Healthcare industry BW

G protein-coupled receptors and their importance for research and development

Brian Kobilka and Robert Lefkowitz were awarded the 2012 Nobel Prize in Chemistry for their groundbreaking discoveries of the inner workings of G protein-coupled receptors (GPCRs). These transmembrane receptors play a key role in the processing of odours and the recognition of hormones. The work of the two American scientists has had an impact on many researchers around the world. In the following interview, Professor Dr. Daniel Legler, head of the Biotechnology Institute Thurgau (BITg) at the University of Konstanz, explains the influence Lefkowitz' and Kobilka's findings have on his work with GPCRs.

BioLago: Professor Legler, it is generally assumed that GPCRs represent around 50% of current drug targets. Why do GPCRs play such a big role in the pharmaceutical industry?

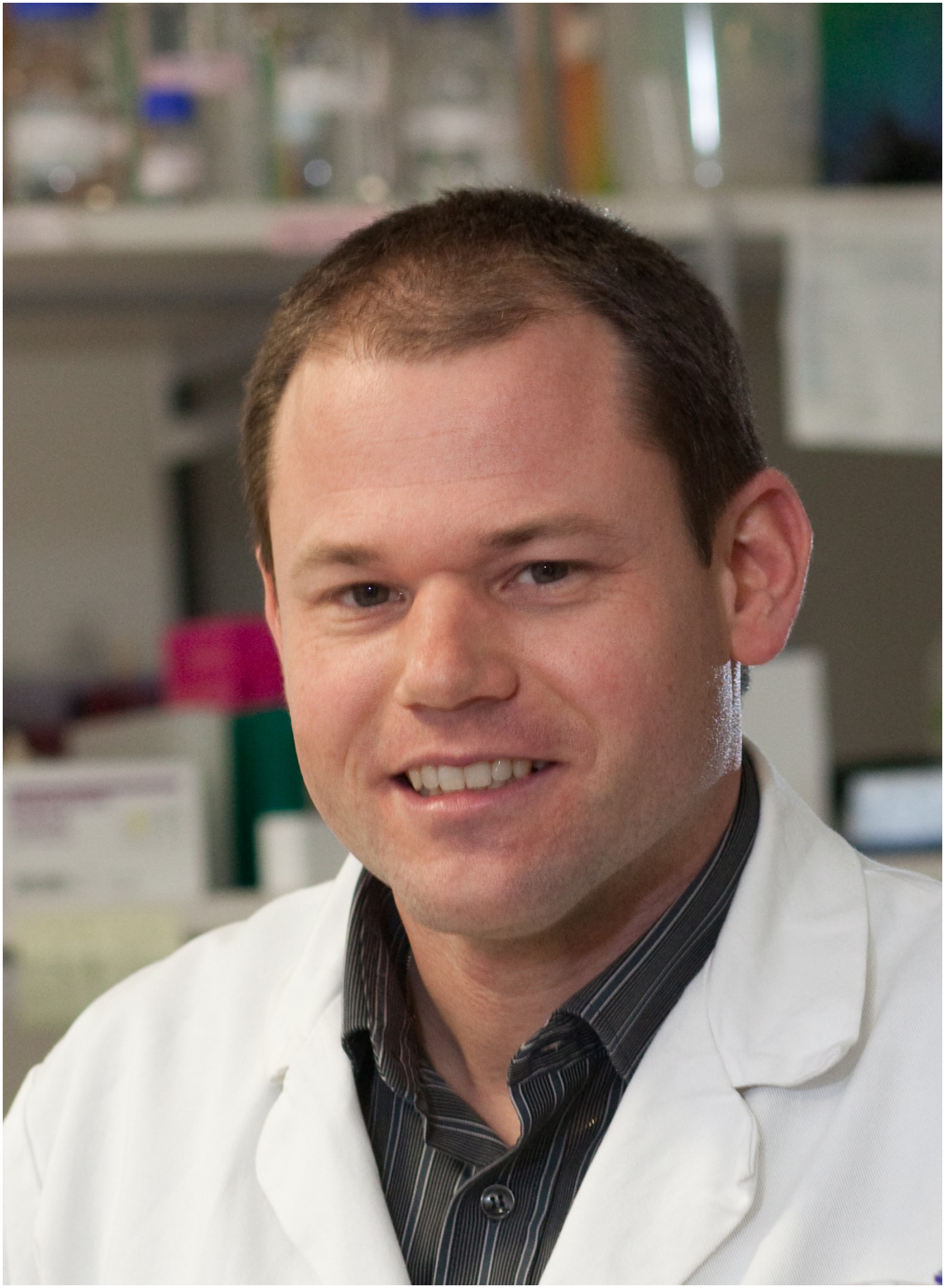
Daniel Legler: The family of G protein-coupled receptors (GPCRs) is rather big and comprises several hundred different proteins. In addition, GPCRs are involved in the transmission of external signals into the cell. The GPCR family includes receptors that are responsible for the recognition of light, taste, odours, hormones, pain, neurotransmitters and many other things. Or in other words, most physiological processes are based on GPCR signalling. This is why the GPCR family is of huge pharmaceutical importance.

Is Lefkowitz' and Kobilka's development the result of long-term, persistent work or is it the result of one particular moment when the two researchers found the needle in the haystack?

The two Nobel laureates have spent many years on GPCRs. As far back as 1970, Lefkowitz and his colleagues carried out binding studies with radioactively labelled hormones without knowing that these hormones bind to GPCRs. In 1986, Lefkowitz and Kobilka were involved in the cloning of the gene encoding the beta-2 adrenergic receptor, a GPCR that is activated by adrenaline. 25 years later, Kobilka and co-workers succeeded in elucidating the three-dimensional structure of the complex of beta-2 adrenergic receptor, extracellular ligand and intracellular G protein. These groundbreaking discoveries, alongside many other findings of researchers around the world, have already led to the discovery of numerous drugs, and many more GPCR-targeting drugs will be developed in future.

Why was the deciphering of the GPCRs so complex and previously impossible?

The aforementioned long period of time needed for elucidating the structure of GPCRs clearly shows that basic research is enormously time-consuming and arduous work. The experimental investigation of GPCRs is relatively difficult; the polypeptide chain of the GPCRs passes through the



Prof. Dr. Daniel Legler, head of the Biotechnology Institute Thurgau (BITg) at the University of Konstanz.
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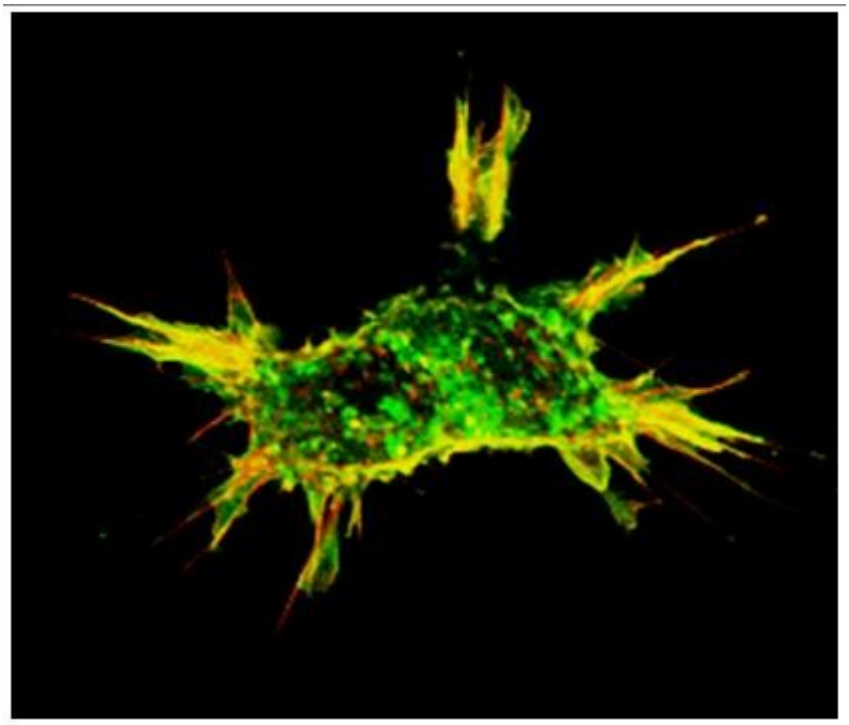
plasma membrane seven times, which gives them excellent hold in the membrane. They are

therefore difficult to access and isolate for experimental purposes. Should a researcher be in the fortunate position to have isolated a GPCR, he or she will find that the transmembrane receptor only functions in an appropriate lipid/membrane environment and nowhere else. GPCRs alter their topography when bound to a ligand. This conformational change is a prerequisite for the transmission of signals and the interaction with a G protein inside a cell.



Investigation of the blood of cancer patients showed that lymphocytes can kill cancer cells.

Your work at the Biotechnology Institute Thurgau (BITg) at the University of Konstanz involves, amongst other things, chemokines, which bind to one of several GPCR subgroups. What is their function?

We deal mainly with compounds that are involved in cell movement and activation. Compounds that are able to induce chemotaxis in nearby cells are called chemokines. Most chemokines are soluble molecules and bind to the chemokine receptors that belong to the GPCR family. One of our research projects concentrates on the two chemokines CCL19 and CCL21, which are permanently produced in lymph nodes and lymphatic tissue. They attract immune cells from a long distance. We also concentrate on the signalling pathways that are induced by chemokines in order to attract cells to the chemokine source. Chemokines direct immune cells to the lymph nodes, which represents a basic prerequisite for the formation of an immune response against pathogens.

What is known about GPCRs and their role in the development of cancer?

An interesting finding is that certain cancer cells, for example breast cancer and prostate cancer cells, express the chemokine receptor CCR7 in order to move towards the chemokines CCL19 and CCL21 and form metastases in the lymph nodes. The chemokine family comprises around 50 proteins that control cell migration. This is why they play a crucial role in embryonic development, organ formation, the defence against pathogens and the metastasis of cancer cells.

You are also studying dendritic cells? How do these cells and lymphocytes manage to efficiently invade lymph nodes and induce an immune response against cancer cells?

Dendritic cells are white blood cells and work as guardians of the immune system. Once a pathogen invades the body, it will be recognised by dendritic cells in peripheral tissue and proteins of the pathogen are processed into so-called antigens. At the same time, dendritic cells start expressing the chemokine receptor CCR7 and start to migrate in the lymph into the nearest lymph nodes where they present the pathogen-derived antigens to the lymphocytes. Specific lymphocytes have the ability to eliminate infected cells and pathogens. They are instructed by the dendritic cells, multiply, leave the lymph nodes and continue on to the pathogen. Most lymphocytes constantly express the chemokine receptor CCR7 on their surface and are attracted by CCL19 and CCL21. Thus, lymphocytes patrol the entire body via the bloodstream and visit all lymph nodes, always on the search for dendritic cells that present specific antigens.

Have you been able to find out how lymphocytes manage to destroy cancer cells?

Lymphocytes that are able to kill cancer cells have been detected in the blood of cancer patients. The lymphocytes in the lymph nodes must be informed and activated by dendritic cells in order for an efficient immune defence to occur. We have shown in several studies that dendritic cells that are activated by the inflammatory mediator prostaglandin E2 are more efficiently attracted by chemokines and activate lymphocytes much better. It is interesting to note that the receptors that recognise prostaglandin E2 are also members of the GPCR family.

What direct impact has the Nobel laureates' recent discovery had on the research at the BITg?

Some of Brian Kobilka's colleagues resolved the three-dimensional structure of a chemokine receptor related to CCR7 around two years ago. These and many other findings involving GPCRs help to gradually advance basic and pharmaceutical research.

As an affiliated institute of the University of Konstanz, the Biotechnology Institute Thurgau (BITg) carries out application-oriented basic research in the fields of tumour biology, immunology and cell biology. The BITg's major research priorities involve research into the migration of immune defence and cancer cells/formation of metastases, the investigation of dendritic cells for their potential as natural tumour vaccines, the identification of new tumour markers and the development of new immunotherapies against cancer. Prof. Dr. Daniel F. Legler has been the head of the institute since 2005.

Contact:
Prof. Dr. Daniel F. Legler
Biotechnology Institute Thurgau (BITg)
at the University of Konstanz
Unterseestrasse 47
CH-8280 Kreuzlingen
Tel.: +41 (0) 71 678 50 20
Fax: +41 (0) 71 678 50 21
E-mail: daniel.legler(at)bitg.ch

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Nyamsuren Davaasambuu
BioLAGO