Review Article

# The Point behind Translation of Aptamers for Point of Care Diagnostics

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**Abstract** | Owing to the high affinity and specificity in recent years aptamers, have emerged as competitive tools with the potential to replace antibodies in many diagnostic formats. The aptamer industry is continuously growing to create space in research and diagnostics markets. However, translation of aptamer in several applied disciplines is still lagging behind as compared to antibodies. In this article, we discuss the translational aspects of aptamers, current potential of aptamers and strategies to create the "bench-to-bedside" translation of aptamer technology.

**Editor** | Dr. Muhammad Munir, The Pirbright Institute, Woking, Surry, UK.
**Received** | September 01, 2016; **Accepted** | October 17, 2016; **Published** | November 02, 2016
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**Citation** | Sharma, T.K., J.G. Bruno and W.C. Cho. 2017. The point behind translation of aptamers for point of care diagnostics. *Aptamers and Synthetic Antibodies,* 3(1): 36-42.
**Keywords** | Aptamers, Translation of aptamer, Aptamer industry, Point of care diagnostics, SELEX

Aptamers are single stranded DNA (ssDNA) or RNA molecules that are generated through a process of *in vitro* evolution called Systematic Evolution of Ligands by EXponential Enrichment (SELEX) (Tuerk and Gold, 1990). By virtue of their complex 2D and 3D structures, an aptamer binds to its cognate target with high specificity and affinity (Blind and Blank, 2015; Lange et al., 2012; Sharma et al., 2014; Weerathunge et al., 2014). These receptor-like molecules have emerged as strong rivals of antibodies, which are long-standing tools used to capture antigens (Chopra et al., 2014; Sharma and Shukla, 2014a, b). Development of a rapid antigen detection assays always requires specific capture of the ligand. Anti-ligand antibodies are commonly used to specifically capture ligands from various clinical samples including, but not limited to blood, serum, cerebrospinal fluid (CSF) etc. (Citartan et al., 2012; Gopinath et al., 2016). However, antibodies have to be raised in animals, are prone to batch-to-batch variation due to differences in titers elicited in different hosts, and the antibody binding kinetics ($K_{on}$ and $K_{off}$) or on and off-rates cannot be controlled (Bruno, 2014; Bruno and Richarte, 2015). Moreover, antibody preparation time, poor stability and the effect of modification on antibody binding limit their adaptation in rapid formats. In contrast, nucleic acid aptamers, offer advantages over antibodies for ligand capture including but not limited to: **a)** custom synthesis resulting in practically no batch-to-batch variation; **b)** unlimited shelf life when stored as a dry lyophilized reagent at room temperature (*i.e.*, no requirement for a refrigerator); **c)** easy identification of non-competitive pair of aptamers (aptamer candidates than binds at two distinct sites of same molecules). **d)** Well defined single site conjugation chemistry **e)** Ability to tailor desired affinity and specificity even after SELEX (Post-SELEX modification and affinity maturation) **f)** In cases

where antigens (Ag) are present as a part of immunocomplex (Ag complex with Antibody) an aptamer can be an ideal diagnostic reagent for antigen detection because being a synthetic reagent no such antibody is present against these aptamers and **g)** Due to well established synthesis protocol and ease in synthesis aptamers are cost effective diagnostic reagents and an estimated cost of aptamer is under US$2,000/g and less than a cent per test (Blind and Blank, 2015; Kedzierski et al., 2013; Ozer et al., 2014). Aptamers have recently celebrated 25th anniversary of their discovery and since inception aptamers have offered a great opportunity to be explored in various areas of science and technology including, but not limited to, diagnostics, imaging, drug delivery, therapeutics, biosensing, environmental monitoring and analytical applications (Gopinath et al., 2016). Moreover, due to the ability to bind their targets tightly and specifically various aptamers have been utilized in immunoassays and other related diagnostic formats (Gopinath et al., 2016).

The advent of point-of-care diagnostics (POCD) has spurred a great interest among researchers, clinicians and health care providers due to the increased speed of diagnostics without compromising the diagnostic quality and accuracy that can be provided at a lower price (Pai et al., 2012; Xiang and Lu, 2012). Innovation in rapid POCD tests creates several next generation assays that can analyze blood sugar levels, metabolites and can determine pregnancy within a few minutes using appropriate body fluids (Gopinath et al., 2016; Pai et al., 2012; Xiang and Lu, 2012). Similarly, on-site contamination of water with microbes or metal ions can easily be detected. This allows the rapid communication of results followed by necessary therapeutic interventions on the very first clinical encounter. Pai et al. (2012) suggested that the speed of a POC test followed by communication of results to the clinicians are the two most critical parameters that govern the success of a POC test. Though an ideal POC test may follow the "ASSURED" criteria: affordable, sensitive, specific, user friendly, robust, and deliverable and perform outside the laboratory but even if a diagnostic test is not following one or more of such criteria but delivering the results and communicating the information in a single day, then also that particular test must be recognized as a POC test as it is fulfilling the diagnostic need (Pai et al., 2012). Therefore, any test homogenous (mix and read, no immobilization and washing are required) or heterogeneous (immobilization and washing are required) that can be completed within a day and disseminate the result to the clinician on same day can be regarded as a POC test and may include lateral flow, Fluorescence Resonance Energy Transfer (FRET) and non-FRET assays, Enzyme-Linked Immunosorbent Assay (ELISA) or Aptamer-Linked Immunosorbent Assay (ALISA), Apta-PCR (aptamer-mediated polymerase chain reaction), aptamer-mediated electrochemical and nanoparticles based assays. Fortunately, aptamers work well in all of the aforementioned and related formats and have the ability to compete against antibodies very strongly with the potential to replace antibodies in all possible point-of-care formats and it is evident by a large number of published reports where detection of diseases associated protein biomarkers and small molecules are demonstrated using aptamers but unfortunately a clear translation from research to product is somehow missing (Bruno, 2009, 2012c, 2014, 2015; Chen and Yang, 2015). We herein discuss potential strategies that may enhance "bench to bedside" or "research to product" translation.

## Potential of Aptamers and Aptamer Industry

The market potential of aptamer is continuously growing in various applications including but not limited to diagnostics, bio-sensing, biomarker discovery, drug discovery therapeutics and research tool development. We also believe that the diagnostic ability of nucleic acid aptamers is not yet explored to its fullest. The possible reason could be the huge investment and thus commitment of diagnostic companies for the production of antibodies (poly or mono-clonal) followed by their reluctant and ignorant behaviour towards aptamers and the advantages they offer (Baird, 2010). Moreover, even research laboratories hesitate to replace antibodies with aptamers despite knowing their advantages probably due to fear of trying new technology and replacement of their optimized protocols with newer one or may be due to anxiety of spending time on optimization (Baird, 2010). If we compare the translation aspect of aptamers with that of monoclonal antibodies (mAb), it becomes clear that mAbs also took almost 4 decades to reach real translation (Bruno, 2015). Though in terms of translation aptamers seem to be lagging behind antibodies. However, some serious efforts made by aptamer companies cannot be ignored. Approximately 50 aptamer companies are actively engaged in aptamer research with prime focus on at least

**Table 1:** *List of aptamer companies and their country of location*

| S.N. | Company | Country of location |
|---|---|---|
| 1 | AptaBharat Innovation | India |
| 2 | Aptahem | Sweden |
| 3 | AptaBiosciences | Singapore & UK |
| 4 | Apta Biotherapeutics | South Korea |
| 5 | Aptamer Sciences | South Korea |
| 6 | Apta Targets | Spain |
| 7 | AptusBiotech | Spain |
| 8 | AptaIT | Germany |
| 9 | AuramerBio | Newzeland |
| 10 | Apterna | UK |
| 11 | Aptamer Group | UK |
| 12 | amsBio | UK |
| 13 | ATDBio | UK |
| 14 | Aptadx | UK |
| 15 | Aptamer Solutions | UK |
| 16 | AstraZeneca | UK |
| 17 | AMBiotech | USA |
| 18 | Aptitude Medical | USA |
| 19 | Aptagen | USA |
| 20 | Aptamatrix | USA |
| 21 | Alpha Diagnostic International | USA |
| 22 | Avacta | USA |
| 23 | Archemix | USA |
| 24 | Altermune | USA |
| 25 | BBI Group | UK |
| 26 | BasePair Technologies | USA |
| 27 | CD genomics | USA |
| 28 | Firefly Bioworks | USA |
| 29 | Ice9Biotechnologies | USA |
| 30 | Izon Science | UK |
| 31 | Iba Gmbh | Germany |
| 32 | LFB Biotech | France |
| 33 | LC Science | USA |
| 34 | Novaptech | France |
| 35 | Neoventure Biotech. | Canada |
| 36 | Nal von Minden | Germany |
| 37 | Ophthotech | USA |
| 38 | OTC Biotech | USA |
| 39 | Oak Biosciences | USA |
| 40 | NOXXON Pharma Ag | Germany |
| 41 | Piculet Biosciences | Netherland |
| 42 | Pure biologics | Poland |
| 43 | Ribomic | Japan |
| 44 | Somalogic | USA |
| 45 | Tobira Therapeutics | USA |
| 46 | Tocris Bioscience | USA |
| 47 | Trilink Biotech | USA |
| 48 | Vivonics | USA |
| 49 | Vivonics | USA |
| 50 | Veraptus | China |

one of the following areas: diagnostics, therapeutics, and development of novel technologies for various applications. Though developed countries are leading the field in terms of aptamer industry, developing countries including Asian subcontinent (India, China and South Korea) are also swiftly contributing to the growth of aptamer industry. A comprehensive list of various aptamer companies and their location is tabulated in Table 1. Among these aptamer companies many of them have been established in the last 5-6 years, some major players include, but are not limited to, NeoVentures Biotechnologies (Canada), OTC Biotech (USA), Base Pair Biotechnologies (USA), Aptagen (USA), Aptamer Sciences (Pohang, Korea), the Aptamer Group (U.K.) and a few others. Neo Ventures showed great promise by developing and commercialization of their OTA-sense and Afla-sense technology, an aptamer based concentration and purification column for the detection of ochratoxin and aflatoxin respectively in corn, wheat, beer and wines (Penner, 2012). Aptagen developed Apta-Beacon technology for bio-sensing. Aptamer Sciences has a range of aptamer products under their trademark including AptoCyto and a variety of aptamers against plethora of targets for flow cytometry application. The remainders of the aptamer companies are primarily focusing on development of the aptamer-based research tools such as development of aptamers as a substitute of antibodies for the detection of small molecules, proteins, transcription factors, bacterial and viral pathogens protein purification and western blot applications. The Aptamer Group recently launched their technology called Aptabind, an aptamer-based therapeutics and protein purification technology based on aptamer-mediated chromatography. Another major aptamer player called SomaLogic (USA), has developed the SOMAscan platform, an aptamer array that has capability to detect more than 1,000 proteins down to subpicogram levels in serum and other body fluids and has already identified biomarkers for various diseases such as tuberculosis, prostate cancer and more recently for idiopathic pulmonary fibrosis (Kraemer et al., 2011; Nahid et al., 2014; Rohloff et al., 2014).

This technology has paved the new way in the diagnostic arena and can be utilized to identify both novel pathogen or host associated markers for diagnostic and treatment monitoring. These aforementioned achievements are quite encouraging for the field but many more such translations are yet to come in order to swiftly lead to aptamer commercial success.

## Strategies to Improve the Translation of Aptamers

In order to achieve the successful "bench to bedside" translation an aptamer must follow the 4 rules as described by Penner (2012): **(1)** The developed aptamer-based product/assay must be cheaper than the existing product. However, if no such competitive test/assay is available in the market then also the developed test must be cost effective so that the benefit to the user can be maximized. **(2)** The developed test must exhibit same level of sensitivity regardless of batch. **(3)** The test should show a high level of sensitivity so as to match the country-specific regulatory standards and **(4)** the developed test must clearly demonstrate advantages (one or more) over the existing immunoassay products. In our opinion one more rule can be added to this list as a **5th** rule: If the aptamer-based assay is integrated with an instrument then this instrument must be more portable and affordable. Apart from these rules for a successful "bench to bedside" translation of aptamer research one should clearly define the target product profile (TPP) or end user that are going to use the test at the very beginning of research which will certainly minimize labor and post-development modifications and alterations. There are five TPP that are helpful at various levels like TPP1 (home/industry), TPP2 (communities), TPP3 (clinics), TPP4 (diagnostics labs or labs present in industry settings) and TPP5 (hospitals) (Denkinger and Pai, 2012; Pai et al., 2012). Pre-defining the TPP may increase the speed of success and can help in designing a diagnostic prototype matching the end user requirements. However, as such no one has defined the TPP for aptamer research.

We herein made an attempt to define TPPs for aptamer research. Since aptamers are equally applicable for clinical diagnostics and food industry setting (quality control), Thus, we have included both diagnostics and industry application (Figure 1). Further, it is advisable that instead of creating a new prototype, which is quite challenging and time-consuming. If you can combine your aptamer/aptasensors with an existing routinely used well-accepted device, it will certainly enhance the speed of translation and may enable omission of various steps including the design manufacturing and validation of the prototype. One such example is the pioneering work of Lu (2011) where he and his colleague combine the sensing ability of aptamers with a routinely used Personal Glucose Monitor (PGM) device by conjugating the analyte specific aptamer with invertase, an enzyme that converts sucrose to glucose and fructose. The authors accurately detected interferon-gamma, cocaine, uranium and adenosine down to the micro (cocaine and adenosine) and nanomolar ranges (Lu, 2011). In another study, a colorimetric cocaine aptasensor was coupled to an android application resulting in smart phone-based bio-sensing that is again a good example of aptamer-enabled applications of daily use "gadgets" for bio-sensing (Smith et al., 2014).

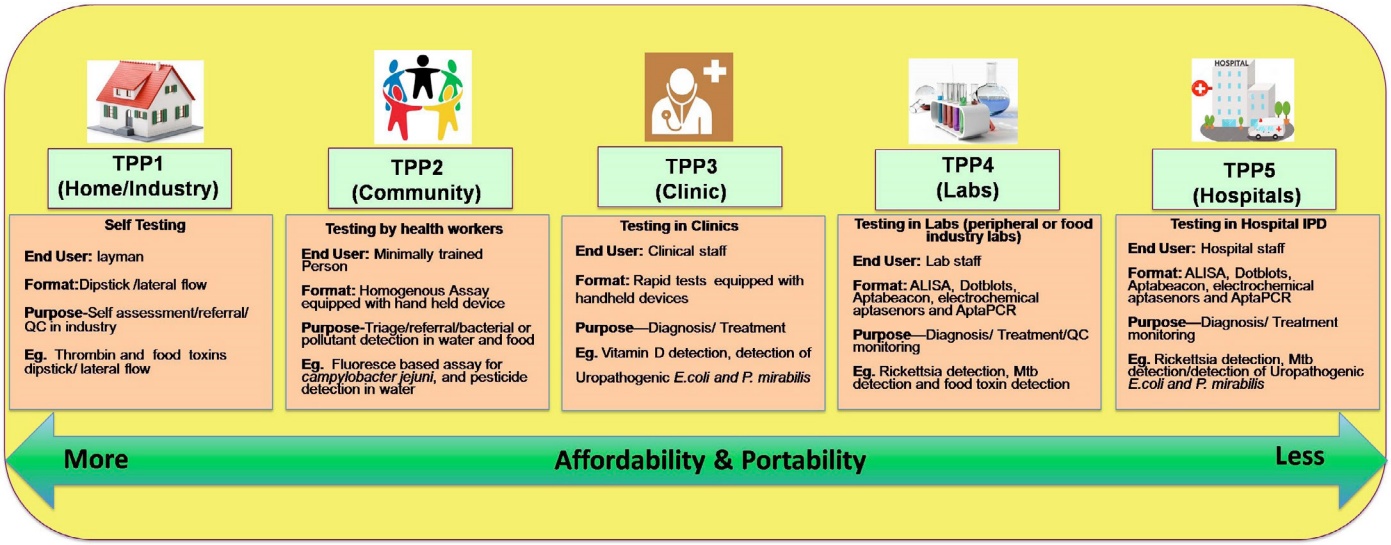


**Figure 1:** *Representation of Target product Profiles (TPPs) for aptamer research. The concept of TTPs is adapted from Pai et al. (2012)*

The other strategy for successful translation of aptasensors includes the development of "bind and detect" homogenous assays to address the specific need where antibody cannot perform or poorly performs (Bruno, 2009, 2012b, 2015). Such assays can clearly demonstrate the advantage of aptamers vs. antibodies and may divert the attention of the research community towards aptamers. This FRET assay is reported by Bruno et al. (2011a), (2011b) and (2012) for the precise quantification of microgravity-induced urinary bone loss markers and serum vitamin D levels (Bruno et al., 2001, 2008, 2010, 2011, 2012; Ilgu et al., 2016). This FRET assay can be coupled to commercially available QuantiFluor™ (Promega Corp.) or any other portable fluorometer to address the diagnostic need in resource-limited settings (Bruno et al., 2011, 2012). Similarly, Bruno et al. (2009) developed a novel plastic-adherent aptamer-based quantum dot-based fluorescent assay for the detection of *Campylobacter jejuni* (Bruno et al., 2009). Furthermore, the anti-stokes ability of lanthanide upconverting nanophosphors / nanoparticles (UCNPs) may be exploited in combination with aptamers to develop an affordable "bind and detect" homogenous assay for clinical application. The anti-stokes ability of these UCNPs can reduce the autofluorescence (background fluorescence) problem commonly encountered when dealing with biological fluids (Duan et al., 2012; Fang et al., 2014; Wu et al., 2014). For successful translation of technology, both researchers and entrepreneurs must focus on the development of more handy platforms like lateral flow/dip stick formats. This will certainly enhance the image of aptamers in health care sectors and make them more popular for TPP1. Researchers have already achieved a few leads in this direction, like aptamer-based lateral flow test strips for thrombin, aflatoxin, ochratoxin, cocaine, adenosine and *E.coli* (Chen and Yang, 2015). It is high time to be capitalizing on these leads to make a successful "bench to bed side" translation. In order to match the sensitivity of regulatory standards multivalent aptamer constructs may be a good idea since in several studies they have shown promising improvements in aptamer affinity and sensitivity. Also, we envision that one should test the developed aptamers in all possible formats (lateral flow, beacons, electrochemical, ALISA etc.) so as to get an appropriate platform to work for a diagnostic test.

## Future of Aptamer-based Diagnostics

Aptamers have the ability to perform in almost every diagnostic format including homogenous multiplex assays where antibodies may fail or poorly perform suggesting that in the future there is a fair chance to replace antibodies with aptamers in diagnostics. A PubMed search for "aptamer in diagnostic" on August 29, 2016, yielded 1477 hits, while phrase "aptamer in bio-sensing" resulting 1456 hits. These large numbers of hits seem to indicate that the field of aptamers is flourishing in the arenas of diagnostics and bio-sensing. This also suggests opportunity for capitalizing on fruitful aptamer-based diagnostic products that work exceptionally well. Moreover, based on the active engagement of several companies in aptamer development with a main focus on diagnostics and bio-sensing streams, we envision a bright future for aptamers in the diagnostic market. The ease of scale up and speed of aptamer development would certainly contribute to success of aptamer-based diagnostics. One cautionary note from our side is that one should also evaluate the stability of aptamers in diagnostic format, which would certainly build confidence in the developer and also in the end user. Also, the aptamer community should choose more clinically relevant aptamer targets so as to convert aptamer leads into acceptable and much needed products. This will certainly overcome the hesitation of lab users and clinicians generated due to entrenched antibody-based assays. Then aptamers should come up as next generation reagents in the molecular tool kit of diagnostic labs.

## Acknowledgments

T.K.S. wish to thank Department of Biotechnology, Govt. of India for Innovation Award.

## Conflict of Interest

T.K.S. owns 65% stake in AptaBharat Innovation Pvt. Ltd. India and JGB owns 8% stakes in OTC Biotechnology USA.

## Authors' Contribution

All authors have contributed in writing and revising the manuscript.

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