



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Surface Plasmon Resonance: A Boon for Viral Diagnostics

Pranveer Singh, Mahatma Gandhi Central University, Motihari, India

© 2017 Elsevier Inc. All rights reserved.

Introduction

Viral diagnosis and surveillance are necessary steps in containing the spread of viral diseases. These measures help in the deployment of appropriate therapeutic interventions, thus ensuring effective management and control of disease. In the past, the commonly employed viral detection methods were either cell-culture or molecule-level assay based. Most of these assays are laborious and expensive, require special facilities, and provide a slow diagnosis. Biosensor-based approaches largely circumvent these limitations and therefore provide an attractive alternative as validated after successful commercialization of glucose and other biosensors.

In light of continuously emerging new viral strains, precise, timely and cost-effective viral diagnosis has become an important factor for the effective management of viral disease. The past decades have seen a spurt in the development of antiviral therapies and diagnostic protocols as against conventional culture-based methods. Viral diagnosis can be performed by direct or indirect methods. Direct methods look for intact viruses or viral nucleic acids or proteins. Indirect methods involve culturing of clinical samples followed by infection of cells, eggs or animals to isolate viruses. These viruses are then confirmed via serological detection methods utilizing antibodies against viral antigens induced by viral infection. Indirect methods of viral diagnosis include complement fixation tests, the hemagglutination inhibition test, immunofluorescence, the enzyme-linked immunosorbent assays, and the Western blot assay. However, these methods have inherent disadvantages as they are limited to laboratories, are time consuming, lack sensitivity, and most importantly, may not identify newly emerging viral strains. Examples include Zika virus, swine and bird flu viruses, Nipah virus, and Chikungunya virus. These issues are largely circumvented by molecular diagnostic protocols based on nucleic acid amplification (NAAT) test. Molecular diagnostics rely on the polymerase chain reaction (PCR) that amplifies the viral DNA or RNA using (RT-)PCR. This protocol has successfully addressed the diagnostic issues for human immunodeficiency virus (HIV) (Mulder *et al.*, 1994), hepatitis B and C viruses (Berger *et al.*, 1998), and cytomegalovirus (CMV) (Boeckh and Boivin, 1998; Pavel *et al.*, 2016). Timely and precise diagnosis provided via PCR has made this technique a gold standard for viral diagnosis. PCR is further improvised and diversified to nested-PCR, real-time PCR, digital PCR ligase chain reaction, and loop-mediated isothermal amplification methods, etc. However, PCR-based molecular diagnostics have their share of pitfalls as well, including requirements for well-equipped laboratory facilities and qualified and trained personal as well as high costs. Optical biosensors have removed these disadvantages as they offer a rapid, cost effective, sensitive, label free, reproducible method for diagnosing a particular virus. Due to their many advantages, optical biosensors are increasingly used in a variety of clinical and nonclinical applications. A wide array of analytes that includes toxins, drugs, antibodies, tumour biomarkers, tumour cells and intact viruses can be detected in highly sensitive and selective manner. This article will focus on the detection protocols for intact viruses that utilize antibody, glycan and aptamer based bioreceptor surfaces. The current review highlights progress and development toward the detection of intact viruses. Additionally, this article emphasizes description and examples of applications of optical biosensors in medicine, with special reference to viral diagnostics.

Optical Biosensors

Optical biosensors offer distinct advantages over traditional analytical techniques in providing real-time and label-free detection of biological and chemical substances in a highly sensitive, specific and cost effective manner. The advantages include high specificity, sensitivity, small size and cost-effectiveness. Optical biosensing is further complemented with multidisciplinary approaches like microelectronics, microelectromechanical systems (MEMSs), micro/nano-technologies, molecular biology, biotechnology and chemistry. These developments, coupled with the advantages of optical biosensing, have led to an exponential growth in applications over the last decade. Optical biosensors are applied in healthcare, environmental analyses, and the biotechnology industry. These applications benefit from many advantages including low concentration and amount of analyte required, rapid analysis completion, and sensor chip reusability (Dey and Goswami, 2011; Damborský *et al.*, 2016).

An optical biosensor is a compact analytical device having a biorecognition element integrated with a transducer system. Optical biosensors emit an optical signal, which is directly proportional to the concentration of the analyte. The biorecognition elements used by biosensors are generally biological materials, including enzymes, antibodies, antigens, receptors, nucleic acids, whole cells and tissues. Based on the signal transduction method utilized, biosensors can be grouped into different categories: optical, electrochemical, thermometric, piezoelectric, and magnetic. Among these, optical biosensors are the most common. Optical biosensors utilize the interaction of optical fields (i.e., the electric field) with the analyte for optical detection. Optical biosensing can be performed in a label-free or label-based manner. Label-free protocols involve interaction of the analyte with the transducer for signal detection while label-based protocols label the analyte and the optical signal is generated by colorimetric, fluorescent or luminescent methods (Damborský *et al.*, 2016).

Surface Plasmon Resonance (SPR)

Pharmacia Biosensor AB (now Biacore) developed the first commercial SPR-based biosensor. Currently, SPR-based biosensors are produced by a number of manufacturers. SPR-based biosensors are currently the most commonly used devices for optical biosensing applications. SPR-based sensing has recently emerged as a valuable technique for measuring binding constants, association and dissociation rate constants, and stoichiometry for bimolecular binding interaction kinetics in a number of emerging biological areas (Singh, 2014, 2016a).

The practical applications of SPR analyses includes kinetic analysis, equilibrium analysis and concentration analysis. Kinetic and equilibrium analyses are used to characterize bimolecular interaction (ligand–analyte binding, antibody–antigen interaction, receptor characterization etc.) in a label-free, real-time manner (Fig. 1). Concentration analysis of an analyte can also be done using SPR, provided a specific ligand is available and it can be immobilized on a sensor chip surface. Concentration is then quantified by the measurement of direct binding or from the rate of binding in mass transport limited mode. Concentration analysis has applications in healthcare, biopharmaceutical production, clinical point-of-care (POC) diagnostics, environmental analysis, food monitoring, defense and security (Singh, 2014, 2016a). SPR analyses were utilized to diagnose different stages of Epstein–Barr virus through detection of antibodies against different antigens present in the virus (Riedel *et al.*, 2014). SPR-based food monitoring includes detection of antibiotics in milk samples (using a portable six-channel SPR sensor) and mycotoxin patulin (immunochemical SPR) (Hunt and Armani, 2010; Damborský *et al.*, 2016). SPR was also utilized to monitor the binding kinetics of dengue antibody with corresponding dengue antigen in real-time manner (Jahanshahi *et al.*, 2016).

Detection and Quantification of Enterovirus 71

The SPR system can be miniaturized for wider application in the field and laboratory. Prabowo *et al.* (2017) have developed such portable detection system for label-free, rapid quantification of human Enterovirus 71 (EV71). These are small RNA viruses belonging to picornviridae family with a very high mutation rate (Fig. 2). The configuration allowed the system to run on low power with an organic LED with red spectral emission as a disposable light source. The signal to noise ratio (SNR) was enhanced by intergrating the area under the reflectivity curve. The detection system utilized the major capsid protein VP1 of EV71 as the biomarker. By combining the SPR assay with the viral plaque assay, the assay time was reduced from days to minutes with a detection limit of approximately 67 virus particles of EV71 per milliliter (vp/ml) in Dulbecco's modified Eagle's medium. This platform could be further improved by incorporating a highly sensitive, real-time, optical biosensor-based assay (Liu and Liu, 2017; Prabowo *et al.*, 2017).

SPR Based on M13 Bacteriophage

Bacteriophage M13 has been recently utilized as a functional nanomaterial in electrical, chemical and optical applications owing to its non-toxic, self-assembly, and specific binding properties. These features make M13 bacteriophage a potential candidate as a receptor for transducing biochemical and bio-optical signals into electrical or optical signal. Additionally, surface properties of M13 bacteriophage can be manipulated via genetic engineering. Kim *et al.* (2016) have described a novel M13 bacteriophage-based, highly sensitive and selective SPR sensor. This sensor utilizes self-assembled, genetically engineered M13 bacteriophage.

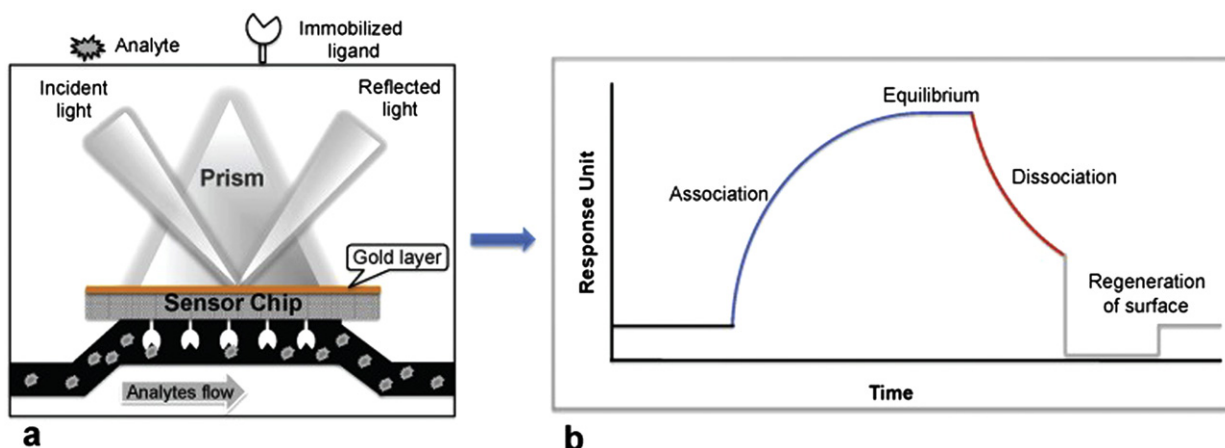


Fig. 1 Surface plasmon resonance (SPR) biosensing platform: (a) SPR biosensing system; (b) Sensogram depicting the ligand interaction with the immobilized biomolecule. Kumar, V., Tan, K.P., Wang, Y.M., *et al.*, 2016. Identification, synthesis and evaluation of SARS-CoV and MERS-CoV 3C-like protease inhibitors. *Bioorganic and Medicinal Chemistry* 24, 3035–3042. ©2016 by the author; licensee MDPI, Basel, Switzerland (Available at: <http://creativecommons.org/licenses/by/4.0/>).

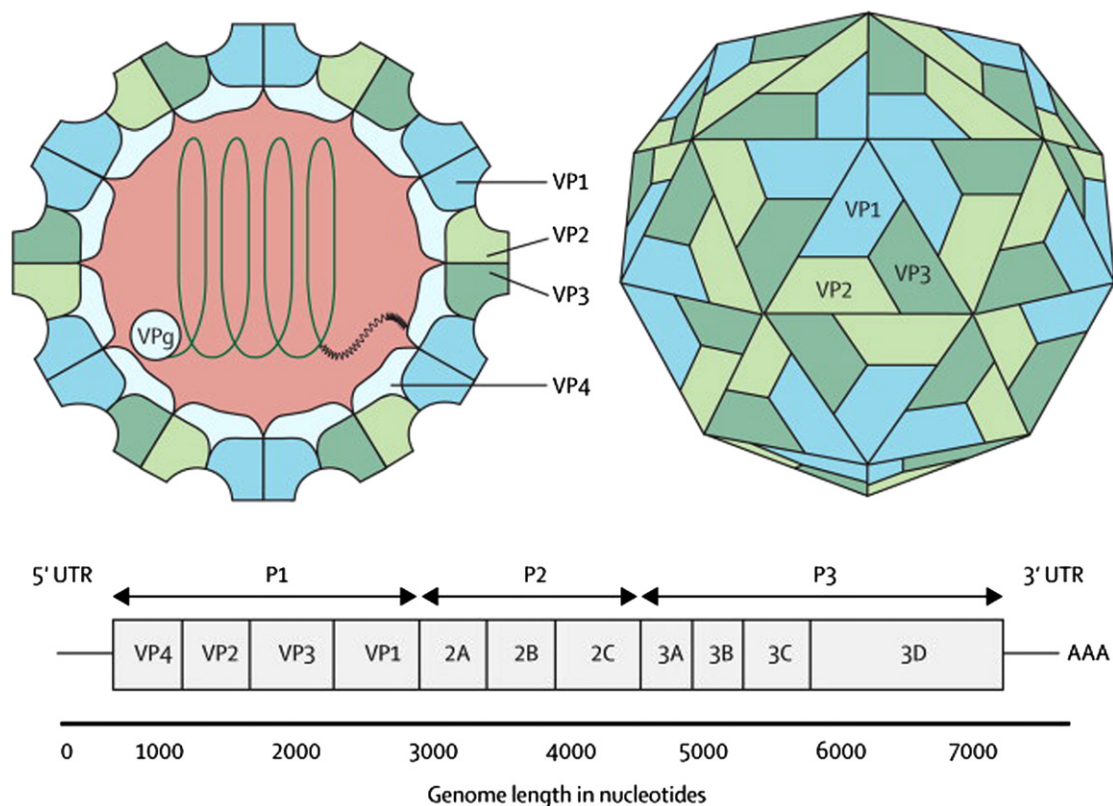


Fig. 2 Enterovirus 71 structure and genome structure of the virion. Reproduced from Liu, C.C., Lian, W.C., Butler, M., Wu, S.C., 2007. High immunogenic enterovirus 71 strain and its production using serum-free microcarrier Vero cell culture. *Vaccine* 25, 19–24.

Self-assembly is advantageous over complicated photolithography or chemical conjugations in terms of simplicity. Sensitivity was further improved by integrating the receptor-connector matrix (a device for interconnecting electronic components using a matrix of independent but interconnectable conductive traces) in specific orientations to reduce measurement error (Kim *et al.*, 2016).

Localized Surface Plasmon Resonance-Based Quantum Dot Nanobiosensors for Immunofluorescence Detection of Viruses

LSPR biosensors detect biomolecules with nanoscale spatial resolution in a label-free manner. This technique finds useful applications in the study of DNA-protein interactions, toxins, proteins and vesicles. Sensor miniaturization can go down to scales unapproachable by other planar microfabrication/microlithography techniques. Also unique to LSPR is the nanoplasmonic resonance condition, which is satisfied in a simple reflected or transmitted light geometry, common to both microscopy and spectroscopy applications, whereas SPR excitation requires incident light that is totally internally reflected. This has given impetus to the LSPR spectroscopy and imaging (LSPRi) integrated into live-cell microscopy studies for the detection of secreted proteins while simultaneously imaging the cells with more traditional techniques such as fluorescence and bright field (Singh, 2016b) (Fig. 3). Takemura *et al.* (2017) have developed a LSPR-induced immunofluorescence nanobiosensor for ultrasensitive, rapid and specific detection of influenza virus and norovirus-like particles (NoV-LPs). This platform is based on a gold nanoparticle (AuNP)-induced quantum dot (QD) fluorescence signal. The mechanism involves conjugation of an anti-neuraminidase (NA) antibody (*anti*-NA Ab) to thiolated AuNPs and the conjugation of anti-hemagglutinin (HA) antibody (*anti*-HA Ab) to alloyed quaternary L-cysteine-capped CdSeTeS QDs. A hot-injection organometallic route was employed for alloyed quaternary CdSeTeS QDs synthesis followed by capping with L-cysteine via a ligand exchange reaction. Similarly, AuNPs were synthesized in HEPES buffer and thiolated with L-cysteine. The detection limit for influenza H1N1 virus was 0.03 pg/ml in deionized water and 0.4 pg/ml in human serum, while for the clinically isolated H3N2, the detection limit was found to be 10 PFU/ml.

PAMONO-Sensor for Quantification of Microvesicles

The plasmon assisted microscopy of nano objects (PAMONO) sensor is utilized for imaging nano objects of biological and non-biological origin (Zybin *et al.*, 2010; Gurevich *et al.*, 2011). PAMONO sensors are ideal for detection and quantification of intact

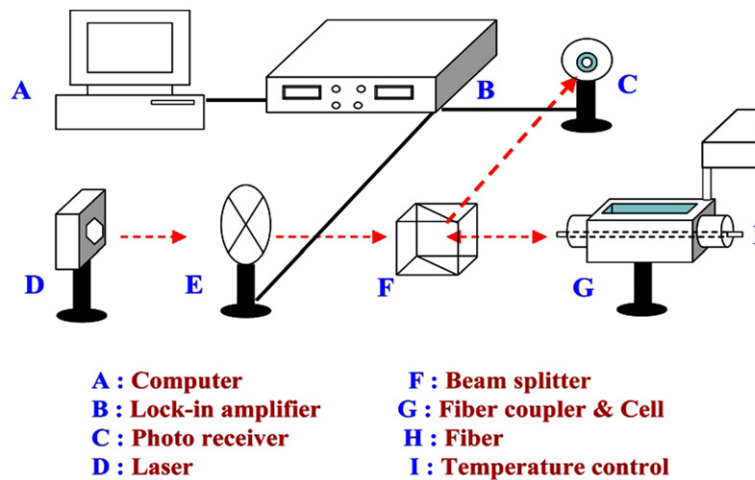


Fig. 3 Workflow of the LSPR biosensing system. Reproduced from Lin, T.J., Chung, M.F., 2008. Using monoclonal antibody to determine lead ions with a localized surface plasmon resonance fiber-optic biosensor. *Sensors (Basel)* 8, 582. ©2008 by MDPI.

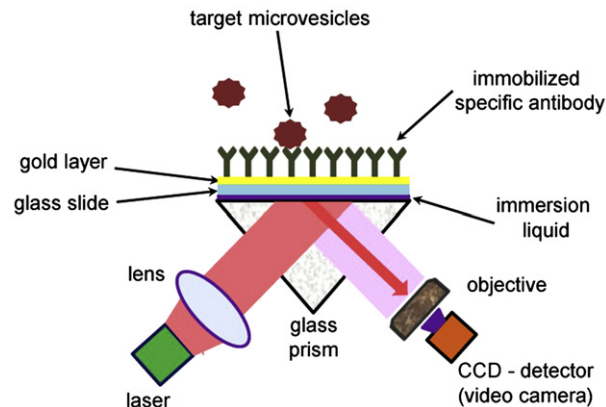


Fig. 4 Schematic of PAMONO-sensor setup used for detection of biological nano-vesicles. Reproduced from Shpacovitch, V., Temchura, V., Matrosovich, M., *et al.*, 2015. Application of surface plasmon resonance imaging technique for the detection of single spherical biological submicrometer particles. *Analytical Biochemistry* 486, 62–69. Licensee MDPI, Basel, Switzerland (Available at: <http://creativecommons.org/licenses/by/4.0/>).

viruses, virus like particles (VLP), nano-vesicles, extracellular vesicles (EVs) and inorganic nanoparticles (NP) (Im *et al.*, 2014; Zhu *et al.*, 2014; Shpacovitch *et al.*, 2015; Figs. 4 and 5). EVs facilitate intracellular communication and information exchange within an organism. PAMONO sensors provide for the imaging of EVs in a real-time, label-free manner without requiring advanced technology for the preparation of sensor slides (Gyorgy *et al.*, 2011; Yanez-Mo *et al.*, 2015; Figs. 4 and 5). In a study, PAMONO sensors were utilized to analyze the detection and quantification of microvesicles (MVs). This involved real-time binding analysis of individual MVs to the sensor surface functionalized by protein A/protein G and anti-target antibody. This binding was followed by elution of MVs from the sensor surface for post-PAMONO analysis of their content, which may act as an indicator of disease status. PAMONO sensor-based diagnostic platforms may help in the analysis of liquid biopsy samples in which the pattern of MV size distribution is indicative of different cargos being ferried.

Glycans

Glycoproteins present on the surface of most viruses are used to recognize the glycans expressed on the surface of host cells. Therefore, an artificial glycan surface can be created for virus detection. This artificial glycan surface requires that affinity and specificity of glycans on this surface must be higher for viral surface proteins than the affinities of host antibodies for the viral proteins. Based on the above, possible glycan surfaces that can be created for viral capture using SPR can be one where glycoproteins express glycans recognized by the virus; natural, purified glycans on a liposome surface, or a multivalent synthetic glycan surface. For example, in case of reovirus, glycoprotein binds to the host α -linked sialic acid residues. Resulting sialoglycoproteins expressed on the red blood cells can be utilized as a biorecognition surface on the SPR platform. This gives an opportunity to compare different strains of reovirus based on different binding capacities of sialic acid.

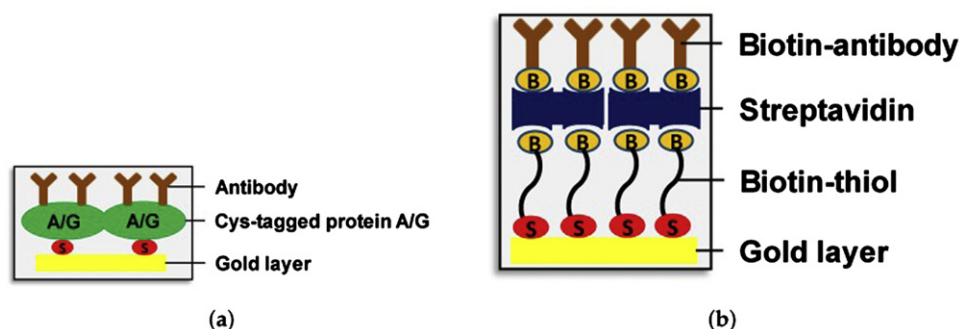


Fig. 5 Schemes of the sensor surface functionalization approaches utilized in PAMONO-sensor. Cysteine-conjugated protein A/G – antibody (without any conjugated tag) (a) and biotin-thiol–streptavidin–biotinylated antibody (b) Gold sensor surface showing self assembling monolayers (SAM) formation to capture the vesicles of interest. Reproduced from Shpacovitch, V., Temchura, V., Matrosovich, M., *et al.*, 2015. Application of surface plasmon resonance imaging technique for the detection of single spherical biological submicrometer particles. *Analytical Biochemistry* 486, 62–69. Licensee MDPI, Basel, Switzerland (Available at: <http://creativecommons.org/licenses/by/4.0/>).

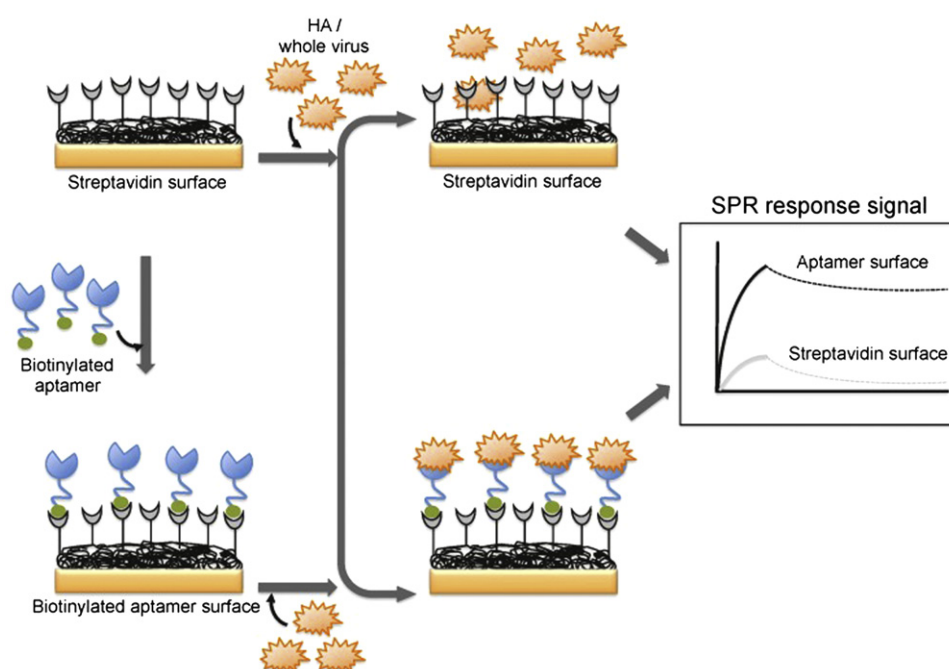


Fig. 6 Schematic of experimental set-up utilizing an aptamer as the biorecognition surface on the SPR platform. Kumar, V., Tan, K.P., Wang, Y.M., *et al.*, 2016. Identification, synthesis and evaluation of SARS-CoV and MERS-CoV 3C-like protease inhibitors. *Bioorganic and Medicinal Chemistry* 24, 3035–3042. ©2016 by the author; licensee MDPI, Basel, Switzerland (Available at: <http://creativecommons.org/licenses/by/4.0/>).

Monitoring Intact Viruses Using an Aptamer as a Bioreceptor

Aptamers are oligonucleotides or peptide molecules that bind to specific target molecules. These are produced by *in vitro* genetic selection that involves isolation from a library of nucleic acids through the process of selection and amplification. Aptamers bind with high affinity and specificity that could surpass the affinity obtained between antibody-antigen binding. In comparison with antibodies, aptamers are smaller in size, easy to synthesize, lack toxicity and immunogenicity. Aptamers therefore find useful application in the fields of imaging, diagnostics, and therapeutics (Misono and Kumar, 2005; Gopinath *et al.*, 2006, 2008, 2012, 2013; Cho *et al.*, 2009; Keefe *et al.*, 2010; Park *et al.*, 2011; Wang *et al.*, 2013; Suenaga and Kumar, 2014; Dougherty *et al.*, 2015). Aptamers are available against corresponding cognate targets that include ions, small molecules, peptides, proteins, viruses and organelles. Aptamers have been isolated against surface proteins of human pathogenic virus (Gopinath, 2007; Shum *et al.*, 2013). Interestingly, some of these aptamers are able to distinguish very closely related families and subtypes (Misono and Kumar, 2005; Gopinath *et al.*, 2006, 2013; Park *et al.*, 2011; Wang *et al.*, 2013; Suenaga and Kumar, 2014; Dougherty *et al.*, 2015; Penmetcha, 2016). High affinity aptamers can be used for the direct detection of intact viruses in virus-contaminated samples. Aptamer-based bioreceptor surfaces have been increasingly used with SPR and other sensing platforms (Fig. 6).

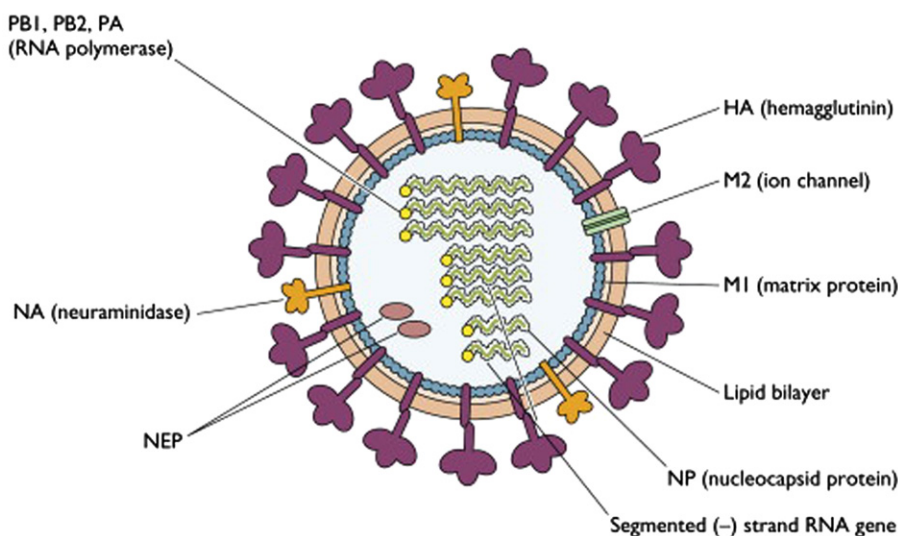


Fig. 7 Structure of Influenza virus. Racaniello, R., 2009. Structure of influenza virus (virology blog). Available at: <http://www.virology.ws/2009/04/30/structure-of-influenza-virus/>.

DNA Aptamers for Influenza Virus

Influenza viruses are negative-sense, single-stranded, segmented RNA viruses. Various subtypes are named according to an H number (hemagglutinin) and an N number (neuraminidase). There are 18 different known H antigens (H1 to H18) and 11 different known N antigens (N1 to N11). Influenza virus was first isolated from a Peruvian bat (Tong *et al.*, 2013; Fig. 7). In a study, a DNA aptamer was selected against HA of avian influenza virus. It discriminated against all other strains of H5N1 and subtypes of influenza virus (Gopinath and Kumar, 2013; Wang *et al.*, 2013). This aptamer was utilized as a biorecognition surface in a SPR sensing system for detection and evaluation of specific avian flu viruses. The analysis gave the concentration of targeted avian influenza virus expressed as hemagglutination unit (HAU) while non-targeted influenza viruses elicited an insignificant response signal (Bai *et al.*, 2012). Similarly, avian influenza virus titers were estimated from poultry swab samples in an hour, which is considerably less than conventional approaches. However, multiple samples cannot be analyzed via this method due to limitations of regenerating the sensor surface. This limitation could be circumvented by using an agent that facilitates simple and quick regeneration of sensor surface that could restore the sensor efficiency without impairing the efficiency of the sensor chip (Bai *et al.*, 2012). In a study, regeneration of the sensor surface involved immobilization of streptavidin (SA) on the CM5 chip, anti-influenza virus (H3N2)-aptamer and bioynlated oligo with different amount (HAU) of influenza virus. Plotting the response signals with HAU of influenza virus showed a linear response and the chip was used for more than 90 cycles. Signal and sensitivity could further be increased by using shorter dextrans and self-assembled monolayers (SAM), thus indicating that a shorter chain length SAM provides a better choice for analyzing intact viruses (Gopinath *et al.*, 2006; Fig. 6).

A study has generated DNA aptamer against influenza virus H1N1 (A/PR/8/34) (Jeon *et al.*, 2004). This aptamer was covalently linked to a conductive polymer for the functionalization of microelectrodes in the microfluidic channel (Kiilerich-Pedersen *et al.*, 2013). This sensor detected virus in the saliva in a matter of a few minutes with a broad dynamic range. This sensor could have a potential application in POC diagnostics for virus detection using aptamers specific for viruses (Kiilerich-Pedersen *et al.*, 2013).

Aptamer Based Impedance Biosensor for Virus Detection

In a study, aptamer and glycan surfaces were combined in an impedance biosensor to facilitate detection of intact virus (Wang *et al.*, 2013). In this study, the authors developed an aptamer specific for avian influenza virus, followed by capturing it on streptavidin-coated magnetic beads. Once the virus was captured on the bead, a complex containing concanavalin A (ConA)-glucose oxidase immobilized on the AuNP was attached to the virus via glycans of ConA. The captured complex comprising 'aptamer-virus-Con-Glucose oxidase-AuNP' was transferred to glucose solution that yields gluconic acid via an enzymatic reaction. This results in increased ionic strength of the solution decreasing the impedance of screen printed interdigitated array electrode (IDE). The described biosensor displayed higher sensitivity compared to biosensors based on aptamers or antibodies alone (Fu *et al.*, 2014).

Sandwich-Type SPR Based Paired of Aptamers

A sandwich-type SPR biosensing platform was designed for the detection of whole avian influenza viruses H5Nx utilizing Multi-GO-SELEX method. This platform has successfully screened aptamers with affinities ranging from 8×10^4 to 1×10^4 EID₅₀/ml.

The aptamers IF10 and IF 22 were specific for H5N1 and bind to the same sites of H5N1. Therefore, IF10 and IF22 were used to design a sandwich-type SPR biosensor. The sensitivity of this biosensing platform was increased by signal amplification with the secondary aptamer conjugated with AuNP (Nguyen *et al.*, 2016).

Nanoparticle-Based Viral Detection

NanoBioAnalytical Platform for “On-Chip” Quantification of Microparticles

Microparticles (MPs) are fragments of submicron dimension (50–1000 nm) derived from different cell types. These particles are shed into the extracellular space under the conditions of stress/injury and are present in plasma and other biological fluids. MPs show altered levels under diseased condition like pre-eclampsia and hypertension and so act as an important biomarker for various vascular and other types of disorders. Additionally, they may play a direct role in the pathology of a disease, thus acting as both biomarker as well as mediator of disease. SPR coupled with atomic force microscopy (AFM) was utilized for the detection and characterization of platelet-derived blood microparticles (PMPs) using surface-specific ligands. The combined platform provides rapid, sensitive, reproducible, and label-free characterization and quantification of MPs (Dylan *et al.*, 2013; Obeid *et al.*, 2016; Singh, 2016a).

Peptide-Functionalized Gold Nanoparticles

Two of the most severe limitations in nanomedicine-based therapy are the availability of appropriate targeting agents to deliver the nanotherapeutics to the affected cells and the ability of the nanosystem to enter the cell. In a study, AuNP were synthesized to target hepatocellular carcinoma (HepG2) cells transfected with SERPINB3 (SB3) protein. SB3 protein is usually undetectable in normal hepatocytes but shows overexpression in hepatocellular carcinoma and hepatoblastoma. SB3 protein is proposed as a cellular target for Hepatitis B virus (HBV). The AuNP were coated with thiols, phosphoryl choline and a 28-mer peptide corresponding to the amino acid sequence of PreS1 protein (PreS1(21–47)) of HBV. SPR was utilized to analyze the interaction of SB3 protein with conjugated AuNP. Results show that PreS1(21–47) peptide is a suitable target for the cells overexpressing SB3 protein as well as the successful internalization of AuNPs. It could be inferred that presentation of protein on the cell surface is integral for efficient recognition (Singh, 2016a; Jha *et al.*, 2017).

Gold Nanobipyramids for Ultrasensitive Detection of Influenza Virus

Gold nanoparticles (AuNPs) are frequently utilized for developing colorimetric biosensors. AuNPs with sharp edges provide higher sensitivity. Gold nanobipyramids (NBPs) and nanorods (NRs) are elongated colloidal plasmonic metal nanocrystals. Their longitudinal plasmon wavelengths can be tuned over a wide spectral range (Lin and Chung, 2008).

Xu *et al.* (2017) have developed highly uniform gold nanobipyramids (Au NBPs) for ultrasensitive colorimetric detection of Influenza virus (H₅N₁ virus). Au NBPs utilize the ability of alkaline phosphatase (ALP) to decompose 4-aminophenyl phosphate (4-APP) to generate 4-aminophenol (4-AP). 4-Aminophenol reduces silver nitrate to metallic silver, which is then deposited on Au NBPs. The metallic silver changes the refractive index of gold, causing a blue shift of LSPR, with a linear range of 0.1–5 mU/ml (corresponding to viral antigen concentrations of 0.001–2.5 ng/ml) and a limit of detection (LOD) of 0.086 mU/ml. This method provides higher sensitivity than gold nanoparticles (AuNPs). Au NBPs also overcome the limitation of poor monodispersity of AuNPs with sharp edges (Singh, 2016a; Xu *et al.*, 2017). AuNBPs show better properties in terms of plasmon peak width, refractive index sensitivity, figure of merit, two photon photoluminescence and Surface enhanced Raman scattering (SERS).

Magnetic Nanoparticles to Enhance the Detection Limit of SPR

Surface functionalized magnetic nanoparticles and magnetic particles are utilized for biosensing applications to recognize specific molecular targets (Isaac and Josephson, 2009). Magnetic nanoparticles conjugated with antibodies specific to viral surfaces undergo self-assembly in the presence of specific viral particles to create supramolecular structures with enhanced magnetic properties. These structures can be detected by magnetic resonance methods like nuclear magnetic resonance (NMR) spectroscopy and magnetic resonance imaging (MRI). Virus-induced assembly leads to changes in magnetic relaxation that allows for highly sensitive detection of virus in biological media. This method has been successfully applied for the detection of adenovirus-5 and HSV-1 at very low concentrations (<10 viral particles/10 μ l). This technique has potential application in NMR-based viral detection and MRI-based viral imaging (Perez *et al.*, 2003).

A study by Phan *et al.* (2016) has provided a protocol to enhance the detection limit of HIV diagnostic assays utilizing magnetic NPs with cynovirin-N. This protocol also provides for the effective concentration of viral particles from larger sample volumes. A cynovirin mutant was expressed and biotinylated, followed by complexing with a thermally responsive polymer-streptavidin conjugate. Binding of a biotinylated mutant with immobilized gp120 was characterized by SPR. Biotinylated Q62C exhibited a disassociation constant (Kd) of 0.6 nM to gp120 (Phan *et al.*, 2016; Singh, 2016a).

Membrane Interaction Studies for Virus Detection

Kinetic Studies of Peptide-Membrane Interactions

The advent of a hydrophobic association (HPA) chip and the lipid-capture (L1) chip has revolutionized the SPR sensing platform to study kinetics of protein/peptide-membrane interactions (Franquelim *et al.*, 2010; Del and Stahelin, 2016). These chips can differentiate between surface adsorption and insertion into the hydrophobic core of the membrane (Besenicar *et al.*, 2006; Singh, 2017). A study using SPR applied a rigid artificial membrane system on the sensor surface to unravel the mechanisms of the HIV fusion inhibitors sifuvirtide and enfuvirtide binding to the membrane. The new fusion inhibitor laid its focus on the HR1 region of gp41 (Dwyer *et al.*, 2008; Naito *et al.*, 2009; Nishikawa *et al.*, 2009). Both sifuvirtide and enfuvirtide interact with the lipid membranes; however, interaction with other lipids like sphingomyelin (SM), characteristics of viral envelopes and lipid rafts is not fully understood (Simons and Vaz, 2004; Veiga *et al.*, 2004; Brugger *et al.*, 2006, 2007; Waheed and Freed, 2009; Franquelim *et al.*, 2008, 2010). SPR studies have shown that sifuvirtide might interact with membrane system by surface adsorption and it might get inserted into the outer leaflets of SM bilayers. HIV membranes have several-fold higher SM and saturated phosphocholine (PC) relative to the eukaryotic membranes. SPR analysis has shown that sifuvirtide has 32-fold higher affinity for saturated phospholipids like DPCC than POPC, suggesting its capacity to bind saturated phospholipid in a selective manner (Brugger *et al.*, 2006; Franquelim *et al.*, 2010; Cao *et al.*, 2017).

Relationship Between Binding Characteristics of Fusion Inhibitors to Biomembranes and Their Clinical Efficacies

Enfuvirtide and sifuvirtide are first and second generation fusion inhibitors, respectively. These fusion inhibitors have different functional domains and target sites. Sifuvirtide is clinically more effective as compared to enfuvirtide, largely due to its adsorption on rigid lipids like DPPC and SM on the viral envelop, the site where most of the fusion-related glycoprotein receptors are inserted (Chungen *et al.*, 2009; Franquelim *et al.*, 2010; Veiga *et al.*, 2004; Ping *et al.*, 2010; Brugger *et al.*, 2006; Sargent and Schwyzer, 1986). However, both can combine together to exert a synergistic effect in HIV inhibition (Pan *et al.*, 2009). Findings from SPR-based studies have revealed the mode of interaction of peptide-HIV fusion inhibitors with biomembrane systems and the importance of rigid lipids that act as the additional targets of HIV fusion inhibitors (Besenicar *et al.*, 2006).

Inhibition of the Membrane-Attack Complex by Dengue Virus NS1 through Interaction With Vitronectin and Terminal Complement Proteins

Dengue virus is single-stranded positive RNA virus. It belongs to family Flaviviridae. Five serotypes of this virus have been reported so far. All of these serotypes can lead to the full spectrum of disease, i.e., Dengue fever. Dengue virus has a genome size of 11 kbp of positive single-stranded RNA genome that encodes structural (capsid protein C, membrane protein M, envelope protein E) and non-structural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5) (Rodenhuis-Zybert *et al.*, 2010). Nonstructural protein 1 (NS1) of Dengue virus is a conserved glycoprotein that interacts with the membrane and is secreted into the plasma of Dengue infected patients. NS1 inhibits the terminal complement pathway involving the important complement-regulator prote *in vitro* nectin (VN). A study by Conde *et al.* (2016) has characterized the NS1-VN interaction through ELISA and SPR. Mechanistic details show that NS1 alone or in conjugation with VN inhibits the formation of membrane attack complex (MAC) and C9 polymerization. The findings from the study indicate the role of NS1 as a terminal inhibitor of the complement system (Conde *et al.*, 2016).

Membrane Binding of HIV Protein

The viral assembly process in HIV involves binding of viral structural protein *Gag* with plasma membrane. This assembly is required for the viral particle formation, as any defect in membrane binding of *Gag* will lead to the impairment of the viral particle production. Molecular mechanisms underlying the *Gag*-membrane binding were characterized by SPR NMR, liposome flotation centrifugation, and fluorescence lipid bead binding (Olety *et al.*, 2016).

Immunological Assays for Viral Detection

Natural Killer (NK) Cells

Natural killer (NK) cells, as a part of the innate immune response, kill virally infected cells and malignant cells. NK cells depend on surface receptors for their function. Among the diverse array of surface receptors, homodimeric Ly49 receptors regulate the activity of NK cells by sensing major histocompatibility complex class I molecules (MHC-I). However, the mechanism of binding is yet to be understood. A study has evaluated and characterized the thermodynamic and kinetic parameters for the interaction of NK Ly49 receptors and MHC-I ligands. Results show that interactions are diffusion controlled and enthalpy driven in contracts with the activation-controlled and entropy-driven interactions between Ly49s with the viral immune-evasin m157. This mechanistic difference is attributed to the different functional responses, for example, one where NK cells scan for killing the virus infected cells and the other to escape the immune-evasins like m157 by virus (Takemura *et al.*, 2017).

Monitoring Intact Viruses Using an Antibody as a Bioreceptor

To detect intact virus, three different types of bioreceptor surfaces are used, viz. antibody-, glycan-, and aptamer-based. Of these, aptamer-based bioreceptor surfaces have been increasingly used with SPR and other sensing platforms. Schofield and Dimmock have pioneered the analysis of intact virus using SPR (Schofield and Dimmock, 1996). They immobilized a mAb (HC10 recognizing hemagglutinin HA derived from influenza virus, A/fowl plague/Rostock/34 (H7N1)) via amine coupling on a CM5 sensor chip. Results have established the protocol, where the interaction of entire viral particles having dimension of 120 nm with mAb could be monitored. Since then many plant and animal viruses have been analyzed using SPR systems (Hardy and Dimmock, 2003; Boltovets *et al.*, 2004; Baac *et al.*, 2006; Nilsson *et al.*, 2010; Wang *et al.*, 2010; Chenail *et al.*, 2011; Yakes *et al.*, 2013). Another study reported quantification of influenza virus based on inhibition of HA antibody binding (Nilsson *et al.*, 2010). This method was found to be several-fold more sensitive than an immunodiffusion assay.

Antibodies (both monoclonal and polyclonal) have been utilized as biorecognition surfaces for detecting intact viruses with a variety of sensing platforms. These platforms include nanowire field effect transistors (Patolsky *et al.*, 2004), interferometers (Ymeti *et al.*, 2007), impedance-based detectors (Hnaïen *et al.*, 2008; Wang *et al.*, 2009, 2011; Shirale *et al.*, 2010), electrochemical detectors (McClellan *et al.*, 2012), resonators (Lum *et al.*, 2012), waveguide-mode (Gopinath *et al.*, 2013), and surface acoustic wave sensors (Baca *et al.*, 2015). These biosensors are very promising for the detection of wide range of viruses. However, use of antibodies for biorecognition for binding to viral surface proteins has limitations, as the sensitivity is entirely decided by the affinity and stability of antibodies, which may also show cross reactivity with other proteins. There might be variability in different batches of antibodies, and the stability of an antibody may decrease during the course of analysis. Therefore, it is not possible to compare the sensitivity and specificity of these sensors (Baker, 2015).

Label Free Checkerboard Assay to Determine Overlapping Epitopes of Ebola Virus VP-40

Ebola virus was first reported from erstwhile Zaire. The genus Ebolavirus belongs to family Filoviridae and order Mononegavirales. The primary reservoir is bat, and it is transmitted to humans through body fluids. The disease caused by Ebolavirus is ebolavirus disease (EVD), which has very high mortality rate in infected humans, particularly in the developing world (Kuhn *et al.*, 2010).

SPR provides a robust and sensitive method to evaluate monoclonal and recombinant antibodies in label-free fashion. A panel of antibodies targeting VP40 of Ebola virus were examined for their binding with immobilized VP40. Through this process several anti-VP40 antibodies were identified that can be utilized for the detection of Ebola virus through sandwich type immunoassays (Anderson *et al.*, 2017).

Fluoroimmunosensor Based SPR for Norovirus Detection

Norovirus is highly infectious and can cause acute gastroenteritis infection in all age groups with a relatively low viral load (<20 virus particles) (Morillo and Timenetsky, 2011). Norovirus shows huge diversity, displaying more than 33 genotypes, thus necessitating a diagnostic device with the ability to detect all the available genotypes of the virus (Kageyama *et al.*, 2004). However, the strain GII.4 is responsible for most of the epidemics, indicating its persistence in the population. It can cause re-infection or affect individuals infected with similar or different strains in the previous exposure. The emergence of new mutations in the P2 subdomain of P domain of the virus capsid protein results in altered antigenicity and binding properties with histo-blood group antigens (HBGA), resulting in new strains causing epidemics (Allen *et al.*, 2008, 2009; Shanker *et al.*, 2011; Debbink *et al.*, 2012; Eden *et al.*, 2013; Jones *et al.*, 2014). Lack of *in vivo* disease models and reproducible *in vitro* replication systems has hindered the study of norovirus (Jiang *et al.*, 1992; Tan *et al.*, 2003; Tan and Jiang, 2005; Siebenga *et al.*, 2007; Lindesmith *et al.*, 2008, 2011). Immunoassay-based detection of norovirus is not feasible as developing corresponding antibodies for different antigens related with different genotypes is not possible. Recently, cross-reactive antibodies for different genotypes of norovirus were isolated (Higo-Moriguchi *et al.*, 2014). In a recent work, cross-reactive antibodies for various genotypes of norovirus have been isolated (Higo-Moriguchi *et al.*, 2014). Surface plasmon resonance-assisted fluoroimmunoassay (SPRF), or surface plasmon field-enhanced fluorescence spectroscopy (SPFS) provide extremely sensitive biosensing platforms (Attridge *et al.*, 1991; Libermann and Knoll, 2000; Roy *et al.*, 2002; Toma *et al.*, 2013). SPRF works through electric field induction via SPR using a fluorescent label. This sensor excites quantum dot fluorescent dyes by SPR induced electric field on an aluminum film. A study has developed a compact and sensitive V-trench biosensor for onsite detection of norovirus (Nomura *et al.*, 2013; Ashiba *et al.*, 2017; Figs. 8 and 9). However, evaluating higher concentrations of norovirus in the environment will require further sensitivity enhancement for SPRF to distinguish between multiple similar or related strains. This study utilized a fluorescent label with large Stokes shift and quantum dot fluorescent label to increase the sensitivity. Detection of norovirus was done involving sandwich assay with phosphonic acid, SAM and cross-reactive antibodies. This platform was found applicable to all the genotypes of norovirus, while captured antibody was reactive to genogroup II and detection antibody to 13 genotypes in genogroup I and II.

Herpes Simplex Virus Particles Interact With Chemokines and Enhance Cell Migration

Glycoprotein G has important immunomodulatory function to play in viral life cycles, for example, Herpes simplex virus (HSV). A study has characterized the chemokine binding ability of HSV and its functional consequences. SPR was utilized to characterize the binding of human chemokine with HSV with high affinity. This interaction is mediated by envelope glycoprotein gG in case of

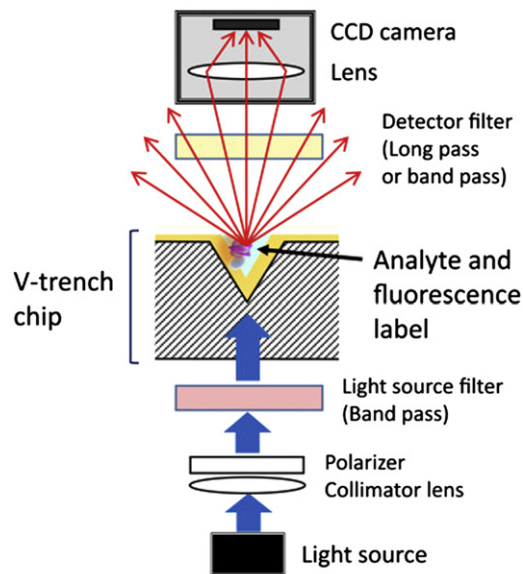


Fig. 8 Experimental set up of an V-trench optical biosensor. Reproduced from Ashiba, H., Sugiyama, Y., Wang, X., *et al.*, 2017. Detection of norovirus virus-like particles using a surface plasmon resonance-assisted fluoroimmunosensor optimized for quantum dot fluorescent labels. *Biosensors and Bioelectronics* 93, 260–266.

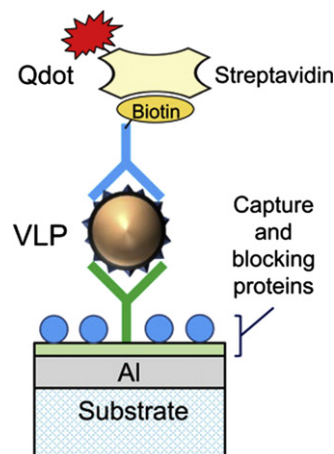


Fig. 9 Schematic of V-trench biosensor used for the detection of Norovirus virus-like particles. Reproduced from Ashiba, H., Sugiyama, Y., Wang, X., *et al.*, 2017. Detection of norovirus virus-like particles using a surface plasmon resonance-assisted fluoroimmunosensor optimized for quantum dot fluorescent labels. *Biosensors and Bioelectronics* 93, 260–266.

HSV1. For HSV2, gG is cleaved, releasing the chemokine binding domain. The findings provide the mechanistic details of how HSV modulates the host immune system (Martínez-Martín *et al.*, 2016).

SPR & ELISA Combined Ultrasensitive Detection of Influenza A Nucleoprotein

Immunoassay-based diagnostics are available for influenza virus but these are marred by lower sensitivity and reproducibility. This study utilized a SPR platform and digital ELISA for the detection of influenza virus utilizing neutralizing antibodies against viral nucleoprotein A. Selected antibodies that have displayed good reactivity in both the systems (SPR and ELISA) showed high disassociation constants. Only one antibody was found to capture the nucleoprotein directly in the lysis buffer. Results provide another alternative for the ultrasensitive immunoassay-based detection of influenza virus (Leirs *et al.*, 2016).

Antigenic Fingerprinting via SPR

SPR binding analysis was performed to characterize infections with H7 highly pathogenic avian influenza (HPAI) viruses. Results show strong correlation between HA1 binding antibodies (HA1 binding mostly contributed by IgA antibodies) and H7N7 HI

titres. Antibodies against NA7 are less frequent but have binding sites close to the sialic acid binding site. Strong antibody response was also found against PA-X, a putative virulence factor in H7N7 exposed individuals, thus indicating immune recognition of the virus during infection. This was unknown so far in human. This will pave the way for effective prophylactic and therapeutic strategies against the influenza virus (Khurana *et al.*, 2016a,b).

Kinetic and Structural Studies of Interactions Between Glycosaminoglycans and Langerin

Langerin expressed in Langerhans cells is a C-type lectin, crucial for blocking HIV transmission by capturing and internalizing HIV into Birbeck granules for their elimination. Zhao *et al.* have performed real-time, label-free quantitative binding studies involving Langerin and GAGs under variable physiological conditions of pH, salt, etc. and also varied concentrations of Ca^{2+} and Zn^{2+} ions. They observed strong binding of langerin to heparin, particularly with longer heparin oligosaccharides. Such studies are important to elucidate the underlying molecular mechanisms for the design of therapeutics for HIV (Zhao *et al.*, 2016).

Proteomics-Based Protocols for Viral Detection

SPR Based Analysis of Coronavirus Protease Inhibitors

Corona viruses (CoV) are emerging at a fast pace, attaining pandemic proportions in no time. Severe acute respiratory syndrome (SARS) is a fatal respiratory illness caused by CoV, SARS-CoV. It was a highly contagious infection, affecting around 8000 people and killing around 800 globally (Stadler *et al.*, 2003). Around 2012, a new CoV emerged as Middle East respiratory syndrome coronavirus (MERS-CoV), causing large-scale death in Asia (Chan *et al.*, 2015; Durai *et al.*, 2015; Kumar *et al.*, 2016). SARS-CoV is an RNA virus sharing very little homology with other CoVs (Holmes, 2003). Two proteases in SARS-CoV, namely 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro) are conserved across the CoV genera and serve as a crucial antiviral targets as they are cleaved to generate mature active proteins (Anand *et al.*, 2003; Stadler *et al.*, 2003). Polyphenols are potent inhibitors of these protease though more strongly affecting PLpro than 3CLpro. SPR was utilized to investigate the structural properties that impart polyphenols with this characteristic. Using SPR, PLpro was immobilized on the sensor chip and the test compounds were allowed to pass over the sensor surface to check the interaction. The study shows polyphenols from *Broussonetia papyrifera* have inhibitory activity against CoV proteases. This inhibitory action stems from the number of prenyl groups present in the polyphenol (Fernandes *et al.*, 1991; Papandreou *et al.*, 2002; van de Laar *et al.*, 2005; Whitby *et al.*, 2005; Ryu *et al.*, 2010; Chang *et al.*, 2013; Ji-Young *et al.*, 2017). The SPR-based investigation identified the most potent anti-CoV agent.

Evolution of Betacoronavirus Receptor Binding Motifs

The Middle East respiratory syndrome coronavirus (MERS-CoV) is a bat-derived coronavirus (Fig. 10). This virus can cross species barriers and spread among circulating bats. It is very important to put bats and virus under surveillance to check its spread. The receptor binding domain (RBD) of the coronavirus spike (S) protein recognizes host receptors to mediate virus entry and is therefore a key factor determining the viral tropism and transmission capacity. A study by Huang *et al.* (2016) has characterized RBD to the host receptors via SPR providing structural details of RBD being composed of core and external subdomain and

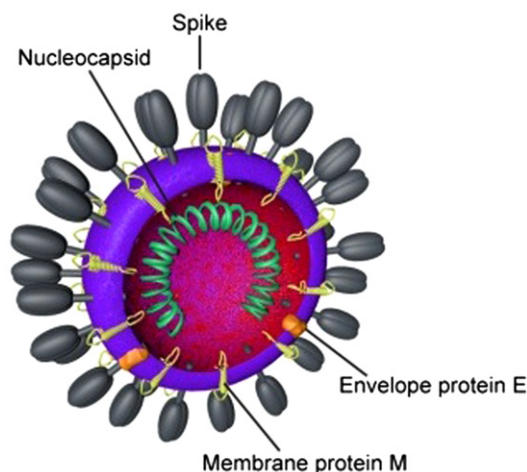


Fig. 10 Coronavirus virion. Reproduced from Belouzard, S., Millet, J.K., Licitra, B.N., Whittaker, G.R., 2012. Mechanisms of coronavirus cell entry mediated by the viral spike protein. *Viruses* 4, 1011–1033.

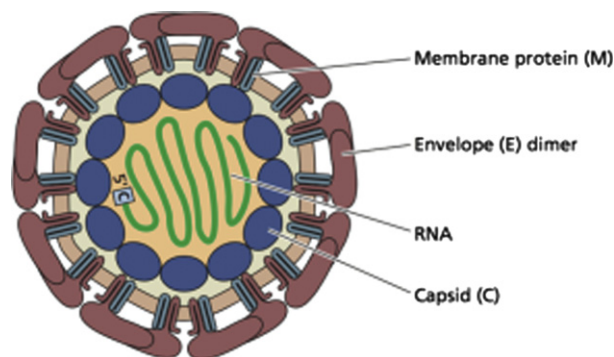


Fig. 11 Structure of Zika virus. Racaniello, R., 2016. Structure of Zika virus (virology blog). Available at: <http://www.virology.ws/2016/01/28/zika-virus/>.

intersubdomain that anchors external subdomain to core subdomain. The structural insights provide crucial information on the evolutionary trajectory of betaCoV (Huang *et al.*, 2016).

Human SAMD9 Interaction With M062

Deleterious mutation in human Sterile α motif domain protein 9 (SAMD9) gene may lead to cancer, inflammation, attenuated immune response and developmental arrest. A crucial host range factor M062 from myxoma virus (MYXV) is found to be antagonistic to the human SAMD9. Using SPR, *in vitro* kinetics of interaction between SAMD9 and M062 was characterized to identify the regions critical to the function of SAMD9. An infection assay revealed that exogenously expressed N-SAMD9 inhibits wild type MYXV infection. The findings provide molecular insight into the mechanism that leads to the suppression of antiviral function of SAMD9 (Nounamo *et al.*, 2017).

Zika Virus Envelope Protein Interaction With Glycosaminoglycans

Zika virus (ZIKV) belongs to family *Flaviviridae* obtaining its name from the Zika forest of Uganda from where it was first isolated in 1947. Zika virus spreads infection through daytime-active *Aedes* mosquitoes, such as *A. aegypti* and *A. albopictus* (Fig. 11). From the time of its origin, it was confined to the equatorial belt from Africa to Asia. However, it is now showing an eastward spread across the Pacific Ocean to the western hemisphere, leading to epidemics, particularly in Latin America. A recent pandemic of Zika virus has posed a serious threat due to its role in development of severe fetal abnormalities. The situation has become so alarming that Brazil, where this virus emerged most strongly has declared that women should avoid conceiving until the threat is over. SPR-based binding studies involving Zika virus envelop protein to glycosaminoglycans (GAGs) were examined in real-time to elucidate the role of GAGs in cell entry, placenta and brain. Envelop protein binds strongly to heparin, which is a highly sulfated GAG, suggesting electrostatic interactions. SPR-based competition assays utilizing variable chain length heparin oligosaccharides show that envelop binds strongly with longer heparin oligosaccharides. This study highlights the role of GAGs as attachment factors to reveal the mechanism of pathogen entry (Kim *et al.*, 2017).

Molecular Inhibitors Against Serine Protease From Zika Virus

The Zika NS2B/NS3 protease plays an important role in viral replication, and hence, forms a crucial drug target to block viral replication. Competition SPR and Inhibition analysis by enzyme kinetics were applied to identify a compound with optimum inhibitory activity and binding affinity (Lee *et al.*, 2017).

Inhibition of Chikungunya Virus by Picolinic Acid That Targets Viral Capsid Protein

Chikungunya virus (CHIKV) belongs to genus alphavirus and family *Togairidae*. It has a single-stranded positive RNA genome of 11.6 kb. CHIKV contains both structural (capsid and envelop glycoproteins E1 and E2) and non-structural proteins. E2 mediates host cell entry through receptor mediated endocytosis. E1, through its fusion peptide, initiates membrane fusion, releasing nucleocapsids into the host cytoplasm and causing infection (Caglioti *et al.*, 2013). The binding of transmembrane glycoprotein E2 with capsid proteins in a hydrophobic pocket plays a crucial role in the Alphavirus life cycle. A study has characterized the interaction of dioxane-based derivatives like picolinic acid in the conserved hydrophobic pocket of capsid protein by SPR, ITC and fluorescence spectroscopy. Subsequent reduction in the viral mRNA and viral load was confirmed by QRT-PCR. This study will pave the way for developing pyridine based antiviral therapeutics particularly against alphavirus (Sharma *et al.*, 2016).

Identification of a Novel Complex Between the Nucleoprotein and PA (1–27) of Influenza A Virus Polymerase

SPR was utilized to study the binding kinetics of ribonucleoprotein (RNP) complexes with polymerase acidic subunit of influenza virus. RNPs are crucial to viral replication and transcription. Therefore, elucidating the mechanism involved in their assembly may

provide a target to block/inhibit the replication of virus. In a study, polymerase acidic subunit PA(1–27) and NP complex assembly was characterized by SPR, fluorescence utilizing RNP and Pull down assays in infected cells (Vidic *et al.*, 2016).

Vaccines

SPR Aided Vaccine Design

Enveloped viruses like HIV and influenza viruses are studied with respect to the neutralizing sites for antibodies for vaccine design. However, non-enveloped viruses are less studied with respect to the neutralizing antibody response. Reovirus was studied with respect to the binding of two neutralizing antibodies with attachment to protein $\sigma 1$ of reovirus. The study revealed the vulnerable sites for viral neutralization, mechanism to block viral infection and conformation adopted during viral cell entry. During cell entry, protein $\sigma 1$ attaches with glycan receptors and junctional adhesion molecule-A (JAM-A). SPR and cell binding assays show that the tested antibodies interfere with JAM-A attachment through steric hindrance (Dietrich *et al.*, 2017; Singh, 2014, 2016a,b).

VSV-Ebola Vaccination

In a study, Vesicular stomatitis virus (VSV)-Ebola vaccine was administered at 3 million, 20 million and 100 million plaque-forming units (pfu) along with homologous VSV-Ebola vaccine boost in healthy volunteers. Whole genome fragment phage display libraries displayed linear and conformational epitopes of ebola virus glycoprotein and showed rich diversity of antibody epitopes in individuals vaccinated with higher pfu. SPR studies also revealed higher glycoprotein binding following single vaccination with higher pfu correlating strongly with neutralization titers. Isotype analysis showed major IgM response following second vaccination leading to *in vitro* neutralization of virus. These findings may provide a clue to the development and evaluation of new vaccine targets effective against ebola (Khurana *et al.*, 2016a,b).

Conclusions

Timely diagnosis of viral infections is crucial for predicting the outbreak of disease before it assumes endemic and pandemic proportion. This is particularly important in wake of continuously emerging newer and more virulent strains of virus. Rapid evolution of virus has outpaced the conventional surveillance protocols like antigenic, serological and agglutination assays, which lack robustness, reproducibility, simplicity and shelf-life. Current need is for a protocol that is rapid, portable and cost-effective, with high sensitivity and specificity. In this regard, optical biosensors that feature portability, sensor miniaturization, and the ability to screen many samples at a time are finding more use in biomedical diagnostics as compared to other comparable techniques that lack miniaturization and high throughput. Surface Plasmon resonance is particularly important as it offers highly sensitive and specific kinetic analysis of biomolecular interaction in label-free manner. However, optical biosensors require highly trained manpower, advance laboratory infrastructure, which might be a limiting factor for resource-constrained setups in developing or under developed countries or in far-flung remote areas. Therefore, there is a need to rationalize and improvise the optical biosensing platforms in terms of portability, cost involved, affordability, user-friendliness and ready-to-use mode. This will maximize its benefit in the field based diagnostic applications in remote areas aiding it to emerge as a reliable diagnostic tool for common man than being a ultra-sophisticated device within the confines of laboratory accessible to few academic elites.

Acknowledgements

Author gratefully acknowledges input from various sources.

References

- Allen, D.J., Gray, J.J., Gallimore, C.I., Xerry, J., Iturriza-Gomara, M., 2008. Analysis of amino acid variation in the P2 domain of the GII-4 norovirus VP1 protein reveals putative variant-specific epitopes. *PLOS ONE* 3, e1485.
- Allen, D.J., Noad, R., Samuel, D., *et al.*, 2009. Characterisation of a GII-4 norovirus variant-specific surface-exposed site involved in antibody binding. *Virology Journal* 6, 150.
- Anand, K., Ziebuhr, J., Wadhwani, P., *et al.*, 2003. Coronavirus main proteinase (3CLpro) structure: Basis for design of anti-SARS drugs. *Science* 300, 1763–1767.
- Anderson, G.P., Liu, J.L., Zabetakis, D., Legler, P.M., Goldman, E.R., 2017. Label free checkerboard assay to determine overlapping epitopes of Ebola virus VP-40 antibodies using surface plasmon resonance. *Journal of Immunological Methods* 442, 42–48.
- Ashiba, H., Sugiyama, Y., Wang, X., *et al.*, 2017. Detection of norovirus virus-like particles using a surface plasmon resonance-assisted fluorimmunosensor optimized for quantum dot fluorescent labels. *Biosensors and Bioelectronics* 93, 260–266.
- Attridge, J.W., Daniels, J.B., Deacon, J.K., Robinson, G.A., Davidson, G.P., 1991. Sensitivity enhancement of optical immunosensors by the use of a surface plasmon resonance fluorimmunoassay. *Biosensors and Bioelectronics* 6, 201–214.
- Baac, H., Hajos, J.P., Lee, J., *et al.*, 2006. Antibody-based surface plasmon resonance detection of intact viral pathogen. *Biotechnology and Bioengineering* 94, 815–819.

- Baca, J.T., Severns, V., Lovato, D., Branch, D.W., Larson, R.S., 2015. Rapid detection of Ebola virus with a reagent-free point-of-care biosensor. *Sensors* 15, 8605–8614.
- Bai, H., Wang, R., Hargis, B., Lu, H., Li, Y., 2012. A SPR aptasensor for detection of avian influenza virus H5N1. *Sensors* 12, 12506–12518.
- Baker, M., 2015. Blame it on the antibodies. *Nature* 521, 274–276.
- Berger, A., Braner, J., Doerr, H.W., Weber, B., 1998. Quantification of viral load: Clinical relevance for human immunodeficiency virus, hepatitis B virus and hepatitis C virus infection. *Intervirology* 41, 24–34.
- Besenicar, M., Macek, P., Lakey, J.H., Anderluh, G., 2006. Surface plasmon resonance in protein-membrane interactions. *Chemistry and Physics of Lipids* 141, 169–178.
- Boeckh, M., Boivin, G., 1998. Quantitation of cytomegalovirus: Methodologic aspects and clinical applications. *Clinical Microbiology Review* 11, 533–554.
- Boltovets, P.M., Snopok, B.A., Boyko, V.R., *et al.*, 2004. Detection of plat viurses using a surface plasmon resonance via complexing with specific antibodies. *Journal of Virological Methods* 121, 101–106.
- Brugger, B., Glass, B., Haberkant, P., Leibrecht, I., Wieland, F.T., 2006. The HIV lipidome: A raft with an unusual composition. *Proceedings of National Academy of Sciences of the United States of America* 103, 2641–2646.
- Brugger, B., Krautkramer, E., Tibroni, N., *et al.*, 2007. Human immunodeficiency virus type 1 Nef protein modulates the lipid composition of virions and host cell membrane microdomains. *Retrovirology* 4, 70.
- Caglioti, C., Lalle, E., Castilletti, C., Carletti, F., Capobianchi, M.R., 2013. Chikungunya virus infection: An overview. *The New Microbiologica* 36, 211–227.
- Cao, P., Dou, G., Cheng, Y., Che, J., 2017. The improved efficacy of Sifuvirtide compared with enfuvirtide might be related to its selectivity for the rigid biomembrane, as determined through surface Plasmon resonance. *PLOS ONE*. (doi:10.1371).
- Chan, J.F., Chan, S.K., Lau, K.K., 2015. Middle East respiratory syndrome coronavirus: Another zoonotic betacoronavirus causing SARS-like disease. *Clinical and Microbiological Review* 28, 465–522.
- Chang, J., Warren, T.K., Zhao, X., *et al.*, 2013. Small molecule inhibitors of ER α -glucosidases are active against multiple hemorrhagic fever viruses. *Antiviral Research* 98, 432–440.
- Chenail, G., Brown, N.E., Shea, A., Feire, A.L., Deng, G., 2011. Real-time analysis of antibody interactions with whole enveloped human cytomegalovirus using surface plasmon resonance. *Analytical Biochemistry* 411, 58–63.
- Cho, E.J., Lee, J.W., Ellington, A.D., 2009. Applications of aptamers as sensors. *Annual Reviews in Analytical Chemistr* 2, 241–264.
- Chungen, P., Hong, L., Zhi, Q., Shibo, J., 2009. Synergistic efficacy of combination of Enfuvirtide and Sifuvirtide, the first and next generation HIV fusion inhibitors. *AIDS* 23, 639–641.
- Conde, J.N., da Silva, E.M., Allonso, D., Coelho, D.R., Andrade, I.D., 2016. Andrade Inhibition of the membrane attack complex by dengue virus NS1 through interaction with vitronectin and terminal complement proteins. *Journal of Virology* 14, 9570–9581.
- Damborský, P., Švitel, J., Katrlík, J., 2016. Optical biosensors. *Essays in Biochemistry* 60, 91–100.
- Debbink, K., Donaldson, E.F., Lindesmith, L.C., Baric, R.S., 2012. Genetic mapping of a highly variable norovirus GII.4 blockade epitope: Potential role in escape from human herd immunity. *Journal of Virology* 86, 1214–1226.
- Del, V.K., Stahelin, R.V., 2016. Using surface plasmon resonance to quantitatively assess lipid-protein interactions. *Methods in Molecular Biology* 1376, 141–153.
- Dey, D., Goswami, T., 2011. Optical biosensors: A revolution towards quantum nanoscale electronics device fabrication. *Journal of Biomedical and Biotechnology* 2011, 1–7.
- Dietrich, M.H., Ogden, K.M., Katen, S.P., *et al.*, 2017. Structural insights into reovirus $\sigma 1$ interactions with two neutralizing antibodies. *Journal of Virology* 91, e01621-16. doi:10.1128/JVI.01621-16.
- Dougherty, C.A., Cai, W., Hong, H., 2015. Applications of aptamers in targeted imaging: State of the art. *Currents Topics in Medicinal Chemistry* 15, 1138–1152.
- Durai, P., Batool, M., Shah, M., Choi, S., 2015. Middle East respiratory syndrome coronavirus: Transmission, virology and therapeutic targeting to aid in outbreak control. *Experimental and Molecular Medicine* 47, e181.
- Dwyer, J.J., Wilson, K.L., Martin, K., *et al.*, 2008. Design of an engineered N-terminal HIV-1 gp41 trimer with enhanced stability and potency. *Protein Science* 17, 633–643.
- Dylan, B., Sarah, S., Charlie, S.T., *et al.*, 2013. Microparticles: Biomarkers and beyond. *Clinical Science* 124, 423–441.
- Eden, J.S., Tanaka, M.M., Boni, M.F., Rawlinson, W.D., White, P.A., 2013. Recombination within the pandemic norovirus GII.4 lineage. *Journal of Virology* 87, 6270–6282.
- Fernandes, B., Sagman, U., Auger, M., *et al.*, 1991. b1-6 branched oligosaccharides as a marker of tumor progression in human breast and colon neoplasia. *Cancer Research* 51, 718–723.
- Franquelim, H.G., Loura, L.M., Santos, N.C., Castanho, M.A., 2008. Sifuvirtide screens rigid membrane surfaces. Establishment of a correlation between efficacy and membrane domain selectivity among HIV fusion inhibitor peptides. *Journal of American Chemical Society* 130, 6215–6223.
- Franquelim, H.G., Veiga, A.S., Weissmuller, G., Santos, N.C., Castanho, M.A., 2010. Unravelling the molecular basis of the selectivity of the HIV-1 fusion inhibitor sifuvirtide towards phosphatidylcholine-rich rigid membranes. *Biochimica Biophysica Acta* 1798, 1234–1243.
- Fu, Y., Callaway, Z., Lum, J., *et al.*, 2014. Exploiting enzyme catalysis in ultra-low ion strength media for impedance biosensing of avian influenza virus using a bare interdigitated electrode. *Analytical Chemistry* 86, 1965–1971.
- Gopinath, S.C.B., 2007. Antiviral aptamers. *Archives in Virology* 152, 2137–2157.
- Gopinath, S.C.B., Awazu, K., Fujimaki, M., Shimizu, K., Shima, T., 2013. Observations of immune-gold conjugates on influenza viruses suing Waveguide-mode sensors. *PLOS ONE* 8, e69121.
- Gopinath, S.C.B., Hayashi, K., Kumar, P.K.R., 2012. Aptamer that binds to the gD protein of herpes simplex virus 1 and efficiently inhibits viral entry. *Journal of Virology* 86, 6732–6744.
- Gopinath, C.B., Kumar, P.K.R., 2013. Aptamers that bind to the hemagglutinin of the recent pandemic influenza virus H1N1 and efficiently inhibit agglutinin. *Acta Biomaterialia* 9, 8932–8941.
- Gopinath, S.C.B., Misono, T.S., Kumar, P.K.R., 2008. Prospects of ligand-induced aptamers. *Critical Reviews in Analytical Chemistry* 38, 34–47.
- Gopinath, S.C.B., Sakamaki, Y., Kawasaki, K., Kumar, P.K.R., 2006. An efficient RNA aptamer against human influenza B virus hemagglutinin. *Journal of Biochemistry* 139, 837–846.
- Gurevich, E.L., Temchura, V.V., Überla, K., Zybin, A., 2011. Analytical features of particle counting sensor based on plasmon assisted microscopy of nano objects. *Sensors and Actuators B Chemical* 160, 1210–1215.
- Gyorgy, B., Szabo, T.G., Pal, Z., *et al.*, 2011. Membrane vesicles, current state-of-the-art: Emerging role of extracellular vesicles. *Cellular and Molecular Life Sciences* 68, 2667–2688.
- Hardy, S.A., Dimmock, N.J., 2003. Valency of antibody binding to envelop virus particles as determined by surface plasmon resonance. *Journal of Virology* 77, 1649–1652.
- Higo-Moriguchi, K., Shirato, H., Someya, Y., *et al.*, 2014. Isolation of cross-reactive human monoclonal antibodies that prevent binding of human noroviruses to histo-blood group antigens. *Journal of Medical Virology* 86, 558–567.
- Hnaïen, M., Diouani, M.F., Helali, S., *et al.*, 2008. Immobilization of specific antibody on SAM functionalized gold electrode for rabies virus detection by electrochemical impedance spectroscopy. *Biochemical Engineering Journal* 39, 443–449.
- Holmes, K.V., 2003. SARS coronavirus: A new challenge for prevention and therapy. *Journal of Clinical Investigation* 111, 1605–1609.
- Hunt, H.K., Armani, A.M., 2010. Label-free biological and chemical sensors. *Nanoscale* 2, 1544–1559.
- Huang, C., Qi, J., Lu, G., *et al.*, 2016. Putative receptor binding domain of bat-derived coronavirus HKU9 spike protein: Evolution of betacoronavirus receptor binding motifs. *Biochemistry* 55, 5977–5988.
- Im, H., Shao, H.L., Park, Y.I., *et al.*, 2014. Label-free detection and molecular profiling of exosomes with a nano-plasmonic sensor. *Nature Biotechnology* 32, U490–U495.
- Isaac, K., Josephson, L., 2009. Magnetic nanoparticle sensors. *Sensors* 9, 8130–8145.

- Jahanshahi, P., Wei, Q., Jie, Z., Ghomeshi, M., Sekaran, S.D., 2016. Kinetic analysis of IgM monoclonal antibodies for determination of dengue sample concentration using SPR technique. *Bioengineered* 17, 1–9.
- Jeon, S.H., Kayhan, B., Ben-Yedidia, T., Arnon, R., 2004. A DNA aptamer prevents influenza infection by blocking the receptor binding region of the viral hemagglutinin. *Journal of Biological Chemistry* 279, 48410–48419.
- Jha, S., Ramadori, F., Quarta, S., Biasiolo, A., Fabris, E., 2017. Binding and uptake into human hepatocellular carcinoma cells of peptide-functionalized gold nanoparticles. *Bioconjugate Chemistry* 28, 222–229.
- Jiang, X., Wang, M., Graham, D.Y., Estes, M.K., 1992. Expression, self-assembly, and antigenicity of the Norwalk virus capsid protein. *Journal of Virology* 66, 6527–6532.
- Ji-Young, P., Heung, J.Y., Hyung, W.R., Su, H.L., Kyung, S.K., 2017. Evaluation of polyphenols from *Broussonetia papyrifera* as coronavirus protease inhibitors. *Journal of Enzyme Inhibition and Medicinal Chemistry* 32, 504–512.
- Jones, M.K., Watanabe, M., Zhu, S., *et al.*, 2014. Enteric bacteria promote human and mouse norovirus infection of B cells. *Science* 346, 755–759.
- Kageyama, T., Shinohara, M., Uchida, K., *et al.*, 2004. Coexistence of multiple genotypes, including newly identified genotypes, in outbreaks of gastroenteritis due to Norovirus in Japan. *Journal of Clinical Microbiology* 42, 2988–2995.
- Keefe, A.D., Pai, S., Ellington, A.D., 2010. Aptamers as therapeutics. *Nature Reviews in Drug Discovery* 9, 537–550.
- Khurana, S., Chung, K.Y., Coyle, E.M., Meijer, A., Golding, H., 2016a. Antigenic fingerprinting of antibody response in humans following exposure to highly pathogenic H7N7 avian influenza virus: Evidence for Anti-PA-X antibodies. *Journal of Virology* 90, 9383–9393.
- Khurana, S., Fuentes, S., Coyle, E.M., *et al.*, 2016b. Human antibody repertoire after VSV-Ebola vaccination identifies novel targets and virus-neutralizing IgM antibodies. *Nature Medicine* 22, 1439–1447.
- Kiilerich-Pedersen, K., Dapra, J., Cherre, S., Rozlosnik, N., 2013. High sensitivity point-of-care for direct virus diagnosis. *Biosensors and Bioelectronics* 49, 374–379.
- Kim, S.Y., Zhao, J., Liu, X., Fraser, K., Lin, L., 2017. Interaction of Zika virus envelope protein with glycosaminoglycans. *Biochemistry* 56, 1151–1162.
- Kim, W.G., Song, H., Kim, C., *et al.*, 2016. Biomimetic self-templating optical structures fabricated by genetically engineered M13 bacteriophage. *Biosensors and Bioelectronics* 85, 853–859.
- Kuhn, J.H., Becker, S., Ebihara, H., *et al.*, 2010. Proposal for a revised taxonomy of the family Filoviridae: Classification, names of taxa and viruses, and virus abbreviations. *Archives of Virology* 155, 2083–2103.
- Kumar, V., Tan, K.P., Wang, Y.M., *et al.*, 2016. Identification, synthesis and evaluation of SARS-CoV and MERS-CoV 3C-like protease inhibitors. *Bioorganic and Medicinal Chemistry* 24, 3035–3042.
- Lee, H., Ren, J., Nocadello, S., *et al.*, 2017. Identification of novel small molecule inhibitors against NS2B/NS3 serine protease from Zika virus. *Antiviral Research* 139, 49–58.
- Leirs, K., Tewari, K.P., Decrop, D., Pérez-Ruiz, E., Leblebici, P., 2016. Bioassay development for ultrasensitive detection of influenza A nucleoprotein using digital ELISA. *Analytical Chemistry* 88, 8450–8458.
- Liebermann, T., Knoll, W., 2000. Surface plasmon field enhanced fluorescence spectroscopy. *Colloids Surface A* 117, 115–130.
- Lin, T.J., Chung, M.F., 2008. Using monoclonal antibody to determine lead ions with a localized surface plasmon resonance fiber-optic biosensor. *Sensors (Basel)* 8, 582.
- Lindesmith, L.C., Donaldson, E.F., Baric, R.S., 2011. Norovirus GII.4 strain antigenic variation. *Journal of Virology* 85, 231–242.
- Lindesmith, L.C., Donaldson, E.F., Lobue, A.D., *et al.*, 2008. Mechanisms of GII.4 norovirus persistence in human populations. *PLOS Medicine* 5, e31.
- Liu, J.J., Liu, K.C., 2017. Rapid detection and quantification of Enterovirus 71 by a portable surface plasmon resonance biosensor. *Biosensors and Bioelectronics* 92, 186–191.
- Lum, J., Wang, R., Lassiter, K., *et al.*, 2012. Rapid detection of avian influenza H5N1 virus using impedance measurement of immune-reaction coupled with RBC amplification. *Biosensors and Bioelectronics* 38, 67–73.
- Martínez-Martín, N., Viejo-Borbolla, A., Alcami, A., 2016. Herpes simplex virus particles interact with chemokines and enhance cell migration. *Journal of General Virology* 97, 3007–3016.
- McClellan, M.S., Domier, L.L., Bailey, R.C., 2012. Label-free virus detection using silicon photonic microring resonators. *Biosensors and Bioelectronics* 31, 388–392.
- Misono, T.S., Kumar, P.K.R., 2005. Selection of RNA aptamers against human influenza virus hemagglutinin using surface plasmon resonance. *Analytical Biochemistry* 342, 312–317.
- Morillo, S.G., Timenetsky, M.C., 2011. Norovirus: An overview. *Revista Da Associação Médica Brasileira* 57, 453–458.
- Mulder, J., McKinney, N., Christopherson, C., *et al.*, 1994. Rapid and simple PCR assay for quantitation of human immunodeficiency virus type 1 RNA in plasma: Application to acute retroviral infection. *Journal of Clinical Microbiology* 32, 292–300.
- Naito, T., Izumi, K., Kodama, E., *et al.*, 2009. SC29EK, a peptide fusion inhibitor with enhanced alpha-helicity, inhibits replication of human immunodeficiency virus type 1 mutants resistant to enfuvirtide. *Antimicrobial Agents and Chemotherapy* 53, 1013–1018.
- Nguyen, V.T., Seo, H.B., Kim, B.C., *et al.*, 2016. Highly sensitive sandwich-type SPR based detection of whole H5Nx viruses using a pair of aptamers. *Biosensors and Bioelectronics* 86, 293–300.
- Nilsson, C.E., Abbas, S., Bennemo, M., Laesson, A., Hamalainen, M.D., 2010. A novel assay for influenza virus quantification using surface plasmon resonance. *Vaccine* 28, 759–766.
- Nishikawa, H., Nakamura, S., Kodama, E., *et al.*, 2009. Electrostatically constrained alpha-helical peptide inhibits replication of HIV-1 resistant to enfuvirtide. *International Journal of Biochemistry and Cell Biology* 41, 891–899.
- Nomura, K., Gopinath, S.C.B., Lakshmi Priya, T., *et al.*, 2013. An angular fluidic channel for prism-free surface-plasmon-assisted fluorescence capturing. *Nature Communications* 4, 2855.
- Nounamo, B., Li, Y., O'Byrne, P., *et al.*, 2017. An interaction domain in human SAMD9 is essential for myxoma virus host-range determinant M062 antagonism of host anti-viral function. *Virology* 503, 94–102.
- Obeid, S., Ceroi, A., Mourey, G., *et al.*, 2016. Development of a NanoBioAnalytical platform for “on-chip” qualification and quantification of platelet-derived microparticles. *Biosensors and Bioelectronics* 93, 250–259.
- Olety, B., Veatch, S.L., Ono, A., 2016. Visualization of HIV-1 gag binding to giant unilamellar vesicle (GUV) membranes. *Journal of Visualized Experiments* 113, e54293.
- Pan, C., Lu, H., Qi, Z., Jiang, S., 2009. Synergistic efficacy of combination of Enfuvirtide and Sifuvirtide, the first and next generation HIV fusion inhibitors. *AIDS* 23, 639–641.
- Papandreou, M.J., Barbouche, R., Guieu, R., *et al.*, 2002. The alpha-glucosidase inhibitor 1 deoxyxojirimycin blocks human immunodeficiency virus envelope glycoprotein-mediated membrane fusion at the CXCR4 binding step. *Molecular Pharmacology* 61, 186–193.
- Park, S.Y., Kim, S., Yoon, H., *et al.*, 2011. Selection of an antiviral RNA aptamer against hemagglutinin of the subtype H5 avian influenza virus. *Nucleic Acid Therapeutics* 21, 395–402.
- Patolsky, F., Zheng, G., Hayden, O., *et al.*, 2004. Electrical detection of single viruses. *Proceedings of National Academy of Sciences USA* 101, 14017–14022.
- Pavel, D., Juraj, S., Jaroslav, K., 2016. Optical biosensors. *Essays in Biochemistry* 60, 91–100.
- Penmetcha, K.R.K., 2016. Monitoring intact viruses using aptamers. *Biosensors* 6, 40.
- Perez, J.M., Simeone, F.J., Saeki, Y., Josephson, L., Weissleder, R., 2003. Viral-induced self-assembly of magnetic nanoparticles allows the detection of viral particles in biological media. *Journal of American Chemical Society* 125, 10192–10193.
- Phan, J.C., Nehilla, B.J., Srinivasan, S., *et al.*, 2016. Human immunodeficiency virus (HIV) separation and enrichment via the combination of antiviral lectin recognition and a thermoresponsive reagent system. *Pharmaceutical Research* 33, 2411–2420.
- Prabowo, B.A., Wang, R.Y., Secario, M.K., *et al.*, 2017. Rapid detection and quantification of Enterovirus 71 by a portable surface plasmon resonance biosensor. *Biosensors and Bioelectronics* 92, 186–191.

- Ping, C., Guifang, D., Yuanguo, C., *et al.*, 2010. Unravelling the molecular basis of the selectivity of the HIV-1 fusion inhibitor sifuvirtide towards phosphatidylcholine-rich rigid membranes. *Biochimica et Biophysica Acta* 1798, 1234–1243.
- Riedel, T., Rodriguez-Emmenegger, C., de los Santos Pereira, A., *et al.*, 2014. Diagnosis of Epstein–Barr virus infection in clinical serum samples by an SPR biosensor assay. *Biosensors and Bioelectronics* 55, 278–284.
- Rodenhuis-Zybert, I.A., Wilschut, J., Smit, J.M., 2010. Dengue virus life cycle: Viral and host factors modulating infectivity. *Cellular and Molecular Life Sciences* 67, 2773–2786.
- Roy, S., Kim, J.-H., Kellis, J.T., *et al.*, 2002. Surface plasmon resonance/surface plasmon enhanced fluorescence: An optical component for detection of multicomponent macromolecular adsorption at solid/liquid interface. *Langmuir* 18, 6319–6323.
- Ryu, H.W., Lee, B.W., Curtis-Long, M.J., *et al.*, 2010. Polyphenols from *Broussonetia papyrifera* displaying potent alpha-glucosidase inhibition. *Journal of Agricultural Food Chemistry* 58, 202–208.
- Sargent, D.F., Schwyzer, R., 1986. Membrane lipid phase as catalyst for peptide-receptor interactions. *Proceedings of National Academy of Sciences of the United States of America* 83, 5774–5778.
- Schofield, D.J., Dimmock, N.J., 1996. Determination of affinities of a panel of IgGs and Fabs for whole enveloped (influenza A) virions using surface plasmon resonance. *Journal of Virological Methods* 62, 33–42.
- Shanker, S., Choi, J.M., Sankaran, B., *et al.*, 2011. Structural analysis of histo-blood group antigen binding specificity in a norovirus GII.4 epidemic variant: Implications for epochal evolution. *Journal of Virology* 85, 8635–8645.
- Sharma, R., Fatma, B., Saha, A., *et al.*, 2016. Inhibition of chikungunya virus by picolinate that targets viral capsid protein. *Virology* 498, 265–276.
- Shirale, D., Bangar, M.A., Park, M., *et al.*, 2010. Label-free chemiresistive immunosensors for viruses. *Environmental Science and Technology* 44, 9030–9035.
- Shpacovitch, V., Temchura, V., Matrosovich, M., *et al.*, 2015. Application of surface plasmon resonance imaging technique for the detection of single spherical biological submicrometer particles. *Analytical Biochemistry* 486, 62–69.
- Shum, K.T., Zhou, J., Rossi, J.J., 2013. Aptamer-based therapeutics: New approaches to combat human viral diseases. *Pharmaceuticals* 6, 1507–1542.
- Siebenga, J.J., Vennema, H., Renckens, B., *et al.*, 2007. Epochal evolution of GII.4 norovirus capsid proteins from 1995 to 2006. *Journal of Virology* 81, 9932–9941.
- Simons, K., Vaz, W.L., 2004. Model systems, lipid rafts, and cell membranes. *Annual Reviews in Biophysics Biomolecular Structure* 33, 269–295.
- Singh, P., 2014. *Surface Plasmon Resonance*. New York, NY: Nova Science Publishers.
- Singh, P., 2016a. SPR biosensors: Historical perspectives and current challenges. *Sensors & Actuators: B. Chemical* 229, 110–130.
- Singh, P., 2016b. LSPR biosensing: Recent advances and approaches. In: Giddes, C.D. (Ed.), *Reviews in Plasmonics*. Switzerland: Springer, pp. 211–238.
- Singh, P., 2017. G protein coupled receptors: A potential candidate for drug discovery. *International Journal of Pharmacology (Special Issue)*. [Epub ahead of publication].
- Stadler, K., Masignani, V., Eickmann, M., *et al.*, 2003. SARS-beginning to understand a new virus. *Nature Review Microbiology* 1, 209–218.
- Suenaga, E., Kumar, P.K.R., 2014. An Aptamer that binds efficiently to the hemagglutinins of highly pathogenic avian influenza viruses (H5N1 and H7N7) and inhibits hemagglutinin-glycan interactions. *Acta Biomaterialia* 10, 1314–1323.
- Takemura, K., Adegoke, O., Takahashi, N., *et al.*, 2017. Versatility of a localized surface plasmon resonance-based gold nanoparticle-alloyed quantum dot nanobiosensor for immunofluorescence detection of viruses. *Biosensors and Bioelectronics* 89, 998–1005.
- Tan, M., Huang, P., Meller, J., *et al.*, 2003. Mutations within the P2 domain of norovirus capsid affect binding to human histo-blood group antigens: Evidence for a binding pocket. *Journal of Virology* 77, 12562–12571.
- Tan, M., Jiang, X., 2005. The P domain of norovirus capsid protein forms a subviral particle that binds to histo-blood group antigen receptors. *Journal of Virology* 79, 14017–14030.
- Toma, K., Vala, M., Adam, P., *et al.*, 2013. Compact surface plasmon-enhanced fluorescence biochip. *Optic Express* 21, 10121–10132.
- Tong, S., Zhu, X., Li, Y., *et al.*, 2013. New world bats harbor diverse influenza A viruses. *PLOS Pathogens* 9, e1003657.
- van de Laar, F.A., Lucassen, P.L., Akkermans, R.P., *et al.*, 2005. α -Glucosidase inhibitors for patients with type 2 diabetes: Results from a Cochrane systematic review and meta-analysis. *Diabetes Care* 28, 154–163.
- Veiga, S., Henriques, S., Santos, N.C., Castanho, M., 2004. Putative role of membranes in the HIV fusion inhibitor enfuvirtide mode of action at the molecular level. *Biochemical Journal* 377, 107–110.
- Vidic, J., Noiray, M., Bagchi, A., Slama-Schwok, A., 2016. Identification of a novel complex between the nucleoprotein and PA(1-27) of influenza A virus polymerase. *Biochemistry* 55, 4259–4262.
- Waheed, A.A., Freed, E.O., 2009. Lipids and membrane microdomains in HIV-1 replication. *Virus Research* 143, 162–176.
- Wang, R., Lin, J., Lassiter, K., *et al.*, 2011. Evaluation study of a portable impedance biosensor for detection of avian influenza virus. *Journal of Virological Methods* 178, 52–58.
- Wang, R., Wang, Y., Lassiter, K., *et al.*, 2009. Interdigitated array microelectrode based impedance immunosensor for detection of avian influenza virus H5N1. *Talanta* 79, 159–164.
- Wang, R., Zhao, J., Jiang, T., *et al.*, 2013. Selection and characterization of DNA aptamers for use in detection of avian influenza virus H5N1. *Journal of Virological Methods* 189, 362–369.
- Wang, S., Shan, X., Patel, U., *et al.*, 2010. Label-free imaging, detection, and mass measurement of single viruses by surface plasmon resonance. *Proceedings National Academy of Sciences USA* 107, 16028–16032.
- Whitby, K., *et al.*, Pierson, T.C., Geiss, B., 2005. Castanospermine, a potent inhibitor of dengue virus infection *in vitro* and *in vivo*. *Journal of Virology* 79, 8698–8706.
- Xu, S., Ouyang, W., Xie, P., *et al.*, 2017. Highly uniform gold nanopyramids for ultrasensitive colorimetric detection of influenza virus. *Analytical Chemistry* 89, 1617–1623.
- Yakes, B.J., Papafraqou, E., Conrad, S.M., *et al.*, 2013. Surface plasmon resonance biosensor for detection of feline calicivirus, a surrogate for norovirus. *International Journal of Food Microbiology* 162, 152–158.
- Yanez-Mo, M., Siljander, P.R., Andreu, Z., *et al.*, 2015. Biological properties of extracellular vesicles and their physiological functions. *Journal of Extracellular Vesicles* 4, 27066.
- Ymeti, A., Greve, J., Lambeck, P.V., *et al.*, 2007. Fast, ultrasensitive virus detection using a young interferometer sensor. *Nano Letters* 7, 394–397.
- Zybin, A., Kuritsyn, Y.A., Gurevich, E.L., Temchura, V.V., Überla, K., 2010. Real-time detection of single immobilized nanoparticles by surface plasmon resonance imaging. *Plasmonics* 5, 31–35.
- Zhao, J., Liu, X., Kao, C., *et al.*, 2016. Kinetic and structural studies of interactions between glycosaminoglycans and langerin. *Biochemistry* 55, 4552–4559.
- Zhu, L., Wang, K., Cui, J., *et al.*, 2014. Label-free quantitative detection of tumor-derived exosomes through surface plasmon resonance imaging. *Analytical Chemistry* 86, 8857–8864.