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Technische Universität München

News Release

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Protein design for medicine

TUM scientists design cup-like proteins for tumor therapy applications

Small cup-shaped proteins (lipocalins) in tears and blood protect us from germs and transport vitamins and hormones. Researchers from the TU München (TUM) and the TUM biotech spin-off "Pieris" have now altered these lipocalins in such a way that they can be used in cancer treatment – as an alternative to the established therapeutic antibodies. The scientists have reported on their findings in the two prestigious journals "Proceedings of the National Academy of Sciences of the U.S.A." and "Journal of the American Chemical Society."

The micronutrient iron is essential for practically all living organisms. That is why after an infection many microbes cast a kind of chemical mini-bait (siderophores) that scavenges iron ions in body fluids. The human immune system takes advantage of germs' appetite for iron to ward them off. Cup-shaped proteins in tears or blood, so-called lipocalins, scavenge the mini-bait together with the iron, and thus curb the spread of the germs. But lipocalins have further functions in the body: In the bloodstream, for instance, they transport poorly water-soluble vitamins or sensitive hormones. Each lipocalin generally responds to only one single substance, which it absorbs in its cup-like binding pocket.

Researchers on the team of Prof. Arne Skerra from the Center for Food and Life Sciences Weihenstephan (WZW) at the TU München, together with colleagues from Pieris AG (Innovation and Start-up Center IZB in Freising-Weihenstephan) and the University of York (Great Britain) have taken a decisive step towards turning human lipocalins into useful tools for cancer therapy. Using protein design and genetic engineering the researchers altered the cup-like structure in such a way that a lipocalin can bind to specific defense cells and block the molecule CTLA-4, which plays a role in the immune response. During an infection the body's immune system is in a state of alert, and CTLA-4 is responsible for ensuring this state turns back to normal after a few days. However, this kind of all-clear is undesirable during immune therapy in cancer treatment. Here the immune system is alerted to the cancer cells through a kind of vaccination and should remain in a state of alarm until the tumor has been defeated. Therapeutic antibodies that bind to CTLA-4, thereby intensifying the immune response, are currently being tested on patients.

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Skerra and his colleagues established that the newly constructed lipocalin binds to CTLA-4 just like an antibody – which is why the researchers named their antibody-like lipocalins "anticalins." Anticalins have many advantages over antibodies: They are eight times smaller and can thus readily enter tissue spaces. Furthermore, the production of anticalins is much less costly, which is of great significance in pharmaceutical production processes. Finally, anticalins are easy to combine with other proteins by means of standard biotech procedures, and can thus provide them with additional biochemical functions.

In this way the TUM researchers bestowed attributes upon a lipocalin allowing it to capture a small molecule with a radioactive metal ion (yttrium). In the future this anticalin can be combined with another anticalin that recognizes cancer cells. One possible therapy envisions injecting the patient with this twin protein, which disperses through the body via the bloodstream and adheres to the tumor. Surplus, unbound twin-protein molecules are decomposed and discharged by the liver and kidneys. Only then is the patient injected with the radioactive molecules. The twin protein molecule adhering to the tumor scavenges on these. Because the radioactive molecules are very small, the unbonded excess is discharged via the kidney and thus cannot harm the body. In the tumor, however, the bound radioactivity destroys the cancer cells with great precision.

Scientific research on cancer diagnostics and therapy has pursued similar ideas with double binding structures for some time. However the approaches used so far have always centered on very hard to generate antibody conjugates that had to be chemically bonded and elaborately purified. "So far, only a single one of these constructs has been approved as a drug," explains Prof. Skerra. "Our principle of biologically merging an anticalin with another protein is much easier to handle and therefore stands a much better chance of making the leap from research to medical application." Skerra is excited about the future of anticalins: "We were surprised ourselves how many different functions lipocalins can fulfill through protein design. This protein family, which has hitherto been given little attention, holds great potential for the future."

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Publications:

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Technische Universität München (TUM) is one of Europe's leading universities. It has roughly 420 professors, 6,500 academic and non-academic staff (including those at the university hospital "Rechts der Isar"), and 23,000 students. It focuses on the engineering sciences, natural sciences, life sciences, medicine, and economic sciences. After winning numerous awards, it was selected as an "Elite University" in 2006 by the Science Council (Wissenschaftsrat) and the German Research Foundation (DFG). The university's global network includes an outpost in Singapore. TUM is dedicated to the ideal of a top-level research based entrepreneurial university.

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