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EDITORIAL

Therapeutic Aptamers March On

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"Nothing in biology makes sense except in the light of evolution" declared biologist Theodosius Dobzhansky in his seminal 1973 essay.[1] This sentiment extends to aptamers, the topic highlighted in our special issue of *Molecular Therapy—Nucleic Acids*. Aptamers are short single-stranded oligonucleotides that can bind with high affinity and specificity to target molecules, and which are derived through a process of directed chemical evolution called SELEX (systemic evolution of ligands by exponential enrichment). SELEX was first described 24 years ago by Tuerk and Gold[2] and Ellington and Szostak,[3] and this approach has since yielded a flourishing area of aptamer research for a wide range of applications, including: *in vitro* diagnostics, *in vitro/in vivo* biosensor technologies, biomarker discovery and targeted therapies. The first aptamer therapy, Pegaptanib (Macugen), was approved in 2004 by the US Food and Drug Administration for the treatment of neovascular age-related macular degeneration.[4] Today, the pipeline of therapeutic aptamers is encouraging, with at least 10 candidates undergoing clinical trials for diseases that range from cancer and heart disease to type II diabetes.[4]

The speed and success with which new applications can be developed is dependent on advances in critical areas of aptamer research. The last few years have seen many new developments in novel SELEX approaches, with new reagents and methods for the selection of successful aptamers that have a wide range of biological functions.[5–7] These efforts have been coupled with improvements in the characterization of aptamers using high-throughput sequencing and concomitant bioinformatics and secondary structural analyses. The new wave of SELEX technologies and applications is explored in a review by Ozer *et al.*[8] It is worth highlighting advances in cell-based and microfluidic/microarray-based SELEX approaches, which are already having a significant impact on the field. For example, cell-based SELEX tools have yielded aptamers with unique properties for binding (and internalizing) to cell receptors *in vivo*. These new tools (and others) are explored as targeted therapies and as aptamer–drug conjugates in reviews by Sun *et al.*[9] and Zhou and Rossi.[10]

This special issue highlights novel ways in which aptamers are applied for both therapeutic and diagnostic applications. Two studies focused specifically on the application of aptamers for intracellular uptake. Porciani *et al.*[11] investigated different aptamer conformers in relation to its interaction with the transferrin receptor. The previously published DNA aptamer, GS24, was targeted to the mouse transferrin receptor (mTfR) and aptamer conformational stability and cellular internalization was improved in cancer cells. Not only is TfR an ideal biomarker for cancer diagnosis, but transferrin (Tf) derivatives can act as vectors for drug payloads, hence the value of aptamer-mediated targeting of TfR. Kruspe *et al.*[12] conjugated the photosensitizer chlorin e6 (ce6) to a human interleukin-6 receptor (IL-R6) binding RNA aptamer. In this example, the treatment of IL-R6-positive subcutaneous lymphomas was achieved via photodynamic therapy. While this represents a very promising approach, it will be interesting to see whether solid tumors, which are less accessible to photodynamic therapy via irradiation, can be treated in the same way.

In an elegant proof-of-principle study, Muharemagic *et al.*[13] ingeniously applied aptamers to enhance oncolytic virus-mediated cancer therapy using aptamer-facilitated virus protection (AptaVIP). Here, two separate aptamers were applied: one aptamer blocks neutralizing antibodies by binding to the antigen binding fragments (Fab) and a second aptamer binds to the virus to "shield" it from neutralizing antibody recognition. By combining the aptamers in a multivalent complex, both approaches synergistically prevented neutralization of the virus and enhanced infectivity of cancer cells. The next step is to test this approach *in vivo* to prevent viral clearance and increased oncolytic efficiency.

Lastly, Zeng *et al.*[14] have developed a novel aptamer diagnostic technology for facile detection of circulating tumor cells in whole blood and marrow aspirates of lymphoma patients. A biosensor was devised that consists of an aptamer sequence conjugated to paired fluorochrome-quencher molecules. The aptamer used was targeted to the CD30 receptor, a biomarker for circulating tumor cells. Following internalization and lysosomal degradation, the fluorochrome was released, resulting in specific emission signals in the targeted cells. This system has the advantage of providing significantly more stringent levels of sensitivity for detecting specific cells of interest, and may even be adapted for targeted therapeutics.

Overall, while there are clearly important challenges remaining; aptamers are proving to be a versatile and adaptable technology that has the potential to become an attractive tool for diagnostic and therapeutic applications. It is only a matter of time before we see more aptamers in the clinic.

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1. Dobzhansky, T (1973). Nothing in biology makes sense except in light of evolution. *Am Biol Teach* **35**: 125–129.
2. Tuerk, C and Gold, L (1990). Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4 DNA polymerase. *Science* **249**: 505–510.
3. Ellington, AD and Szostak, JW (1990). *In vitro* selection of RNA molecules that bind specific ligands. *Nature* **346**: 818–822.
4. Sundaram, P, Kurniawan, H, Byrne, ME and Wower, J (2013). Therapeutic RNA aptamers in clinical trials. *Eur J Pharm Sci* **48**: 259–271.
5. Ni, X, Castanares, M, Mukherjee, A and Lupold, SE (2011). Nucleic acid aptamers: clinical applications and promising new horizons. *Curr Med Chem* **18**: 4206–4214.
6. Keefe, AD, Pai, S and Ellington, A (2010). Aptamers as therapeutics. *Nat Rev Drug Discov* **9**: 537–550.
7. Esposito, CL, Catuogno, S, de Franciscis, V and Cerchia, L (2011). New insight into clinical development of nucleic acid aptamers. *Discov Med* **11**: 487–496.
8. Ozer, A, Pagano, JM and Lis, JT (2014) New technologies provide quantum changes in the scale, speed, and success of SELEX methods and aptamer characterization. *Mol Ther Nucl Acids* **3**: e1.
9. Sun, H, Zhu, X, Lu PY, Rosato, RR, Wan, T and Zu, Y (2014) Oligonucleotide aptamer: a new tool for targeted cancer therapy. *Mol Ther Nucl Acids* **3**: e1.
10. Zhou, J and Rossi, JJ (2014). Cell-type-specific, aptamer-functionalized agents for targeted disease therapy. *Mol Ther Nucleic Acids* **3**: e169.
11. Porciani, D, Signore, G, Marchetti, L, Mereghetti, P, Nifosì, R and Beltram, F (2014). Two interconvertible folds modulate the activity of a DNA aptamer against transferrin receptor. *Mol Ther Nucleic Acids* **3**: e144.
12. Kruspe, S, Meyer, C and Hahn, U (2014). Chlorin e6 conjugated interleukin-6 receptor aptamers selectively kill target cells upon irradiation. *Mol Ther Nucleic Acids* **3**: e143.
13. Muharemagic, D, Zamay, A, Ghobadloo, SM, Evgin, L, Savitskaya, A, Bell, JC *et al.* (2014). Aptamer-facilitated protection of oncolytic virus neutralizing antibodies. *Mol Ther Nucl Acids* **3**: e167.
14. Zeng, Z, Tung, C-H and Zu, Y (2014). Cancer cell-activatable aptamer-reporter system for one-step assay of circulating tumor cells. *Mol Ther Nucl Acids* **3**: e1.