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Role of Aptamer Sensors in Forensic Science

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ABSTRACT
Aptamers are single stranded or double-stranded DNA oligonucleotides and these DNA oligonucleotides capable of binding to specific molecular targets including peptides, proteins, carbohydrates, toxins, small molecules, and even live cells with high affinity.Aptamers have been reported to be used as diagnostic, therapeutic, and analytical tools. There are wide extend of applications of aptamers which includes clinical determination of different illnesses and infection defenselessness, advancement of personalized solutions, forensic pharmaceutical, forensic toxicology, determination of biowarfare operators, drug analysis, location of microbial defilement, biopharmaceutical fabricating, public health, and molecular study of disease transmission. In the present study, the novel strategies were presented for the discovery of measurable drugs based on nucleic corrosive aptamers that can be combined with differing analytes. It was concluded that innovations of the impedimentary, surface-enhanced Raman scattering, fluorescence-based discovery, microfluidic sensor and surface-plasmon resonance, can be coalesced into the aptamer approach to play their more prominent impact.
Keywords: *Aptamers, Oligonucleotides, Forensic Applications of Aptamers, Aptamer Sensors, Raman Scattering*

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INTRODUCTION

Aptamers are single stranded or double-stranded DNA oligonucleotides and theseDNA oligonucleotides capable of binding to specific molecular targets including peptides, proteins, carbohydrates, toxins,small molecules, and even live cells with high affinity.

Aptamers are able toform a three-dimensional structure, which combines with the target molecules at high specificity and high affinity. Binding of Specific aptamers and ligands occurs due to the molecular interactions like van der Waals forces, electrostatic interactions, formation of hydrogen bond and complement molecular shapes. Aptamers canrecognize minute differences between different target molecules such as distinctions in functional groups (e.g.hydroxyl moiety) or chirality. When integrated with nanomaterials, they may lead to precise detection of different forensic relevant drugs in laboratories. Szostsk first used this technique to identify certain oligonucleotides and then named them as "aptamer". The word "aptamer" has been derived from the Greek word "Aptus", meaning "to fit" whichlater on became the generally accepted term.[3]In 1990, Tuerk and Gold and Ellington and Szostsk created a preparation to target highly specific, high-affinity binding of oligonucleotides. Szostsk named the technology as invitro selection while Gold referred to it as SELEX, which was later mentioned in literature to represent this technology. This technique can be said as new combinational chemistry aimed to establish a library of random oligonucleotides and then selection of a variety of ligands which are able to bond specifically with oligomeric nucleic acid fragments. [21]

One major advantage of this technique is that it has no special requirements for the target molecules. SELEX has developed aptamers for broad types of target molecules like small organic molecules, sugars, amino acids, peptides, proteins, nucleic acids and even cells.[14]

An aptamer's recognition mode is similar to that of antibodies but it has the ability to distinguish quite similar substances which cannot be discriminated even by monoclonal antibodies and thus they are also known as artificial antibodies. Several properties of aptamers make them attractive recognition-agents and in some cases surpass the use of antibodies. In addition, aptamers can be synthesized in vitro and have more stability as compare to antibodies. They can also easily undergo chemical modification and

have non-immunogenic advantages thus ensuring them to become one leading and important research tool in different fields [1].
Aptamer are elements that are attached to target molecules of different sizes with high affinity, and selectivity. They are successfully used in many different sensor applications over the last 30 years. Aptamers have unique advantages such as being able to be produced in a laboratory environment in contrast to antibodies produced via immunoactivity, easy to be amplified, purified and to be produced in an infinite configuration.

APPPLICATIONS OF APTAMERS:

Aptamers have been reported to be used as diagnostic, therapeutic, and analytical tools. There are wide extend of applications of aptamers which includes clinical determination of different illnesses and infection defenselessness, advancement of personalized solutions, forensic pharmaceutical, forensic toxicology, determination of biowarfare operators, drug analysis, location of microbial defilement, biopharmaceutical fabricating, public health, and molecular study of disease transmission.[2]

FORENSIC RELEVANCE OF APTAMERS

In addition to the military, environmental, food safety and medical applications, the use of aptamers in forensic sciences is inevitable.
Drug-related criminal cases especially those that involve drug abusehave been increasing day by day. Abuse of drugs such as morphine, heroine, codeine and cocaine has increased a lot. Till date traditional drug detection methods have been used such as high-performance liquid chromatography and gas chromatography which require a significant amount of time and also these techniques are expensive to some extent.
Several approaches exist based on enzymatic immunoassays but such method lack behind in term of cost & stability. Biosensors offer many advantages when compared with conventional instrumental methods suchas quick reaction, simple operation and wide running of analytes. Aptamers designed by the SELEX innovation were first introduced for detecting forensic drugs. Aptamer technology fulfills the criteria of both being economical and stable, thereby being considered as a more reliable strategy for drug detection base upon the principle of specific binding.[11]

SPECIFICITY OF APTAMERS

Aptamers are exceptionally particular and can separate target analytes and non-specific particles based on their inconspicuous structural variation like presence or absence of a functional group. Aptamers are also enantios elective in nature for example arginine aptamers are 12000 times more specific for L-arginine as compared to D-arginine.
Innovative structures of aptamers such as double split,rolling circle and triple part of aptamers can optimize the LOD of cocaine to micromolar. Another arrangement includes the improvement and enhancement of the flag transduction by utilizing modern materials for e.g. nanoparticles (NPs). A few researches shows satisfactory cocaine determination by utilizing silica, graphene-gold, graphene NPs and fluorescence resonance vitality exchange (FRET) to intensify the signals.Hence the LOD of cocaine can optimise the level of nano mole per liter (nM).
An aptamer-based convention has been outlined to quickly distinguish cocaine in a large working sampleby an evanescent wave fiber (EWF) biosensor which has been an innovation to identify little particles in a wide cluster of applications. The convention was approved to attain satisfactory LOD and brief term for cocaine analysis. The execution of the EWF biosensor was satisfactory applied to particular and reproducible experiments.[34]

DESIGNING OF APTAMER:MANUFACTURING SELEX TECHNIQUE

The Technical Principle of Nucleic Acid Aptamers

1. Establishment of a random oligonucleotide library

Oligonucleotide aptamers have fixed sequences at both the 5' and 3' ends of the molecules whereas the middle section remains as a random sequence which can bind specifically with the target molecule. Both fixed sequences at the ends are used to expand the oligonucleotide chains, select and prepare the transcription of RNA aptamers. [9,10,14] Before a library needs to be built, the fixed DNA oligonucleotide sequences at each end must first be designed. The length of these fixed sequences is typically20-30 nucleotides and contains primer sequences used for PCR amplification and binding sites for restriction endonuclease.[6] The RNA sequences transcribed from the fixed sequences of the DNA oligonucleotide chains must be able to combine with the reverse transcriptase.
In a general design, a random sequence contains 20-40 nucleotides and can form about one thousand fourteen to one thousand twenty-four types of oligonucleotide chainswhich can be synthesized by DNA

synthesizers (usually by a company). [11,12,21]These sequences form chains with a variety of three-dimensional conformations, most of which can be combined with all kinds of target molecules. With the completion of sequence design, the resulting DNA oligonucleotide chains establish the starting DNA oligonucleotide library carrying their random middle sequences.[38]

2. Selection and Enrichment of Aptamers By SELEX (Systematic Evolution Of Ligands By Exponential Enrichment)

After the preparation of the random oligonucleotide library, the next step is to select and enrich aptamers which can bind to the target molecules with high specificity and high affinity. Already established methods of selection include nitrocellulose membrane filtration, separation by affinity chromatography, high-speed centrifugation and electrophoresis.

Consequently semiautomatic or automatic and high-throughput SELEX selecting systems have also been founded,thus decreasing the selection time of aptamers from months to days. The number of repetitions and the simplicity of the process are important indicators in measuring the efficacy of selection and enrichment. Some researchers reported only four rounds of selection and enrichment to obtain aptamers using capillary electrophoresis. [7,14]

There are 3 different steps in SELEX process to get a specific aptamer for a target molecule:

Binding of ligand with target molecule: Random oligonucleotide aptamers made to pass through a column that contains a stationary phase which is already bound with target molecule(target molecule is the molecule for which specific aptamer is need to be designed).Among the Random oligonucleotide aptamers molecule which are specific to the target molecule will form a aptamer-target complex & thus retain in the column whereas rest of the random aptamers will elute out from the column.[15]

Elution of specific aptamers: The aptamers that form aptamer-target complex needs to be eluted out from column by changing the column condition by nitrocellulose filter partitioning.

Amplification of specific aptamers:The eluted aptamers that are specific to the target molecules areamplified by PCR process.

This selection process is repeated 16-18 times to get precise and specific oligonucleotide aptamers. [8,16]

Aptamer's Base Sequencing, Analysis and Molecular Modification

Aptamers obtained by the selection and enrichment process need to be Stabilized, analyzed for their base sequence and level II/stereo structure and to provide affinity as well as specificity. Sometimes RNA aptamers need to be modified because they are sensitive to RNA enzymes and very easily hydrolyzed. This decreases their shelf-life and can shorten the time that RNA aptamers can be used in the body thus, limiting their application.[39] Modification methods include:

1) Addition of rare alkali bases or chemically modified alkali bases to the aptamer's sequences through the addition of the alkali bases to the reaction system at the beginning of synthesizing the oligonucleotide chains.

2) Modification of RNA aptamers at ribose 2 for fluoride, amino and n-oxygen bases or at the 3'-ends of RNA aptamers for fatty acids to reduce the effect of the nucleic acid circumscribing enzyme.

FLUOROPHORES TO THE APTAMERS

Aptamers can be connected to fluorophores after the SELEX process for the Fluorescence Reverberation Vitality Exchange (FRET)-based tests.[30,38] Covalent linkage of fluorophores to the aptamers may impact the aptamer structure and influence ligand authoritative. Joining of fluorophores has been analyzed to influence the binding either through stearic obstacle or by influencing the collapsing properties of the aptamers. [24,27,45]

As the labelling of fluorophore may interfere the ligand binding of aptamer, thus it suggested to practice such labeling technique at the beginning SELEX procedure along with oligonucleotide pool .17,20,31]

ADVANTAGE OF SELEX OVER ANTIBODIES:

Aptamers have replaced antibodies that have been used for detection of target molecules asantibodies have constrained shelf life, need basic strength to remain stable in changing temperatures and humidity. Moreover, labeling of the antibody can cause loss in affinity. SELEX deters the requirement of animal hosts and has comparative advantage in terms of labor,time and refinement when compared to the era of antibodies. [23,26,28]

Aptamers stay stable upon long term storage and transport and additionally have the advantage of reversible denaturation permitting them to be denatured and reused numerous times without the loss of functionality. [18,19,28,32]

Antibodies cannot be produced for exceedingly poisonous substances in vivo though aptamers can be designed for such substance through in vitro conditions. Aptamers can moreover be designed against poisons and small target molecules that don't evoke an immune reaction that's vital for production of antibodies. Aptamers also permit the adaptability to be produced against particular region of the target. Such region-specific targeting is not conceivable to indicate within the generation of antibodies although,

determination of antibodies to epitopes can be accomplished when different monoclonal antibodies are obtained that recognize a single antigen. Aptamers can be generated to recognize their ligands in non-physiological conditions such as pH or in a specific solvent. Aptamers too have an advantage over antibodies in sandwich assays.Hence Aptamers can presently be thought of as widespread receptors similar to the way that antibodies have already demonstrated to be. The advancement of high throughput strategies for the choice of signaling aptamers is potentiating the improvement of sensor arrays that can distinguish expensive numbers of non-nucleic corrosive analytes such as the mycotoxins. The joining of chemically adjusted bases into aptamers radically progresses their stabilities and possibly renders them reasonable for use in homogeneous measures in numerous tests. [20-22]

DETECTION OF DIFFERENT DRUGS BY APTAMERS

Codeine

Codeine is an alkaloid found in opium. It can either be extracted from opium or chemically synthesized by a morphine manufacturer. Upon arrival into the body, the absorption of approximate 10 % of components is converted into morphine through the body's metabolic process. The United Nations considered codeine as one of the less addictive narcotic drugs however it is strictly regulated all over the world. In order to detect codeine, Liangliang Huang *et. al.* developed a sensor for opium alkaloid detection employing the codeine-contraposing DNA aptamers generated by the SELEX technique. The result demonstrates that the biosensor is of good stability, regeneration and specificity, capable of being used to detect codeine. Zahra Hashemian*et. al.* reported a thin-film microextraction method for the analysis of codeine in urine samples using an aptamer. The result showed thatthe detection limit is 3.4 ng/mL in urine. [11,33,44]

Methamphetamine:

Methamphetamine (METH) is a highly addictive synthetic stimulant which causes the body to produce strong pleasant feelings whose effects are sustained for a longtime. For these reasons it has become a widely-used illicit drug around the world since the year 2000. Fast and cost-effective sensing/detection of METH may help the health authorities to control its abuse however, such a sensing system is not available yet due to the lack of suitable METH-sensing probes. Ebrahimi *et. al.* selected a ssDNA aptamer of high binding affinity and specificity to METH through screening a synthetic ssDNA library utilizing SELEX technology. [29,36] The specific aptamer was extracted from a large and diverse random ssDNA initial oligonucleotide library with methamphetamine-modified epoxy-activated sepharose 6B. The selected aptamers (aptaMETH) showed high affinity to the target molecule METH with a 100-nM detection limit which can be efficiently distinguish METH from other molecules of similar structures. The results demonstrated the aptaMETH is of specificity and high affinity against methamphetamine, thus resulting in it as a suitable probe for development of METH sensing aptasensors. [41,43]

Colorimetric method has also been designed by Qiunan Shi *et. al.* for detection of METH in human in which AuNPs solution's color is changed from red to blue. [34]

Cocaine:

Cocaine is a CNS stimulant drug extracted from the coca leaf.Since 1985, cocaine has become the world's major drug due to enhanced purity of cocaine by making use of refining technology. It has several routes of administration (e.g., oral, nasal) and is usually taken at 25-150 mg/dose. Its main effect is a sense of excitement which is experienced within few seconds to a few minutes upon administration. Juewen Liu *et. al.* developed a method to detect cocaine based on colorimetric changes. The intensity of color is directly proportional to the concentration of cocaine and thus quantification can be done in the range of 50μm to 500 μm. This sensor demonstrates a fast color change and is easy to use. This method is quite simple and convenient due to which it can find its applications in many different areas for example electronic industry, environmental monitoringand medical diagnostics. [18,19,34,36,40]

Microfludic sensor technology: R. Kawano et al described a cocaine sensing using a membrane protein channel integrated in a microfluidic device. This sensor utilizes artificial planar lipid bilayers (BLMs) with α-hemolysin transmembrane protein which allows ssDNA to pass through the application of an electric field. In the unfolded state, ssDNA is attached to a cocaine aptamer spanning across the membrane. The aptamer-cocaine complex no longer fitted through the pore upon binding to cocaine and changing conformation. Thus, the cocaine was discriminated by the protein channel as the structure changing from a cocaine molecule to a cocaine aptamer complex. The detection limit of cocaine was determined to be in the range of 10 μM in 25 seconds using this system.

An aptamer-based transitory wave fiber (EWF) biosensor has been devised to quickly distinguish cocaine in a wide working run. The aptamers were conjugated to complementary DNA with fluorescence Labels and such conjugants were at that point immobilized on magnetic globules. After cocaine was presented to compete against the aptamer-DNA conjugants, the discharged DNA in supernatant was identified on the EWF stage. The detection limit was around 10.5 mM.The detection interval was 390 s (6.5 min) and the

duration of the whole procedure was 990 s (16.5 min). Hence, the aptamer-based EWF biosensor may be an attainable arrangement to quickly detect cocaine.[37]

CONCLUSION

The novel strategies were presented for the discovery of measurable drugs based on nucleic corrosive aptamers which can be combined with differing analytes. Innovations of the impedimentary, surface-enhanced Raman scattering, fluorescence-based discovery, microfluidic sensor and surface-plasmon resonance, can be coalesced into the aptamer approach to play their more prominent impact.

Taking advantage of the great selectivity and high affinity of aptamers, the discovery will be more precise and sensitive for the forensic evidence to be conclusive. Furthermore, aptamers are not only the molecular acknowledgment components but also economical, simple to handle, competent of designing to distinguish many sorts of forensic purpose analytes. [40,42]

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