

**Label-free fiber-optic spherical tip biosensor to enable  
picomolar-level detection of CD44 protein**

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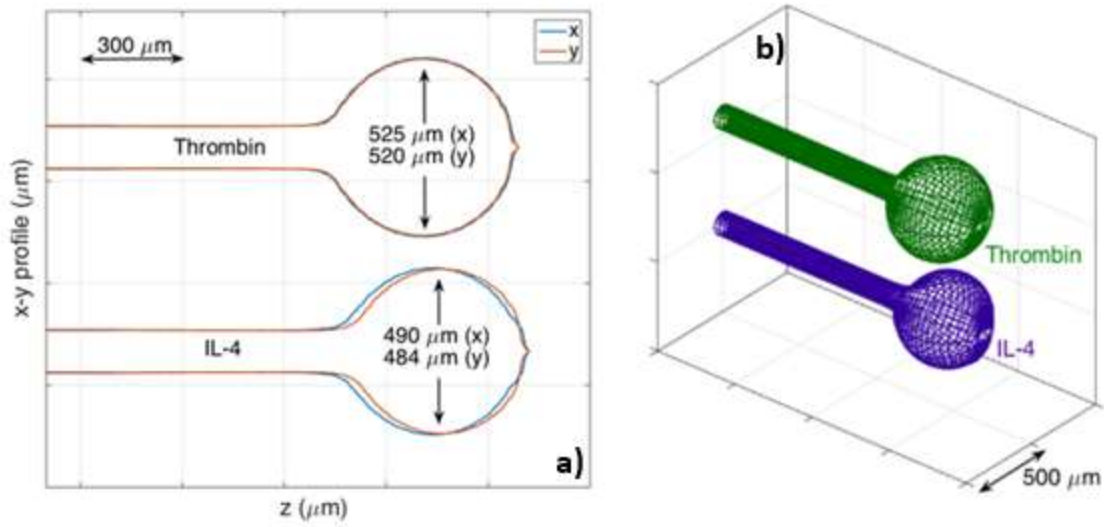
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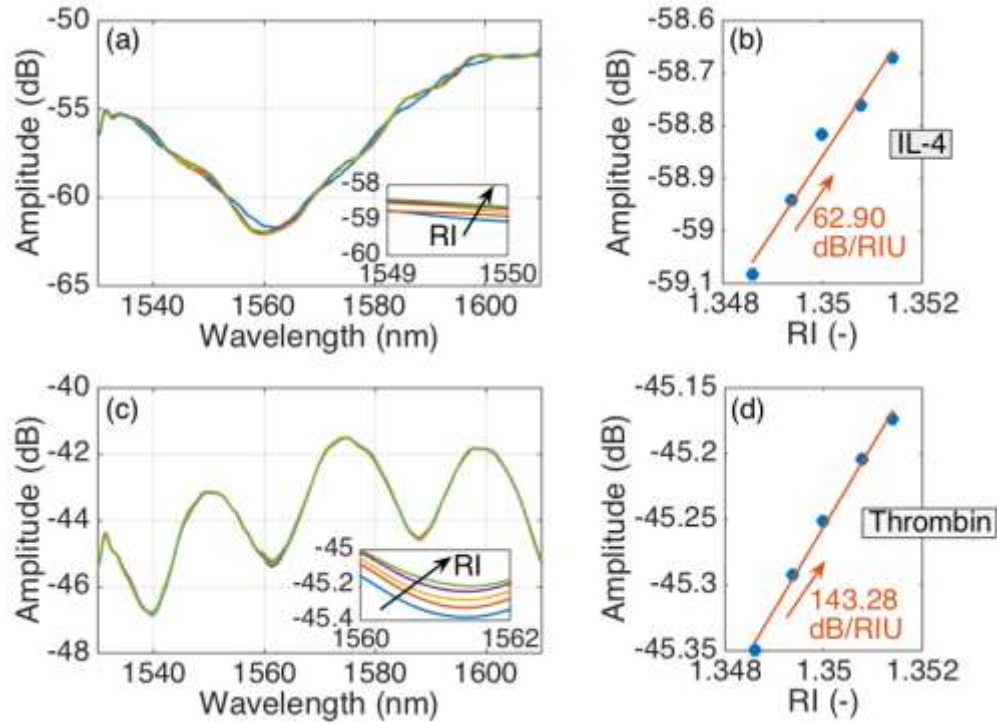
**Table S1.** Parameters used to fabricate fiber optic spherical tips using CO<sub>2</sub> laser splicer (Fujikura LZM-100).

| Parameters               | Diameters (x, y axes), μm |         |         |
|--------------------------|---------------------------|---------|---------|
|                          | 490-484                   | 525-520 | 548-544 |
| Pre-heat (bit)           | 1                         | 1       | 1       |
| Absolute power (bit)     | 342                       | 342     | 342     |
| Relative power (bit)     | 80                        | 60      | 153     |
| Break-add power (bit)    | 80                        | 10      | 130     |
| Feeding speed (mm/sec)   | 0.2                       | 0.1     | 0.2     |
| Rotator speed (deg./sec) | 90                        | 65      | 150     |
| Diameter adjustment (μm) | 10                        | 10      | 10      |

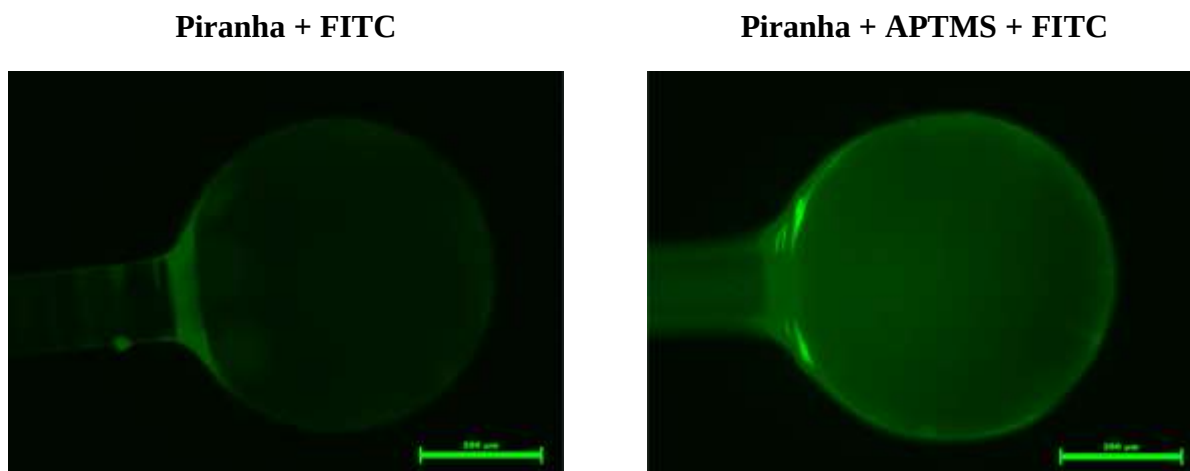


**Figure S1.** Geometrical profile of control fiber optic spherical tip sensors (525-520  $\mu\text{m}$  and 490-484  $\mu\text{m}$ ) functionalized with CD44 antibodies used to detect control proteins (thrombin and IL-4 respectively). (a) Two-sided profilometry of the fiber optic tips obtained from Fujikura splicer as measured by its inner microscope; where diameter on the horizontal and vertical axes ( $x$ ,  $y$ ) for each position along the fiber axis ( $z$ ) is shown; (b) 3D profiles extrapolated from profilometry data by reconstructing the elliptical meshes of the tips for two control sensors;

$$\text{Ellipticity}_{525-520 \mu\text{m}} = 0.1376; \text{Ellipticity}_{490-484 \mu\text{m}} = 0.1560$$

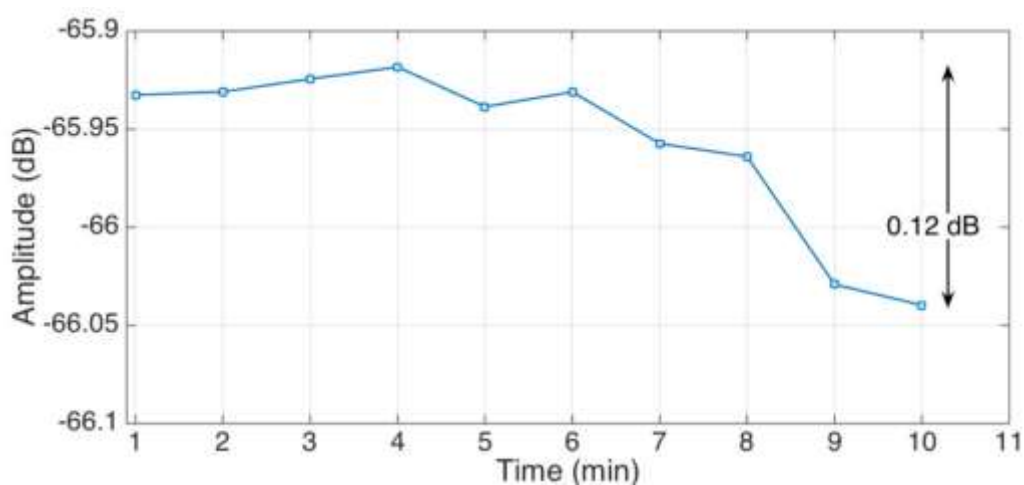


**Figure S2.** RI calibration of control fiber optic spherical tip sensors (**a** and **b**: 525-520  $\mu\text{m}$  further functionalized for thrombin measurement; **c** and **d**: 490-484  $\mu\text{m}$  further functionalized for IL-4 measurement). Different sucrose concentrations were used starting from 10.49% in 5 steps corresponding to RI values of 1.34860 to 1.35140; (**a**, **c**) Amplitude spectra of the sensors in different sucrose concentrations; Inset showing integrated spectral response in the range where sensors had the highest response for sensitivity estimation; (**b**, **d**) Amplitude change as a function of RI change; curves processed with linear regression; for thrombin,  $R^2 = 0.9733$  with an estimated sensitivity of 143.918 dB/RIU while for IL-4,  $R^2 = 0.9513$  with an estimated sensitivity of 62.90 dB/RIU. Arrows show the direction of the RI trend.

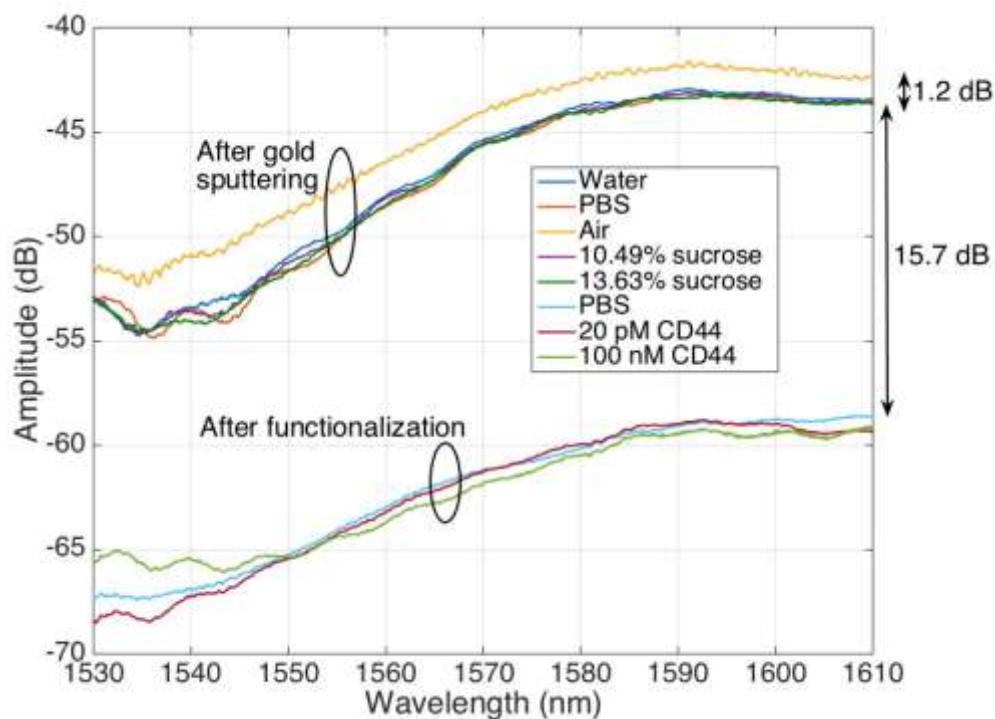


**Figure S3.** FITC analysis of the control (after Piranha treatment) and silanized fiber optic tips (Piranha + APTMS) as visualized by fluorescence microscopy.

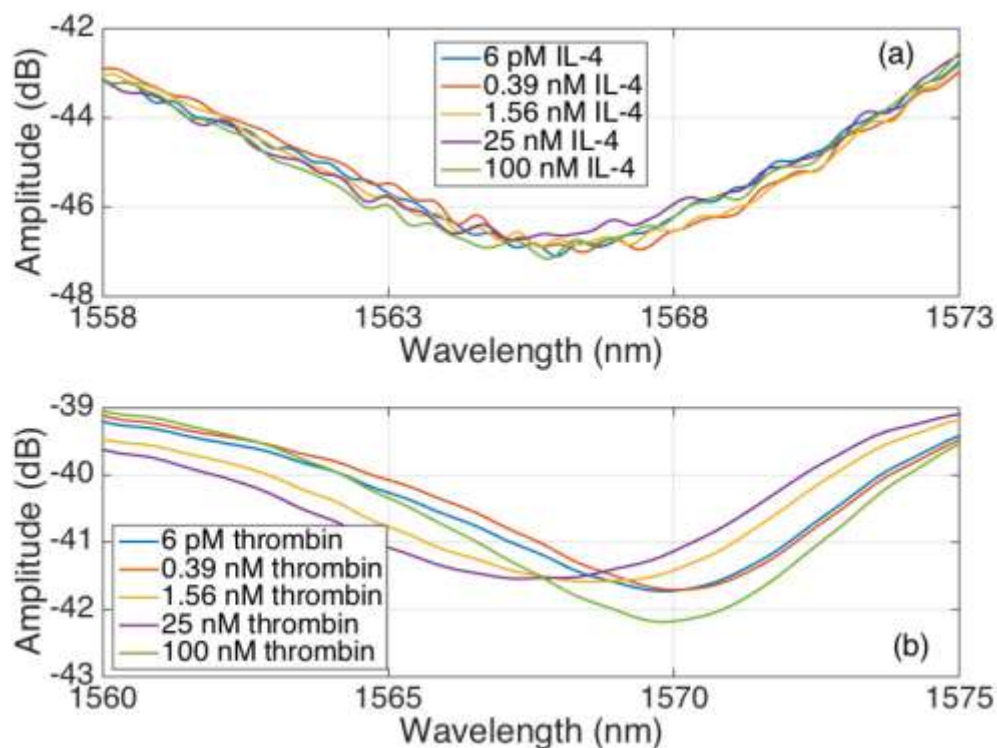
APTMS - (3-Aminopropyl)trimethoxysilane.



**Figure S4.** Amplitude change as a function of time during CD44 protein detection by functionalized fiber optic tip. The spectral response measured every 1 minute at 0.8 nM conc. of the protein (middle concentration) for 10 minutes.



**Figure S5.** Evolution of the spectral amplitude of spherical fiber optic tip (CD44 protein detecting biosensor) after gold sputtering and after full functionalization. Spectra of the sensors in the range from 1530 to 1610 nm in different media are shown including the lowest/highest sucrose concentrations used during calibration; and two concentrations of CD44 protein.



**Figure S6.**

**Figure S6.** Detection of control proteins by spherical fiber optic tip biosensor functionalized with CD44 antibodies; Spectral change occurring during measurement of different concentrations of (a) IL-4 and (b) thrombin by the biosensor is shown; Spectral response in the range shown (between 1558-1573 nm and 1560-1575 nm respectively) were integrated to compare the signal with those of the target protein (**Figure 5**).