

A hot road to new drugs

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The quest for new drugs is generally a lengthy and costly undertaking. German researchers of Ludwig-Maximilians-Universitaet in Munich have now come up with a simpler and more efficient way of going about it. Not only pharmaceutical research but also medical diagnostics and the environment stand to benefit from the new work.

The search for new therapeutic agents is time-consuming and expensive. Pharmaceutical companies may have to screen thousands of compounds for the ability to bind a [target molecule](#) before they hit upon a promising [drug candidate](#). A group of Biophysicists at LMU Munich led by Professor Dieter Braun, a member of the Cluster of Excellence "Nanosystems Initiative Munich" (NIM), and a partner in NanoTemper (an LMU spin-off), have now developed a unique technology called "microscale thermophoresis" that allows to measure intereactions under close-to-native conditions, thus improving the decision making process in drug development.

The technique takes advantage of the Soret effect - the tendency of molecules to drift along temperature gradients, usually from warm to cold. If a compound encounters and binds to another molecule, its thermophoretic parameters change, and its trajectory may even be reversed. This phenomenon can be exploited to determine whether a molecule that is known to play a causative role in a given disease binds to a test substance. In the test, which can be carried out directly on blood samples, the thermodiffusion of a labelled [biomolecule](#) of interest is measured in the presence and absence of a candidate binding agent. If the two bind together to form a complex, the resulting change in their

thermophoretic behaviour can be detected. "Detection of binding activity is the first step on the road to a new drug", says Braun. "The new method also has potential applications in medical diagnostics, and in food and environmental monitoring."

The procedures conventionally used to identify candidate drugs are normally carried out in artificial buffer solutions, and the results often have little relationship to a compound's binding affinity for its target in the blood. The new thermophoretic technique, on the other hand, allows one to perform the binding test directly in a blood sample and therefore gives more reliable results. The substance to be tested is mixed with a blood sample containing a target that is known to be associated with a disease state and has been labelled with a fluorescent tag. A tiny drop of the mixture is taken up into a thin glass capillary tube, and a focused beam of IR-laser light is used to heat a small volume of the solution in the middle of the tube. This gives rise to a temperature gradient that falls off towards the outside. The response of the labelled molecule to the variation in temperature can then be followed using fluorescence methods.

Upon heating of the sample, it immediately becomes apparent whether or not the fluorescent target-molecules in the sample behave differently in the presence of the drug test compound than they do in its absence. Any difference in thermophoresis between the two samples indicates that the test substance binds to the labelled target, and provides the first hint that it may have therapeutic potential. "Our method will not only be a boon to drug discovery", says Braun. "It can also be used in medical diagnostics, food testing and environmental monitoring. One could, for instance, employ it to diagnose autoimmune diseases and infections, or as the basis for a rapid test for the presence of antibiotics in milk or toxic substances in water."

More information: "Optical Thermophoresis for Quantifying the

Buffer Dependence of Aptamer Binding", Philipp Baaske, Christoph J. Wienken, Philipp Reineck, Stefan Duhr und Dieter Braun, *Angewandte Chemie* online, 23 February 2010

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