In order to produce a more versatile, adaptable, and effective method for detection of biological analytes, a self-contained and robust fluorescent optical biosensor architecture utilizing fluorescence resonance energy transfer (FRET) is proposed. This biosensor architecture is then applied to a highly adept liquid-core waveguide platform. FRET is a distance-dependent signal transduction method that occurs between two fluorescent molecules, termed the donor and acceptor. When the donor and acceptor are brought within close proximity, a quantifiable nonradiative energy exchange takes place. In order to launch FRET, a donor-labeled Protein A molecule is bound to an acceptor-labeled capture antibody. When exposed to antigen, the antibody-antigen binding event initiates a conformational change within the structure of the antibody, and thereby induces a measurable change in energy transfer from the donor to the acceptor by altering the distance between the FRET pair. Additionally, effects of quantum dots and gold nanoparticles utilized within the FRET system are studied. The resulting system is then optimized and tested in a liquid-core waveguide platform that is able to retrieve sensitive and accurate measurements. In the current study, the biosensor was used to detect Porcine Reproductive and Respiratory Syndrome virus and human cardiac Troponin I, showing ample sensitivity and a high degree of specificity, as well as rapid response.