Aptamers and Cancer Immunotherapy

The immune system plays a vital role in suppressing and eliminating cancer. Immunotherapeutics targeting tumour cell biology has become a popular field of biomedicine and there remains a great deal of excitement surrounding this. The emergence of antibody therapies against molecular regulators including CTLA-4 and PD-1 have shown positive results in clinical trials and were recently awarded FDA approval to enter the clinic. Unfortunately, these mAbs therapies are not perfect and therefore aptamers may be an attractive alternative to this problem.

Problems with monoclonal antibody therapies

Although recognised as significant breakthroughs in the treatment of solid tumours generating great enthusiasm, immune checkpoint blockade mAbs have been associated with severe toxicities. It is likely that these side effects are due to off-target effects, causing the infiltration of highly activated CD4+ and CD8+ T-cells into the tumour. Once in the tumour, the activated T-cells release potent pro-inflammatory cytokines which similarly affects normal tissue. Importantly, the prolonged half-life of antibody therapies required for effective treatments also serves to exacerbate auto-inflammatory damage. This must be counteracted by with immunosuppressive agents until side effects fade, increasing risk to infection (Pastor et.al, 2016).

Antibody therapy has generated further concern with reported life threatening auto-inflammatory immune responses. Due to the need for recurrent administration, treatment has been shown to elicit T-Cell dependent neutralising antibodies. As a result, this reduces the therapeutic index - specifically in tumour recurrence.

Despite all these caveats, mAbs are still the most extended reagents used in cancer immunotherapy. It is therefore vital to seek novel therapeutic immune checkpoint blockade reagents and identify alternatives which not only show a superior safety profile but also exhibit a greater therapeutic index.

Aptamers in cancer immunotherapy

New treatments for immune regulators must address the following questions:

1. Does the therapeutic initiate the immune system to attack the tumour and trigger co-stimulatory signals within the tumour?
2. Does the therapeutic enhance tumour antigenicity (expression of potent tumour neoantigens)?
3. Does the therapeutic counteract negative signals favouring the immune system in the tumour microenvironment?
Over the last few years, aptamers have gained significant strides in cancer immunotherapy, providing a similar or even superior activity to immune checkpoint blockade mAbs. Their ability to target cells with high specificity causes fewer off-target effects and due to their plasticity, aptamers are promising agnostic and antagonistic agents since they can be engineered to either initiate or block an immune modulatory receptor (Soldevilla, Villanueva, & Pastor 2016).

The initial rise of aptamers in cancer immunotherapy was first marked with the 2F’-RNA aptamer against cytotoxic T-lymphocyte antigen 4 (CTLA-4) which contribute to the suppressor function of regulatory T cells (Tregs) (Tai et al., 2012). Since then, other aptamers have been discovered for immune-checkpoint receptors; including an anti-programmed death-1 ligand (PD-1) DNA aptamer and a 2’F-RNA aptamer targeting the exhaustion associated transmembrane immunoglobulin mucin domain 3 (TIM-3) receptor (Pastor et al., 2016). Moreover, various aptamers have also been discovered to specific immunotargets including R5A1, an anti-IL-10 aptamer and an anti-IL-6R aptamer which recognise their targets with high affinity (Pastor et al., 2016). Similarly an antagonistic aptamer has also been selected for B-cell activating factor receptor (BAFF-R) which showed to inhibit BAFF mediated survival and proliferation of malignant B-cells (Zhou et al. 2013).

Another key strategy calls for activating positive signals whereby aptamers have been selected and engineered for major co-stimulatory receptors including 4-1BB, OX40 or CD28. RNA aptamers have been used as novel anti-cancer therapeutic tools, either alone or in conjunction with small interfering RNA (siRNA) for several therapeutic applications. In 2008, the first directed aptamer to CD8+ T cell costimulatory receptor was selected which showed to inhibit tumour growth in murine models (McNamara et al. 2008). Moreover CD16α receptor, the only Fc receptor expressed on natural killer cells was targeted by a DNA aptamer (Boltz et al. 2011). The Fcy receptor III DNA aptamer was developed to generate a bi-specific aptamer to target antibody-dependant cell-mediated cytotoxicity (ADCC) and to C-Met, a receptor tyrosine kinase overexpressed in tumours cells. Targeting C-Met and after binding with its ligand, activates various cellular signalling pathways including those involved in motility, cell proliferation, migration, and invasion (Organ & Tsao, 2011).This bi-specific aptamer demonstrated to show specific ADCC in both human gastric and cancer cell lines (Boltz et al. 2011).

**Aptamers: an alternative to monoclonal antibodies?**

As synthetic derived reagents with a shorter half-life and a higher penetration rate in tumours, aptamers have emerged as a great new therapeutic class for cancer immunotherapy. Aptamers have demonstrated their ability to tackle the three major challenges in cancer immunotherapy and offer a simpler and cheaper alternative to mAbs in the clinical setting.
About Aptamer Group

Aptamer Group takes a high-throughput approach using liquid handling robotics and dedicated researchers to identify aptamers against novel and significant targets. We are committed to finding the perfect aptamers to your target and use a proprietary selection technique to identify high affinity aptamers with specificity in as short as 3 months.

Aptamer Group's biomarker discovery, diagnostic and therapeutic divisions aim to conduct further research in the prevention, diagnosis, and treatment of cancer. Through our know-how and key collaborators, we are able to help facilitate the development of aptamers as therapeutics or diagnostic devices for your target of interest.

For enquiries, please contact us at info@aptamergroup.co.uk.

References


