The power of alpha

Chemotherapy is often ineffective against refractory tumors. Bayer scientists are now working to overcome the defenses of the cancer cells in these tumors using radiation. A radioactive ingredient is guided through the body until it reaches its site of action and then releases targeted tumor-destroying radiation at that specific location. This novel radioimmunotherapy approach could be a source of new hope for patients with lymph node, prostate or breast cancer.

Paradoxically, the invisible energy used to save lives does so by inducing a destructive effect as it passes through the tissue. Some forms of radiation penetrate deep through the body tissue and can be used to treat tumors. However, they often also damage healthy cells at the same time. Bayer scientists are now working to channel this destructive energy so that it can be directed more effectively against tumors.

Targeting cancer cells: Dr. Alan Cuthbertson, Head of Thorium Research at Bayer HealthCare in Oslo, is working intensively on destroying tumors with alpha radiation.

This requires precise calculation of the radiation dose and targeted delivery to the desired site of action. The scientists are working with the radioactive element thorium-227, an alpha-particle emitting radionuclide. "Thorium emits very energy-rich radiation, albeit over a short distance; it cannot even penetrate through a sheet of paper," explains Dr. Alan Cuthbertson, Head of Thorium Research at Bayer HealthCare in Oslo, Norway. He and his team were part of Algeta ASA, a company that was acquired by Bayer in 2013. These specialists in the use of alpha particle-emittting radionuclides in radiotherapy are working on a means of transporting thorium directly to the tumor where the radioisotope first accumulates and then decays, releasing the alpha particles. "The radiation then destroys cancer cells without damaging the surrounding healthy tissue too severely," explains the Bayer chemist.

To do this, Cuthbertson's team attaches the thorium radionuclide to an antibody, which delivers the radioisotope directly to its site of action in the tumor. "These protein molecules are a natural part of our immune system, capable of recognizing structures called antigens on the surfaces of disease pathogens," says Cuthbertson. And it is this ability - to bind selectively to specific cell structures - that the scientists are leveraging. "We have selected specific antigens expressed on the surface of the tumor cells to which the thorium-labeled antibodies dock with high affinity."

Combination of specific antibody and alpha radiation docks selectively to tumors

Cuthbertson's team, for example, is working with antibodies that are able to recognize non-Hodgkin lymphoma. The Bayer scientists are currently exploring an antibody targeting CD22, a protein found on the surface of certain tumor cells. This antibody is provided by Immunomedics, a U.S. company collaborating with Bayer, which specializes in the development of antibody-based therapies. Bayer's researchers use molecules called chelators to bind the alpha particle-emitting radionuclide to its protein transporter. "These molecules are chemically bonded to the antibodies but are still capable of tightly binding the thorium. Together they form what is termed an antibody chelate complex, which is extremely stable," explains Cuthbertson. And the strength of the combination has a direct impact on the potential success of the drug product, because the thorium has to resist a lot of tempta-

2-10 ***cell layers***

are penetrated by thorium radiation, so its action on the tumor is localized and the surrounding, healthy tissue is left unharmed.

Source: Algeta ASA

Photos: Ilja C. Hendel/laif/Bayer AG (3), Corbis

Dark threat: the illustration shows a tumor cell attempting to penetrate into the surrounding tissue using its long protrusions.


Experts in radioimmunotherapy: while Dessi Mihaylova and Dr. Alan Cuthbertson (photo left) discuss results at the particle detector, Hong Thanh Nguyen (photo right) pipettes the thorium/antibody conjugates in readiness for further analyses.

tions on its journey to its destination. The chemistry developed by the Bayer scientists yields extremely stable conjugates – a vital characteristic because the body is home to many other natural substances which are capable of forming complexes with thorium such as the iron-binding protein transferrin. "If our complex isn't stable enough, transferrin may compete for the thorium and distribute it to the wrong sites in the body via the circulation," explains the Bayer expert.

Local effect at the tumor: alpha radiation has only short-range penetration

The scientists have spent some three years developing the ideal chelator and optimizing the production process for the antibody-thorium conjugate. The technology developed by the Bayer scientists is designed in such a way that, bound to its antibody carrier, the thorium radionuclide travels to the site of the non-Hodgkin lymphoma. After arriving directly at the malignant tissue, the radioactive element decays, releasing the tumor-destroying radiation without causing significant damage to the adjoining healthy tissue. The alpha radiation is extremely localized; it only penetrates a maximum of two to ten cell layers.

Preclinical trials in cell cultures and animal models have already produced promising results. The scientists are therefore planning to test the active substance in initial clinical trials with patients starting before the end of 2015. However, working with radioactive elements presents special challenges. Radiation therapy drugs have only a limited user window. The half-life, i.e. the time at which half the starting dose of thorium-227 has decayed, is 19 days. That is considered optimal for radioimmunotherapy as it allows the antibody time to home in on its target in the body before significant amounts of thorium decay. Bayer's scientists have developed a simple strategy for the initial clinical studies. "We supply the thorium and the antibody conjugate to the hospital pharmacists taking part in the study as two separate components. They prepare the drug product in accordance with our precise instructions," says Cuthbertson. The drug product is then released and ready for delivery to the patients' bedside in the hospital.

Antibodies as sniffer dogs: destroying refractory tumors or undetected metastases

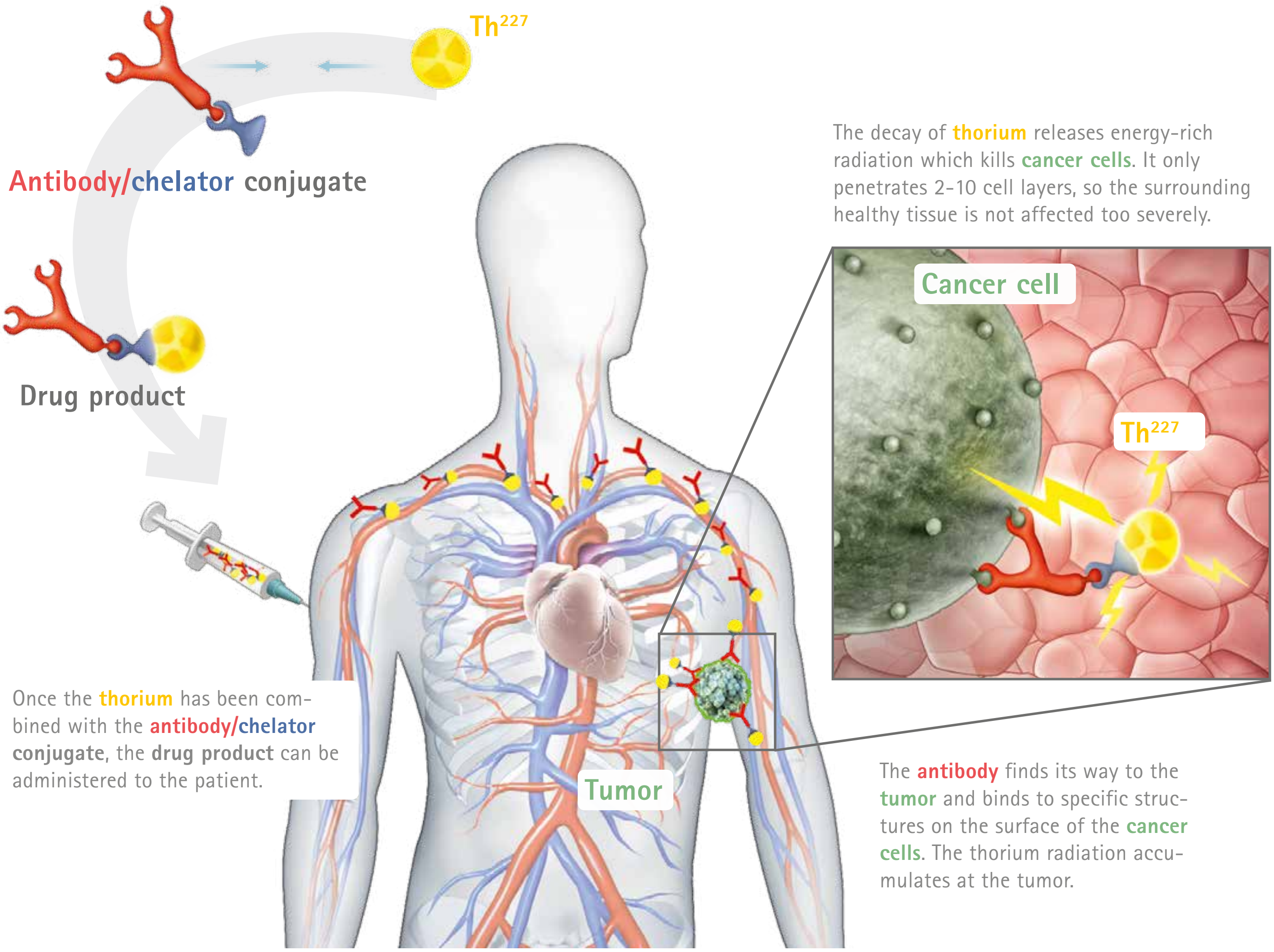
If the antibody-drug conjugate proves its worth in the clinical setting, it could be a source of hope above all to cancer patients with refractory tumors, which can become resistant to treatments such as chemotherapy. Bayer's targeted radiotherapy may overcome many of the cellular mechanisms leading to drug resistance. The cancer cells are unable to mount a defense because the radiation causes irreversible damage to their DNA,

Healing radiation

Radiation therapy is one of three mainstays of cancer treatment, along with chemotherapy and surgery. It is estimated that more than half of all cancer patients undergo radiation treatment for their condition. Doctors most commonly employ ionizing radiation such as X-rays or electron beams from a source outside the body. The radiation generates positively and negatively charged particles from electrically neutral atoms and molecules in the body. These ions are highly reactive and rapidly enter into new compounds, destroying vital components of the tumor cells. Healthy cells in the surrounding tissue are able to repair any damage caused by the radiation to a certain extent themselves. If the radiation dose is too high, however, the affected tissue is destroyed.

Combination to treat tumors

Specific antibodies carry their highly effective payload to the tumor: the radioactive element thorium then releases its energy-rich radiation directly and locally at the cancer cells.



leading to their destruction. Says Cuthbertson, "It can also destroy any tumor cells that aren't currently in the process of dividing. That's something that many chemostatic drugs, for example, cannot do." Another advantage of radioimmunotherapy is that the antibodies find their way to the site of the tumor in the body completely autonomously. "They even attack tumors that are too small to be picked up by imaging techniques, such as very-early-stage metastases," explains Cuthbertson.

Cuthbertson's team of researchers are planning to use the technology in combination with a variety of antibodies while developing new therapies for cancer. "The targeting component of the drug product, the antibody, can be replaced with others, making this a very flexible technology platform," says the Bayer expert. For example, his team is working on coupling the radionuclide to another antibody that binds to the typical structures associated with breast cancer cells. Says Cuthbertson, "The key element is the chelator. The chemistry used to attach this critical component has been optimized and is now robust and reproducible, allowing us to reliably produce a wide variety of stable antibody-thorium conjugates." Cuthbertson is optimistic about the treatment's prospects: "I'm certain that thorium conjugates will establish themselves in cancer therapy – above all to treat refractory tumors that have failed to respond to other approaches."

www.research.bayer.com/thorium
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