TAGCyx Biotechnologies Inc.

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High-affinity DNA aptamers: a new drug modality

TAGCyx Biotechnologies uses its proprietary Xenoligo technology platform to generate novel DNA aptamers containing an artificial nucleotide that have high affinity and selectivity for target proteins. TAGCyx is building a pipeline of Xenoligo aptamers and aptamer–drug conjugates, and is looking for global pharmaceutical partners.

DNA or RNA (oligonucleotide) aptamers can have similar functions to protein-based antibodies, and could offer innovative and cost-effective alternatives to antibody therapeutics. TAGCyx Biotechnologies focuses on the identification and development of novel nucleic acid-based aptamers for various therapeutic applications.

The company's Xenoligo aptamers contain an artificial nucleotide, 7-(2-thienyl)imidazo[4,5-*b*]pyridine (Ds), which enables the generation of aptamers that bind with high affinity and specificity to a wide range of target molecules, including proteins, cells, and toxins. Xenoligo aptamers are synthesized chemically and can be manufactured easily and inexpensively using conventional oligonucleotide synthesis processes, as most of the nucleic acid elements are from natural, i.e. unmodified DNA.

"We believe oligonucleotide aptamers have several advantages compared to monoclonal antibodies, characterized by its synthetic nature such as less antigenicity, simpler CMC, and higher stability than biological products, and can be developed as alternatives to replace them," said Chizuko Koseki, CEO of TAGCyx Biotechnologies. "We also believe that our Xenoligo aptamers provide distinctive superiorities compared to conventional DNA and RNA aptamers, including improved binding capability, specificity and stability."

Based in Tokyo, Japan, TAGCyx was founded in 2007 by Xenoligo inventor Ichiro Hirao, as a spinoff from the Tokyo University/RIKEN research institute. TAGCyx is accelerating its development program after raising $5 million in series B financing from venture capital firms in Japan, and is seeking partners for outlicensing and research collaboration opportunities.

Xenoligo drug discovery platform

TAGCyx has established an innovative nucleic-acid-based drug discovery platform to produce its Xenoligo aptamers. The proprietary Xenoligo technology platform generates high-affinity DNA aptamers that contain an artificial nucleotide with a hydrophobic base (Ds). A modified systematic evolution of ligands by exponential enrichment (SELEX) method is used to select and amplify aptamers that bind to a target of interest (**Fig. 1**).

The proprietary artificial nucleotide, or 'fifth base', offers advantages at different stages of the drug discovery process. Each round of SELEX starts with a library of single-stranded DNA fragments, or oligonucleotides, which contain up to three Ds nucleotides along with the natural nucleotides (T, A, G and C). The addition of Ds increases the structural diversity of molecules in the DNA library, as they do not pair with the natural nucleotides[1].

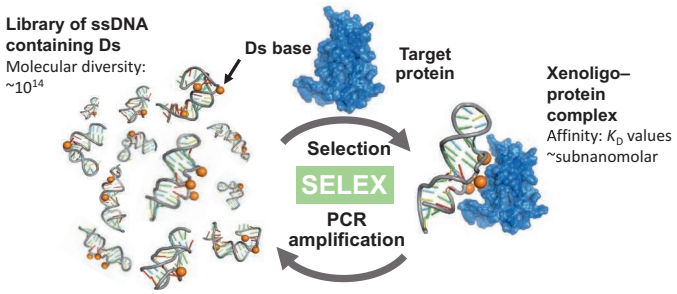

Fig. 1 | Generation of Xenoligo aptamers against a protein target. Adding the proprietary nucleotide, 7-(2-thienyl)imidazo[4,5-*b*]pyridine (Ds), increases the steric diversity of aptamers in the DNA library (left). The hydrophobicity of Ds also provides high-affinity binding to the target protein (right). Xenoligo is amplified using conventional polymerase chain reaction with Px, the complementary base pair to Ds. K_D, dissociation constant; SELEX, systematic evolution of ligands by exponential enrichment; ssDNA, single-stranded DNA.

The hydrophobic Ds nucleotide also enhances the interaction of Xenoligo aptamers with hydrophobic regions of the target, leading to highly potent binding for target proteins[1] whilst natural nucleotides only form hydrogen bonds with the target. Target-bound Xenoligo is amplified using conventional polymerase chain reaction (PCR) employed with diol-modified 2-nitro-4-propynylpyrrole (Px), the proprietary complementary base pair to Ds. PCR selectivity is around 99.9% per PCR cycle, and thus fidelity is the same as for PCR amplification of natural nucleotides.

TAGCyx can also attach a proprietary 'mini-hairpin' structure (patent granted in Japan and pending elsewhere) to the end of the aptamer, in order to improve tolerability to enzymatic degradation and thermostability. Unlike other DNA and RNA aptamers, which require postmodification of the nucleotides in order to obtain stability, the affinity of Xenoligo to the target remains high as Xenoligo does not require such post-modification of nucleotides other than attaching the mini-hairpin[2].

Pipeline of Xenoligo aptamers

TAGCyx is developing Xenoligo candidate aptamers against various protein targets. These include an aptamer that targets interferon-γ with possible indications for autoimmune diseases, and an aptamer that targets von Willebrand factor in development for thrombosis. Both candidates are at the preclinical stage and have demonstrated promising results.

TAGCyx is also advancing a number of programs to develop Xenoligo molecules that bind selectively to tumor cells. These can be used as a drug delivery tool by creating Xenoligo aptamer–drug conjugates, akin to antibody–drug conjugates (ADC). Preclinical studies have demonstrated cytotoxic effects of toxin-conjugated Xenoligo aptamer candidates.

Partnering opportunities

TAGCyx has experience of working with partners in Japan and Europe, as well as with a global pharmaceutical company. It is now seeking further partnerships.

"We are looking for partners to outlicense the aptamers under development in our pipeline," said Akinori Mochizuki, director of business development at TAGCyx. "We are also looking to develop research collaborations for Xenoligo generation, where we will work together with a pharma or biotech partner to generate new aptamers against therapeutic targets of interest."

Opportunities include developing the use of Xenoligo as bi-specific aptamers, and also as a conjugate for delivering payloads such as cytotoxic small molecules, alpha radioactive nucleuses, peptides, small-interfering RNAs and antisense oligonucleotides to specific cell types. Xenoligo is also useful for affinity chromatography. Innovative therapeutic targets identified by academic groups, in fields such as immuno-oncology, inflammation, chronic renal failure and the central nervous system, are of interest too.

TAGCyx is also interested in collaborating with biotech companies to develop innovative properties for therapeutics, such as blood–brain barrier penetration and oral bioavailability.

1. Kimoto, M. et al. *Nat. Biotechnol.* **31**, 453–457 (2013).
2. Kimoto, M. et al. *Nucleic Acids Res.* **44**, 7487–7494 (2016).

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