BIOSENSORS

Signal transduction with a swing

The continuous monitoring of proteins is a current challenge in medical diagnostics. A new electrochemical approach aiming to address this has been described. The method uses antibodies as a recognition element to achieve the real-time measurement of proteins in saliva in the mouth.

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The detection and measurement of biomarkers in patients is essential in the diagnosis and treatment of many diseases. For millennia[1] the standard of care has been removal of a sample from the patient (urine prior to several hundred years ago; blood more recently) followed by offline analysis. This in vitro diagnostic approach, which works well for many analytes, remains the cornerstone of clinical analysis. For some analytes, however, continuous in vivo monitoring would be of significant additional value for clinicians and their patients. In a recent paper in *Nature Chemistry*, a team led by Edward H. Sargent, Shana O. Kelley and co-workers have demonstrated a new approach towards this challenging goal[2].

The majority of successful in vivo biosensing approaches reported to date rely on one of two mechanisms for transducing binding events into a detectable output. In one, recognition is predicated on the specific chemical or enzymatic reactivity of target molecules. For example, the in vivo monitoring of glucose via its enzymatic degradation by glucose oxidase to produce electrochemically detectable products. This method is highly successful; it is the basis for the continuous glucose monitors worn by many people with diabetes. But because it is reliant on the specific enzymatic reactivity of its target, this approach is not generalizable to arbitrary targets, including, importantly, protein biomarkers. In contrast, the second approach, which employs a binding-induced conformational change in the recognition element to produce an optical or electrochemical output, is independent of the enzymatic reactivity of its targets and thus is generalizable as long as one can engineer such a conformational change into the receptor of choice. And while this signal transduction mechanism has proven applicable to receptors comprising short polypeptides, single-domain proteins or nucleic acid aptamers[3], it has not been demonstrated to work with larger recognition elements such as antibodies, which are perhaps the most widespread and important class of bioreceptors used for diagnostics in vitro. Using a newly described signal transduction mechanism[2], however, the antibody barrier has now been breached for real-time detection in saliva.

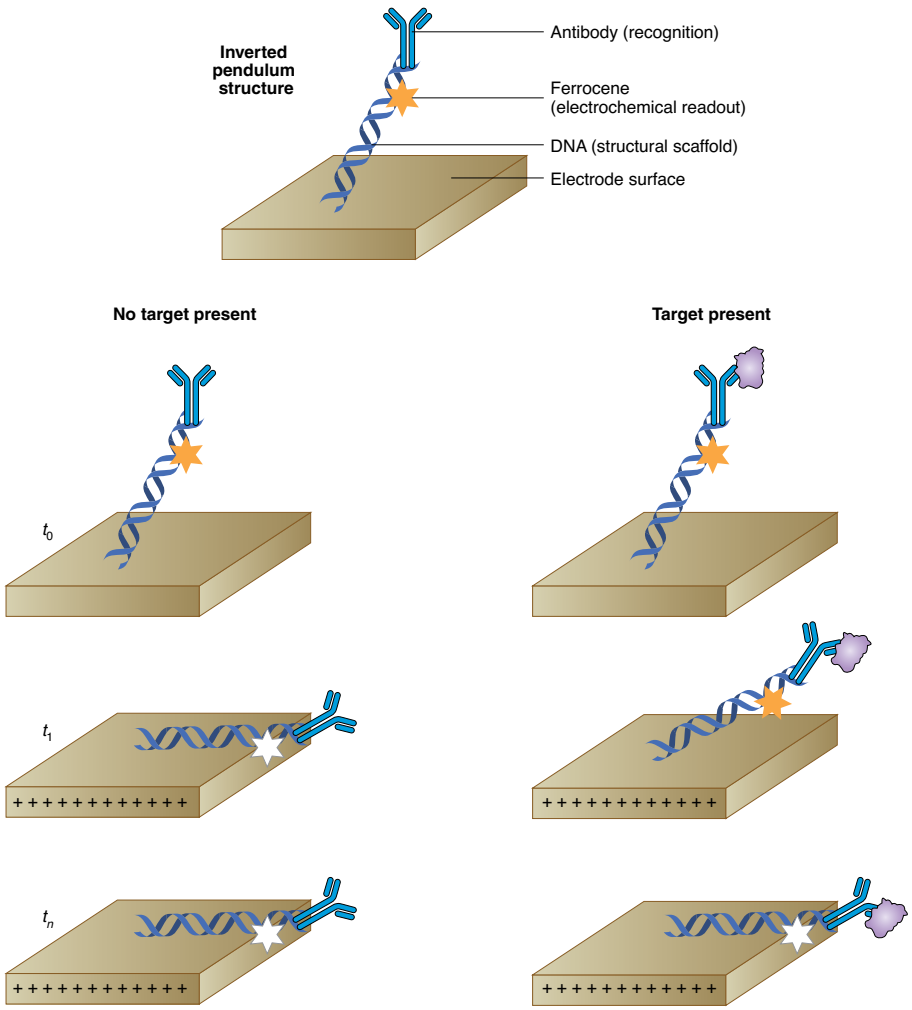

Fig. 1 | Molecular pendulum signal transduction. The inverted pendulum approach converts antibody binding into an electrochemical signal in a reversible manner and without the use of reagents. It is composed of a short, double-stranded DNA scaffold that is attached to an electrode and modified on its distal end with an antibody and the ferrocene redox reporter. When the electrode is held at a positive potential (time = t_1), the negatively-charged pendulum is attracted to the surface, but the kinetics with which it approaches are modulated by the hydrodynamic size of the target. Specifically, the target-free pendulum (left) migrates to the surface more rapidly than the target-bound pendulum (right), thus causing the observed rate of electron transfer to depend on receptor occupancy.

The newly described signal transduction mechanism is based on a molecular pendulum that converts target binding into an electrochemical readout. The approach (Fig. 1), which builds on earlier optical[4] and electrochemical[5] approaches, employs a short, electrode-bound, double-stranded DNA scaffold that is modified on its distal end with an antibody that recognizes the sensor's target, and a ferrocene redox reporter that generates an electrochemical signal. Changing the electrode surface to a positive electric potential (Fig. 1, t_1) pulls the negatively charged DNA pendulum towards the surface, with the dynamics of this motion being controlled by the hydrodynamics of the pendulum. This arrangement means that the kinetics of the pendulum slow when the target binds to the antibody, increasing the hydrodynamic radius of the complex and causing drag (Fig. 1, right). On its own, this change would be challenging to measure. The included ferrocene redox reporter enables electrochemical readout of this kinetic event, with the time constant of the electron transfer relating monotonically to the occupancy of the antibody.

This inverted pendulum approach is general, selective and sensitive. By swapping the target-recognizing antibody, for example, the team achieved the detection of ten proteins varying in size, charge and function. The approach also achieves good limits of detection even when challenged in complex media. For example, using the protein cardiac troponin I (Trop I) as their target, Sargent, Kelley and co-workers demonstrated the ability to measure this clinically important marker of heart failure down to picograms per milliliter in vitro in a variety of biofluids, including saliva, sweat, tears, urine and blood.

As the dynamics of the pendulum recover if the analyte is released from the antibody, the new signal transduction is reversible, suggesting that it should support continuous, real-time measurements. When taken with its selectivity and its lack of any requirement for endogenous reagents, this might imply the ability to monitor specific proteins in vivo. As the first exploration of this, the team placed sensors in the mouths of anaesthetized mice, where they achieved the continuous monitoring of Trop I levels in saliva under the influence of intravenous injection of the target and injections of drugs that cause cardiac damage, resulting in increasing levels of the Trop I biomarker.

The ability to use unmodified antibodies to monitor proteins continuously and in real-time in saliva represents a major step forward in our ability to monitor molecular markers of health and disease. This said, the use of saliva as a sample matrix for quantitative analysis (as opposed, for example, to the qualitative 'yes/no' detection of a pathogen or antibodies indicative of a pathogen) remains largely unproven due to concentration differences between blood and saliva, which can vary with changes to the levels of saliva production[6]. Thus, a greater improvement will be the adaptation of such systems for continuous measurements in the body itself, such as intravenously or subcutaneously. Though many technologies have floundered when moving into these spaces, the ability of this new scaffold approach to measure in blood in vitro suggests this exciting possibility may come to pass. ❐

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Competing interests

The authors declare no competing interests.

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ACTINIDE CHEMISTRY

The blue hue of einsteinium

A complex containing the unstable isotope ^{254}Es has been synthesized on a nanogram scale. Analysis of the fundamental bonding and spectroscopic characteristics of this einsteinium compound shows a blue shift of Es(III) luminescence upon complexation, and the ligand serves as an antenna to sensitize the excited state.

Louise S. Natrajan and Stephen Faulkner

The actinides — those metals with atomic numbers from 90 to 103 that occupy the bottom row of the periodic table — are all radioactive, and none beyond uranium are abundant in nature. Indeed, the transuranic elements were almost completely unknown until the post-Manhattan Project era, when a few were identified from the products of thermonuclear explosions. In particular, elements heavier than plutonium generally have short-lived isotopes, are notoriously difficult to handle, and are typically not available in the kind of quantities most chemists are used to. Even the actinides that can be produced in amounts suitable for characterization using common methods — currently, actinium to einsteinium — require specialist facilities and laboratories. The simplest of investigations, such as recording the colour of a compound by spectrophotometric methods, are convoluted and necessitate a host of precautions.

Reports on the chemistry of actinide elements heavier than curium are particularly rare. In the case of Es (element 99), only a handful of accounts exist, which