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Aptamers: Novel Molecules for Future Therapeutics

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One of the most promising combinatorial chemistry techniques is Systematic Evolution of Ligands by Exponential enrichment, or SELEX [1]. SELEX is also known as *in vitro* selection or *in vitro* evolution and allows the simultaneous screening of a large number of nucleic acid molecules. Functional nucleic acid molecules are selected mainly from a non-functional pool of oligonucleotides by column chromatography or other techniques such as gel shifting assay [2-4]. The functional nucleic acids are called aptamers, which are usually short, single-stranded (ss) nucleic acids such as ssDNA and RNA [2]. Many of the selected aptamers display affinities comparable to those observed for monoclonal antibodies. Unlike antibodies, facile modification of selected aptamers can improve their binding to target molecules and enhance the stability of the aptamers against nuclease activity under physiological conditions [5].

The application of aptamers has been significant in medical and pharmaceutical research fields. For example, a commercial product using SELEX technology, an aptamer of a vascular endothelial growth factor (VEGF), was approved in 2004 and is currently used to cure an age-related macular degeneration disease [6,7]. This anti-VEGF aptamer blocks vessel growth and inhibits neovascularization. The name of the product is Macugen, and is produced and marketed by OSI Pharmaceuticals/Pfizer Inc. [8,9]. Although the anti-VEGF aptamer is based on RNA SELEX, several other potential drug candidates have been discovered by ssDNA SELEX technology. A ssDNA aptamer of thrombin, which functions as an important enzyme in the regulation of the coagulation pathway, has been identified as an extracellular target, and the ssDNA aptamer has been recognized as a very promising anticoagulant drug candidate [10,11]. Other drug candidates using ssDNA SELEX have been found, such as anti-inflammatory aptamers for L-selectin [10], viral infection prevention aptamers for hemagglutinin of influenza virus [12], and anti-progressive renal disease aptamers for platelet-derived growth factor [13]. Recently, we reported that ssDNA SELEX for the metallo-ß-lactamase of *B. cereus* was used to find ssDNA aptamers, which act as inhibitors of the enzyme, and thus providing the possibility of an antibacterial drug for this specific ß-lactam antibiotic resistant bacterial infection [14]. These examples make the discovery of new drugs possible with ssDNA oligonucleotide inhibitors using SELEX technology.

A caveat of ssDNA and RNA aptamers is that modifications of the aptamers are necessary due to the susceptibility to nuclease activity *in vivo*. Resistance to nuclease activity can be improved by a variety of modifications such as phosphorothioate modification, replacement of oxygen with sulfur, etc. Typically, such modifications extend a plasma half-life span to 6-8 hours, and the current maximum half-life span is approximately 24 hours for the aptamer for thrombin, which can be used as anticoagulant drug [15].

Over the past 10 years, aptamer research has been rapidly growing. The successful marketing of VEGF aptamer as a drug encourages scientists to focus on developing aptamers against numerous targets. There is convincing evidence that more aptamers will emerge in the market as drugs in the near future.

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