An antibody-based molecular switch for continuous small-molecule biosensing

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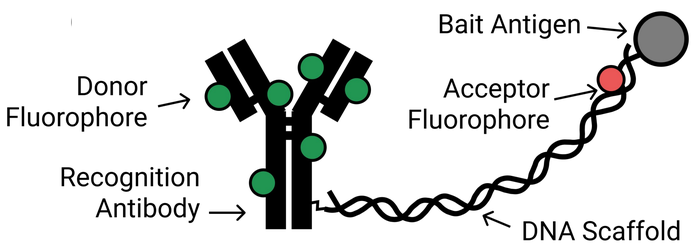
Problem Statement

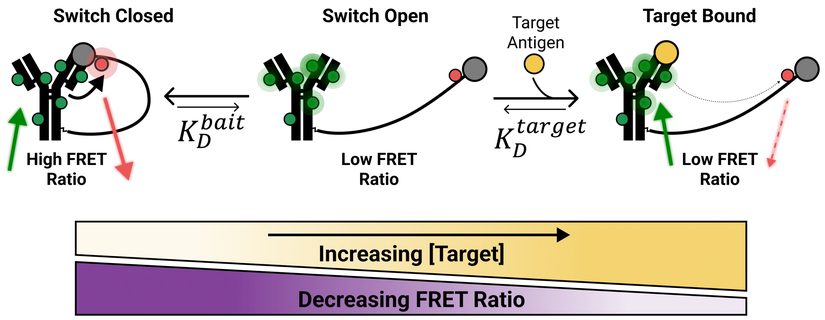
- **Continuous biosensing** has great potential to advance **personalized healthcare**, **early disease detection**, and **inpatient treatment**
- A few continuous sensors have been developed (glucose, blood oxygen), but **there is no method** for creating continuous sensors **for arbitrary biomarkers**
- We present a **generalizable**, **continuous** sensor design for **small-molecules**, and demonstrate it by building a sensor for cortisol

Sensor Design

- The sensor is made of a target-recognizing antibody, linked with a competitive bait-antigen using a DNA scaffold



- The antibody and scaffold are tagged with FRET-capable donor and acceptor fluorescent reporters
- The amount of energy transferred between the donor and acceptor fluorophores—measured as the FRET ratio—is a function of the target concentration

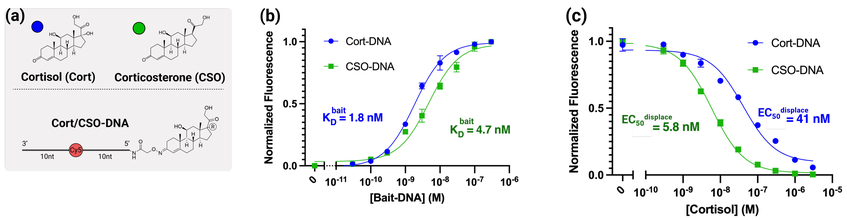


- Because the bait-antigen is conjugated to the conserved region of the antibody, this design can be used to develop a sensor for any target with a suitable antibody

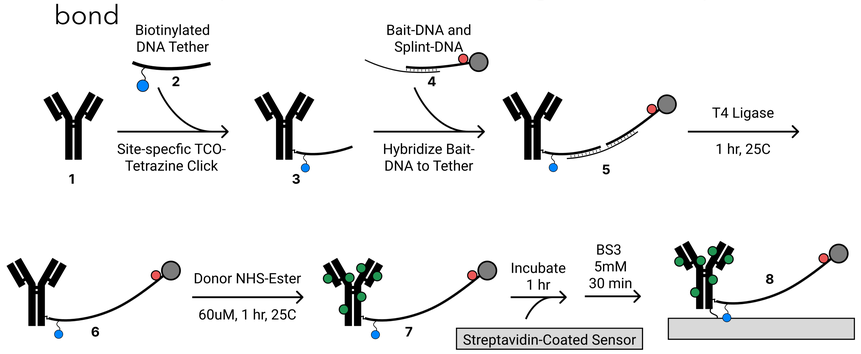
Building a Cortisol Sensor

- We first validate three key aspects of the sensor components:
  a) bait-DNA scaffold conjugation
  b) Binding between the antibody and the bait-antigen
  c) Competition between the bait-antigen and the target

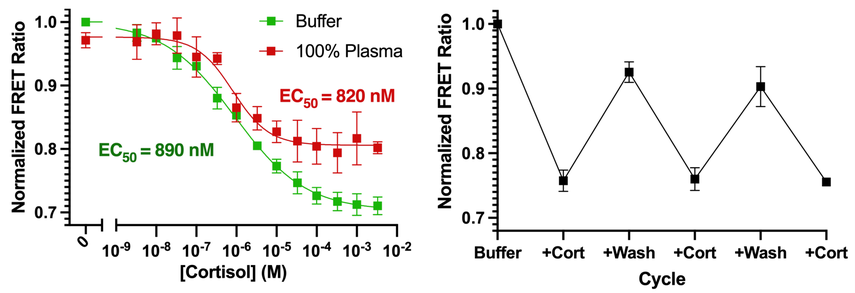
- We screen these properties for two potential bait-antibody pairs



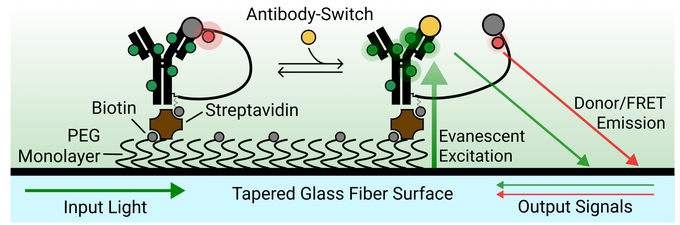
- Based on the preceding results, we decide to move forward with the corticosterone bait molecule
- Next the sensor is assembled using site-specific chemistry and DNA ligation
- The sensor is pulled onto a surface using a biotin-streptavidin bond



- Finally, we test the assembled sensor's response to cortisol. We measure the response curve in both buffer and 100% chicken plasma, and verify the sensor's reversibility

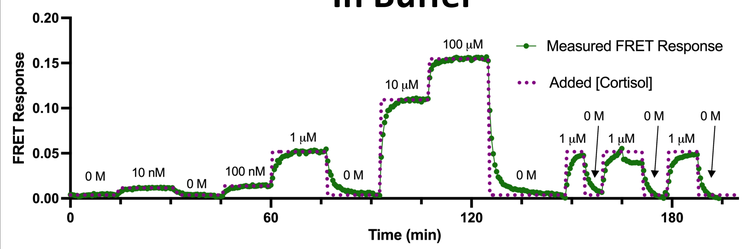


Real Time Sensing

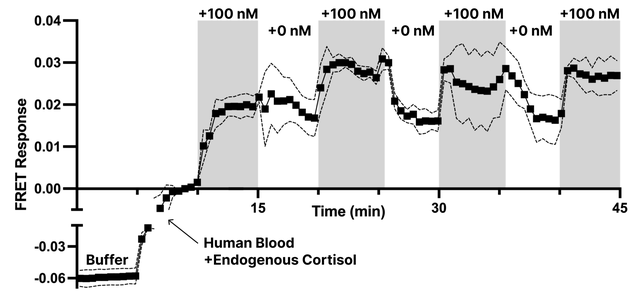


- Using a fiber optic measurement setup[1], we can track the sensor's response to target in real time

In Buffer



In Blood



- The sensor responds continuously to cortisol in both buffer and whole blood. It is fast (~5min response time) and sensitive (LOD 10-100nM)

Conclusions

- We presented a design for a **generalizable**, **continuous small-molecule** sensor
- Using this design, we built a **fast**, **sensitive** sensor for cortisol
- Read the paper for more details!

I. Thompson, J. Saunders *et al.*, An antibody-based molecular switch for continuous small-molecule biosensing. *Sci. Adv.* **9**, eadh4978(2023). DOI:10.1126/sciadv.adh4978

References: 1. A. Hariri, A. Cartwright *et al.* 2023. Continuous optical detection of small-molecule analytes in complex biomatrices. bioRxiv doi: 10.1101/2023.03.03.531030