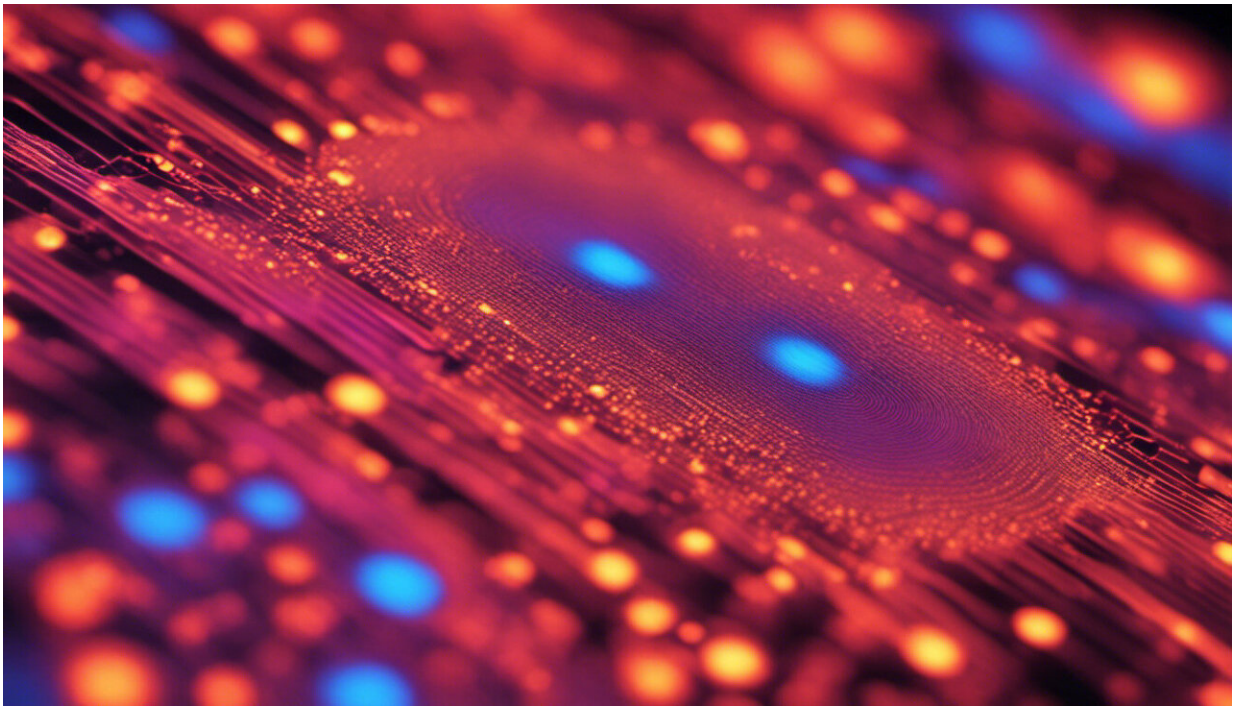
Infrared sensor serves as a new tool for drug discovery

August 28 2018



Credit: AI-generated image (disclaimer)

Scientists have found a new method for analysing how active agents affect a specific protein essential for cell survival. Their research could help to quickly develop drugs with fewer side effects.

The efficacy of many drugs is based on how they manipulate the

metabolism of cells by inhibiting the activity of specific proteins. However, analyses of an active agent's impact on the structure of its target protein have generally used time-consuming and material-intensive procedures.

A team of researchers supported by the EU-funded K4DD project has introduced an alternative way of examining such interactions using an infrared sensor. The study was published recently in the journal *Angewandte Chemie*.

The new method provides information on structural changes in target proteins within minutes and can help narrow down the type of structural change, as stated in a press release by the Ruhr Universität Bochum (RUB). "The sensor is based on a crystal that is permeable for infrared light. The protein is bound on its surface. Infrared spectra are recorded through the crystal, while the surface is rinsed with solutions with or without any active agents."

Heat shock protein

In the journal article the researchers said the investigation of "protein–ligand interactions is crucial during early drug discovery processes." To demonstrate the reliability of their method, they immobilised the heat shock protein HSP90 on an attenuated total reflectance crystal. "This protein is an important molecular target for drugs against several diseases including cancer. With our novel approach we investigated a ligand-induced secondary structural change." The team analysed two specific binding modes of 19 drug-like compounds. "Different binding modes can lead to different efficacy and specificity of different drugs."

The RUB press release refers to HSP90 as a "folding helper that assists newly generated proteins in the cell to form the correct three-

dimensional structure." It adds: "Due to their extremely active metabolism, tumour cells require it very urgently. HSP90-inhibiting active agents constitute an approach for the development of drugs that stop tumour growth."

The press release also notes that the sensor detects changes in the protein's spectral area that is structure-sensitive, the so-called amid region. This is characteristic of a protein's scaffold. "If any changes occur, it is obvious that the active agent has altered the shape of the protein." Project supervisor Prof. Dr. Klaus Gerwert, explains: "Since our sensor acts as a flow system, we can rinse the active agents off the target protein after binding and, consequently, measure how the efficacy changes over time."

One parameter affecting drug efficacy is the life span of the complex formed between a drug and its target protein, whose function must be altered. Active agents that are bound to this protein for a long time could remain effective for an extended period. Tablets with such active agents have to be taken only once a day and they often have fewer side effects, the researchers say. In the journal article they conclude: "Particularly when scaled up in an automated screening platform, our method could be used to identify new drug candidates in the early drug-discovery process."

The research into the infrared sensor was performed under K4DD (Kinetics for Drug Discovery (K4DD)). The project sought to improve the understanding of how potential drugs bind with their target. It was also aimed at developing tools to help researchers determine whether a drug candidate is likely to be safe and effective much earlier in its development process.

More information: K4DD project website: www.k4dd.eu/home/ Jörn Güldenhaupt et al.

Ligand-Induced Conformational Changes in HSP90 Monitored Time Resolved and Label Free-Towards a Conformational Activity Screening for Drug Discovery, *Angewandte Chemie International Edition* (2018). DOI: 10.1002/anie.201802603