent surgery to remove one of her breasts and five lymph nodes. The tissue was sent off to pathology; the 53-year-old was discharged from hospital with pain that was not as bad as she had feared.

> *"Breast cancer patients can now be tested to determine whether or not chemotherapy is necessary"*

Two weeks later, the tumour tissue and the lymph nodes have been examined, the multidisciplinary team has met, and Jana Hermann is sitting in her doctor's office. She looks at him. He is studying his computer screen, running over her medical records – and he says: "chemotherapy".

Marion Kiechle encounters this situation 200 times a year – but from the other side of the desk. She is medical director of the Women's Hospital of the Technical University of Munich, and she knows how hard it is for doctors to give bad news to their patients. "Chemotherapy puts an enormous strain on patients," says Kiechle, "and most of them are very fearful." She recommends chemotherapy only if it is absolutely necessary – as a last resort in fighting the cancer.

Cytotoxic drugs are designed to destroy rapidly proliferating cancer cells – but they are very non-specific and also attack other rapidly multiplying cells. Because of this, patients lose their hair, suffer from nausea, and sometimes their blood count falls. Patients cannot hide the fact that they are having chemotherapy: everyone can see that they have cancer. But most patients want to hide their illness. Jana Hermann is not using her real name. She does not want people who know her to find out that she has cancer. "Chemotherapy," says Kiechle, "can easily become a stigma." That is why she talks to her patients about a test that can determine whether chemotherapy is a sensible option for them. Such a test could save many patients from undergoing the harsh treatment.

Every year almost 500,000 people in Germany are diagnosed with cancer. Half of them get away with surgery alone. But of those for whom surgery is not sufficient, many can only hope that their lives will be prolonged if they take the hard chemotherapy route. 'Chemo' is the treatment of choice if the cancer is at an advanced stage, if it has spread, or if it is aggressive. But although the cytotoxic drugs that are used have improved significantly in recent years and the side effects have been reduced, many patients still find the treatment worse than the cancer itself.

> *"There have been great advances in pathology, but patients are not benefiting as they should"*

Scientists have therefore been trying for decades to reduce the side effects of chemotherapy and find entirely new ways of treating tumours. They are also trying to develop tests that indicate whether a cancer patient really needs chemotherapy – or whether a different type of treatment would be preferable.

Breast cancer patients like Jana Hermann can now be tested to determine whether or not chemotherapy is necessary. In Germany alone, about 15,000 breast cancer patients a year could in future be spared chemotherapy. In other areas of oncology, too, diagnosticians are attempting to test the molecular characteristics of different tumours to design tailored treatments for each patient.

Developing the right tests and treatments will be a major challenge for the coming decades. If the researchers fail, the costs to the healthcare system will be enormous. And patients will have to endure unnecessarily harsh treatments.

"In our society, the female breast is incredibly important – it is a key part of our culture," says Werner Schlake. He is a reticent man, who prefers to talk about the subject face-to-face rather than on the phone. Schlake – who has white hair, a white beard and glasses – is a pathologist in the city of Gelsenkirchen. He is one of around 1,800 pathologists in Germany, and president of the German pathologists' association, the BVDP. Right now he is furious, because the test that could spare thousands of women chemotherapy is not being offered as standard in Germany.

> *"The tests cost roughly €44 million a year,*
> *but would cut the costs of unnecessary chemotherapy*
> *by €145 million"*

"Two hundred and fifty years ago, pathologists made their diagnosis with the naked eye," says Schlake. Then microscopy came along. "We pathologists start off by getting a tissue sample, a piece taken from the tumour. It looks like a worm, two or three centimetres long." This sample is first examined macroscopically by the experts at the pathology institute. Then it is cut into wafer-thin slices, treated with various dyes, and examined under the microscope. The pathologist is looking for specific cell structures. In the pathology lab, each patient's cancer is classified.

"But now," says Schlake, tapping the table top, "now we can even examine the molecular level." In recent years tests have become available that indicate which genes are active in the cancer tissue. Experts call these tests "gene expression tests," and the ones that have been licensed now include MammaPrint, Oncotype, Endopredict and Prosigna.

With breast cancer in particular, says Schlake, the correct diagnosis is vital: a lot hinges on it. "The pathologist makes the diagnosis. Cancer or not, aggressive or not." Only with the correct diagnosis can the doctors select the right therapy – they must decide whether the patient needs radiotherapy or chemotherapy, or whether standard hormone treatment would be sufficient.

The gene expression tests provide the basis for this decision – or rather, this is what they must do in future. At present many breast cancer patients do not get these tests. That is why Schlake is so angry – because there have been great advances in pathology, but patients are not benefiting as they should.

Germany's joint federal committee of health insurance providers approved the gene expression tests on August 10th 2016 – but only for 'outpatient specialty medical care' (Ambulante Spezialfachärztliche Versorgung, or ASV). All patients who want to have the test in ASV can have the cost met through their compulsory health insurance scheme. "That's great," says Werner Schlake – he pauses, leans back, leans forward again – "but it is also a scandal," – because ASV requires certain structures. Established cooperation partners, such as a pathologist and a clinic, must work together and set up a unit to ensure that patients can be cared for outside the hospital system. But these ASV units that would enable every patient to access the tests don't yet exist.

> *"Tissue that until a few years ago was hard to classify can be classified precisely with gene expression tests"*

The gynaecologist Marion Kiechle says that, even in hospitals, the test could in fact be used for all patients. "But we can't charge health insurers for them." The tests, which cost roughly €44 million a year, but would cut the cost of unnecessary chemotherapy by €145 million, have to be cross-financed. The hospital therefore re-allocates unspent money earmarked for other treatments and uses it for the tests.

It is not only pathologists like Schlake who are infuriated by this. The introduction of the gene expression tests that could spare patients unnecessary suffering, while also cutting the cost to the healthcare system, reveals a fundamental flaw in Germany's health insurance legislation.

The lawmakers' aim is to facilitate patients' transition from hospital to outpatient care. At the same time, the intention is to relieve the financial burden on hospitals – which at present are unable to pay for the tests via their charging system. But because the system has not yet been established, patients can get the tests only at breast centres or specialist hospitals like the one Marion Kiechle manages in Munich.

> *"In cancer cells displaying a lot of genetic changes,*
> *targeted drugs rarely work,*
> *but patients can benefit from immunotherapy"*

And yet so many patients could benefit. Schlake picks up a piece of paper on which a map of Germany is printed in red. The number '74,500' is printed on it in bold type. That is the number of new cases of breast cancer in Germany each year. One-third of those diagnosed cannot avoid having chemotherapy, because it is absolutely necessary, Schlake says. Another third definitely do not need chemotherapy. "But until now we have been uncertain about the final third." The number '22,000' is accompanied by a prominent red question mark. These 22,000 patients are usually recommended by their doctors to have chemotherapy. Over-treatment is unpleasant, but not normally fatal.

However, researchers and physicians now know that two-thirds of these 22,000 patients do not in fact need chemotherapy. Even without it they will not develop metastases. "And it is these 14,500 patients that we can now identify", says Schlake. Tissue that until a few years ago was hard to classify can be classified precisely with gene expression tests.

Carsten Bokemeyer is another person who believes in the new world of testing. An oncologist, he is director of Medical Clinic no. II at Hamburg University Hospital in Eppendorf, and chairman of the German Society of Haematology and Medical Oncology. "For the 'right' patients, the new molecular tests enormously enhance the effectiveness of cancer treatment," he says.

X-rays of lung cancer patients regularly prove to him what is possible. The cancer cells that show up as light in colour on the X-ray before treatment start to vanish within a few days of therapy. "They just seem to dissolve," says Bokemeyer.

The new anti-cancer drugs can be divided into several groups. The first group consists of 'small molecules'. These are so tiny that they can penetrate the cell surface and dock onto certain structures. This interrupts signal transmission in the cancer cell: the cell can no longer divide and tumour growth is halted.

Another group involves tyrosine kinase inhibitors, which have been called a "Lazarus drug" – a treatment that can raise the dead – because of their effect on lung cancer patients who have a specific genetic mutation. They can have a similarly miraculous impact on other types of cancer. Imatinib (Glivec) is one example: for patients with chronic myeloid leukaemia, this is a wonder drug. Before its invention, very few drugs were available to these patients, and many died. The substance can block the modified blood stem cells so effectively that the disease can now be virtually cured.

In passive immunotherapy, another new treatment method, antibodies are produced that can recognise structures on the surface of cancer cells. They then block these structures and, through various mechanisms, cause the cells to die or prevent them multiplying further. These "designer antibodies" are now being used to treat breast cancer as well as colon cancer, lymphoma and other malignancies. "For example, in a typical case of lung cancer caused by smoking, the cancer cells display a lot of changes in their genetic makeup," explains Bokemeyer. "These tumours behave particularly aggress-ively. Here the molecularly targeted drugs rarely work, but patients can benefit from active immunotherapy involving what are known as checkpoint inhibitors."

> *"We are learning that some substances*
> *work very well for certain cancer patients*
> *but not for others with the same kind of tumour"*

Carl June of the University of Pennsylvania has helped active immuno-therapy achieve a breakthrough. The doctor has spent more than 20 years working on ways of activating the patient's immune system so that it targets cancer cells in the patient's body. Normally cancer cells disguise themselves and tell the immune system that they are perfectly normal body cells, thereby protecting themselves from attack. But in pioneering studies, the American doctor was able to show that it is possible to take immune cells from the patient's blood and modify them genetically in the lab so that when they are returned to the blood they are able to recognise cancer cells and destroy them.

Among the patients he treated was Emily Whitehead, a young girl who was diagnosed with acute lymphatic leukaemia (ALL) on May 28th 2010, a few days after her fifth birthday. She had chemotherapy for 26 months. The doctors gave her an 85–90% chance of a cure if the chemotherapy was effective. But eighteen months later the cancer was back. Emily's chance of recovery dropped to 30%. She received a second course of chemotherapy and was about to undergo a bone marrow transplant when, two weeks before the planned transplant, she suffered another relapse. A third course of chemotherapy failed. Eventually it was suggested to Emily's parents that Dr June might be able to help their daughter, and so the child took part in a highly experimental study. In April 2012 she received genetically modified immune cells. A few months later it was clear that the active immunotherapy was working. The cancer cells were no longer able to hide from Emily's immune system and they were destroyed. Emily left hospital in June 2012. She is now eleven years old – and still well.

"We are learning that some substances work very well for certain cancer patients but not for others with the same kind of tumour," says Carsten Bokemeyer, the oncologist from Hamburg. Active immunotherapy is highly successful for lung and kidney cancer, malignant melanoma and certain types of lymphoma. It is also likely to be approved for bladder, gastric and breast cancer. "But each of the new treatments has advantages and disadvantages. For example, passive immunotherapy is effective for colon and lymphatic cancer, but it requires two to four months to take effect," says Bokemeyer. For other types of cancer, tests must be performed before treatment starts, to identify which drugs can even be considered.

> *"If we choose therapies wisely,*
> *we will be able to significantly increase the survival*
> *of many cancer patients and avoid subjecting others*
> *to unnecessary treatment"*

At present the new treatments that can supplement or replace chemotherapy are being applied only sporadically. "In Germany, between 10,000 and 15,000 people per year could benefit from modern antibody immunotherapy," says Bokemeyer. That is 15,000 people who doctors have until now often been unable to help.

One of the reasons why more patients are not benefiting from the new therapies is that they are very expensive. Of the €5 billion that are spent on treating compulsorily insured patients each year, more than €1.5 billion is already accounted for by the modern drugs – even though they make up considerably less than a quarter of prescriptions.

Another reason is that the new drugs have not yet been sufficiently tested, and are only approved for special applications.

The new targeted drugs can also have serious side effects such as nausea, vomiting, and blood disorders. Doctors are therefore only allowed to prescribe them if the patients have been tested to check that the treatment will be effective.

Choosing the right therapy for each patient will be an enormous challenge in the coming years. "If we choose wisely, we will be able to significantly increase the survival of many cancer patients and avoid subjecting others to unnecessary treatment," says Bokemeyer. "Otherwise, in using the new substances we will simply be burdening patients with side effects – and imposing costs on the healthcare system."

But it is not only funding that presents problems for modern oncology. Every week, the results of new studies are published, reporting further advances in oncology – basic research is making enormous progress. But nobody yet knows whether this progress will have a lasting effect on patients. There are not enough data. We do not yet have the long-term studies that would show whether a new treatment really prolongs patients' lives.

There are lots of highly specific drugs, but patients cannot be tested to see whether the drugs are an option for them. The international consulting company IMS Health estimates that, by 2020, tests will only be available for a third of the new drugs that are coming on the market.

The era of precision medicine, in which exactly the right drug can be found for each patient, is only just beginning.

Jana Hermann's tissue samples were analysed in a gene expression test. She didn't discover that until she asked. Her doctor hadn't wanted to raise false hopes. Because for Jana Hermann, there is no alternative to chemotherapy.

This article was first published in Welt am Sonntag on 18 September 2016, and is reprinted with permission.
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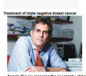

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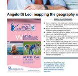

Helping women make the right choices: Europa Donna launches Breast Health Day

Oncology research at Bayer is committed to improving the lives of cancer patients. Bayer's researchers are working together with external partners to develop new therapeutic approaches to this disease.

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The moment my best friend was told his mother had died is one I'll never forget. We were at school together at the time," remembers Dr. Rafael Carretero. Rafael and Francisco were like brothers. They lived close to each other in the same neighborhood in Granada, Spain, played soccer in the street and spent the summers together with their parents, either hiking in the Sierra Nevada or on the beach at La Herradura. But then Rafael experienced how his best friend's warm-hearted and cheerful mother suffered the side effects of chemotherapy and radiation therapy before dying – much too young – of breast cancer. "That hit me really hard and was one of the reasons why I decided to devote my life to fighting cancer – so that other people would be spared this fate," says the Bayer researcher.

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> "We develop therapies that enable the patient's body to detect cancer cells and then defeat them itself.

Dr. Rafael Carretero, cancer researcher at Bayer

Carretero is now 34, a molecular biologist and scientific manager of a laboratory run jointly by Bayer and the German Cancer Research Center (DKFZ). Its employees on the sixth floor of the DKFZ's state-of-the-art building in Heidelberg, Germany, are conducting research to determine how the body's own immune system can be reactivated to combat tumor cells. This approach was also the subject of Carretero's PhD at the Hospital Universitario Virgen de las Nieves in Granada. The battle against cancer has been the common thread through his life. "We want to develop therapies that enable the patient's body to detect cancer cells and then fight them itself without harming healthy cells at the same time," he explains.

What's special about the laboratory in Heidelberg is that scientists from both Bayer and the DKFZ work side by side. "This allows us to pick up on novel research findings as early as possible so that they can be channeled into drug development," explains Dr. Ruth Wellenreuther, alliance manager at the DKFZ. "Research issues have become so complex that no one scientist alone is able to resolve them. Our scientists identify potential new drug targets, and Bayer has extensive libraries of substances and antibodies. The two parties' respective expertises complement each other ideally, which enables us to reach our objective more quickly."

Here is a video of two of Bayer's Heidelberg-based cancer researchers.

The joint laboratory is one aspect of a partnership that has been in existence since 2009. Wellenreuther was involved in developing the framework for the collaboration. "This is an alliance between equals. We clarified all the structural and legal issues right at the beginning, so when we identify a new target we can move straight on to searching for suitable active ingredients." The partnership has already been successful: the first active ingredient to treat brain tumors and leukemia has been undergoing clinical testing in patients for several months now. The substance recognizes proteins that are found only in cancer cells in a subset of patients, an approach that could enable the development of effective, patient-specific therapies.

Alliance Manager at the German Cancer Research Center (DKFZ) Dr. Ruth Wellenreuther greatly appreciates the collaboration with the scientists at Bayer. "It allows us to pick up on research findings as early as possible so that they can be channeled into drug development."

"We are working to develop innovative treatments for patients with serious diseases such as cancer in order to extend their lives and improve their quality of life," says Professor Andreas Busch, member of the Executive Committee of Bayer's Pharmaceuticals Division and head of Drug Discovery. "Our particular strength at Bayer is that we have strong expertise in identifying active ingredients and taking them through all phases of clinical development up to and including drug approval, for the benefit of the patients."

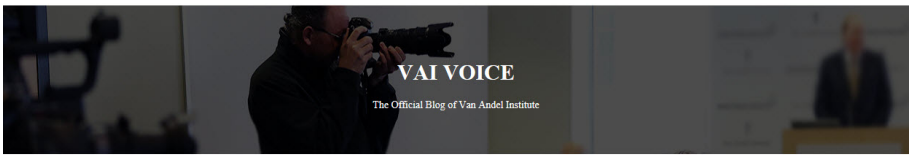
In the battle against cancer, Bayer is pursuing three main approaches: blocking signaling pathways that lead to uncontrolled cell division, selectively docking molecules onto cancer cells to trigger their targeted destruction, and reactivating the immune system to eliminate cancer cells itself. This latter approach is the focus of the research by Carretero and his colleagues. "Our understanding of cancer is constantly improving, but there are still plenty of unanswered questions," says Carretero, before turning his attention to the next test findings from the laboratory. "Our goal is to make cancer curable or be able to transform it into a chronic disease by providing therapeutics that keep tumor cells in check."

Areas of Oncology Research at Bayer

Antibody-drug conjugates
Certain proteins occur more frequently on the surface of cancer cells than in healthy cells. Bayer researchers are developing molecules called antibody-drug conjugates which recognize these proteins. Like a Trojan horse, they dock onto the cancer cells and destroy them with a cell toxin. Antibody-thorium conjugates work in a similar way and transport radioactive thorium-227 to the cancer cells. The resulting energy-rich alpha particles destroy the cancer cells. By using different antibodies, conjugates can be developed for various tumor types.

Blocking oncogenic signaling pathways in specific tumor types
The multiplication of cancer cells is to be halted by intervening in their key molecular processes. One approach aims to block the signaling pathways which prevent cancer cell death and often result in mutations, while another approach seeks to exploit the differences in the metabolic activity of tumor cells. A third approach is investigating cancer stem cells that may result in the development of resistance mechanisms and the failure of chemotherapy and radiation therapy. And a further approach is focused on the epigenetic changes which play a role in malignant cancers. Bayer scientists are working to understand these processes better so they can reverse harmful modifications in diseased cells.

Immuno-oncology
Every day, cancer cells are formed in the human body because of a genetic predisposition or as a result of exposure to cigarette smoke, UV radiation or other environmental influences. They are usually eliminated by the immune system's cells. In certain cases, however, they can evade the immune response and become a harmful tumor. Bayer researchers are working mainly in collaboration with scientists from the DKFZ on approaches leading to a reactivation of the immune system to eliminate the tumor cells without affecting healthy nontumoral cells. The immune system's memory function may result in long-term therapeutic success.



VAI VOICE

The Official Blog of Van Andel Institute

2 AUG 2017

How some medications work and how we can make them better

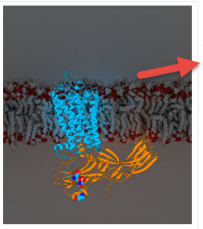
Tags structural biology, VARI, Xu

Or, why you should care about G protein-coupled receptors

Ever wondered how that daily beta blocker is actually lowering your blood pressure? Or how clopidogrel thins your blood and helps stave off heart attack and stroke?

So do Eric Xu, Ph.D., and a team of collaborators at Van Andel Research Institute. For more than a decade, they have been studying a class of receptors on the surface of cells called G protein-coupled receptors (GPCRs) and, last week, they published a new set of findings in *Cell* that reveal the lock-and-key structure of how these receptors interact with one of their key signaling proteins, called arrestins.

Why is this important? Because GPCRs are part of the most active and complex network of communication channels among cells in the human body, and anywhere from 30-40 percent of drugs currently on the market (depending on whom you ask) interact with GPCRs in some way.



Rhodopsin-arrestin. Courtesy of Parker de Waal, Xu Laboratory, Van Andel Research Institute

Xu and the team discovered sequences of three chemical tags called phosphoryl groups that function like the combination to a safe, matching up with pockets on arrestins and allowing them to dock onto GPCRs, effectively block incoming communication on a specific channel.

This is where it gets really important for development of new drugs, in addition to refinement of the ones we already have: if drug development teams know how to stop a cancer from responding to signals for rapid growth, they could theoretically design new therapeutics to improve wellness across a litany of different diseases.

At least that's the hope.

And, because GPCRs are so common—there are an estimated 825 different types of GPCRs—the goal is that drugs could be developed to better treat conditions ranging from retinopathy and depression to HIV and cancer. Fine-tuning the fidelity of signals from the retina to the optic nerve, for instance, could possibly help restore at least partial sight to people with retinopathy.

In addition to answering a longstanding question in basic biology, Xu and the team hope that the information uncovered in their study can be used to design new therapies that have higher potency and greater specificity than some of those currently available.

In other words, they hope to build better drugs that offer higher response rates and fewer side effects.

What is structural biology? And how does it help us improve human health? Click the image below to learn more.

A culture of collaboration: Van Andel Research Institute and Michigan State University

Promising results from study of type 2 diabetes drug in treatment of Parkinson's disease

BLOG HOME

TAGS

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Synthesising proteins from non-natural building blocks?

Synthetic biology is an emerging discipline that is frequently referred to as the art of molecular engineering. Dr. Birgit Wiltschi from the University of Freiburg has been awarded funding from the Baden-Württemberg Ministry of Science, Research and the Arts under the "Biotechnology and Medical Technology Idea Competition" for a highly ambitious project: she wants to learn how proteins can be modified using non-natural building blocks that will enable the engineered proteins to specifically target receptors on cancer cells, amongst other things. What is the current state of technology? How accurately are biochemists able to construct molecular machines from individual components?

Cancer cells divide more frequently than healthy cells. One of the reasons for this is the higher sensitivity of cancer cells to growth factors such as the epidermal growth factor (EGF) that play an important role in the regulation of cell growth, proliferation and differentiation. The molecule binds to the EGF receptor on the surface of cancer cells and induces a complex signalling cascade that leads to the activation of genes that control cell division activities. Many types of tumours have a high density of EGF receptors on their surface and it is therefore easy to induce cell division. State-of-the-art tumour therapies tend to focus on the targeted and effective inhibition of EGF receptors. And this is exactly what Dr. Birgit Wiltschi from Prof. Dr. Wilfried Weber's Synthetic Biology workgroup at the Centre for Biological Signalling Studies (BIOSS) in Freiburg intends to do using synthetic biology methods. "Our goal is to create a new class of EGF receptor inhibitors," said the biochemist. "However, the project is quite risky and we do not know at present whether our approach will lead to the intended objective."

Article
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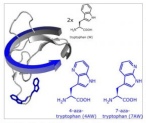
The article is part of the following dossiers


Engineers of life


Cancer therapy and cancer diagnostics

Control of the building-block pool



Left: Model of an EGF molecule with synthetic tryptophane building blocks (blue). Right: model of a natural tryptophane molecule, including two tryptophane variants into which a nitrogen atom was artificially inserted. © Dr. Birgit Wiltschi

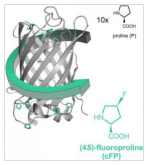
The project, which will be funded for the next nine months under the "Biotechnology and Medical Technology Idea Competition" of the Baden-Württemberg Ministry of Science, Research and the Arts, is still in its early days. Wiltschi and her research group plan to modify the EGF molecule in such a way as to block the function of the EGF receptor on the surface of cancer cells and make cancer cells insensitive to a division signal. Wiltschi's team will use synthetic biology methods rather than genetic manipulation. Genetic modifications of the coding DNA sequence often lead to protein products that no longer function properly, and this is something the researchers would prefer to avoid. In the case of EGF, such modifications might prevent the peptide molecule from binding to its receptor. Wiltschi and her team plan to target a later step in the production of cellular EGF – namely the point in time at which the amino acids are assembled into a polypeptide. This enables the researchers to use amino acids that are normally not used by the cells. Non-natural building blocks of this kind usually only differ slightly from the structure of natural building blocks; in many cases, the modifications only involve the exchange of a few atoms. But they are atoms that possess the properties the researchers are looking for.

Electron microscope image of E. coli bacteria © Rocky Mountain Laboratories, NIAID, NIH

In order to achieve their goal, Wiltschi and her team are using an approach that has been known since the 1950s, but has only gained importance for the production of synthetic proteins in the last few years. The researchers produce EGF in E. coli cells that are unable to produce the handful of amino acids that would be required for them to carry out protein biosynthesis on their own. "This gives us control over the type of amino acid the bacteria use in their proteins," said Wiltschi explaining that the researchers are not only able to use amino acids that are normally required for the synthesis of proteins, but can also add synthetically modified amino acids to the culture medium. Since the synthetic and natural building blocks only have minimal structural differences, the three-dimensional structure of the modified proteins remains largely unaltered. However, some of the non-natural building blocks have extraordinary chemical characteristics, which are able to alter the biological function of the synthetic protein variants, potentially in such a way that EGF binds to its receptor and interferes with, rather than activates, its function.

A Trojan Horse or pipe dreams?

Wiltschi and her team have already been able to show with other proteins that their approach works in principle. For instance, they were able to replace all the proline residues in green fluorescent protein (GFP) by using minimally modified synthetic proline derivatives, in which a proton is exchanged for a fluorine atom. The substitution of a proton with a fluorine atom led to a GFP protein that folded much more quickly and efficiently into its correct spatial structure. "The structure of the proteins remains the same, but the modified proline molecules alter the folding characteristics of the entire molecule," said Wiltschi. "This is the fascination – and the potential – of the technology that is being used."



Left: Model of a GFP molecule with synthetic proline building blocks (green). Right: model of a natural proline molecule, including a proline variant into which a fluorine atom was inserted. © Dr. Birgit Wiltschi

The researchers now hope to use the aforementioned principle to manipulate the chemical characteristics of EGF molecules. If everything goes to plan, the EGF receptor will not be able to differentiate between modified and natural EGF. Nevertheless, it is likely that the receptor will be blocked, thereby blocking the signalling cascade in the cancer cells and the uncontrolled division of cancer cells. Another possibility would be to insert amino acids that have a toxic effect, which would turn EGF into a kind of Trojan horse that will dock to cancer cells and destroy them. "But it remains to be seen whether all this will work," said Wiltschi going on to add "at the moment it is still a pipe dream".

The field of synthetic biology is still very young. Until now, researchers have tested selected methods on model systems and have only been able to show that the methods can be applied. Little is known about the molecular and cellular mechanisms that enable the integration of amino acid analogues into proteins. "Where in the cell do the artificial variants migrate? What exactly happens to them there? Are they part of the cellular metabolism and if so, which enzymes are involved? Wiltschi pointed out that an understanding of the underlying mechanisms is a prerequisite for being able to control specific cellular processes using synthetic biology and use them for specific objectives. There is still a huge amount of basic research to do before the potential of this technology can be exploited in the field of cancer research.

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