Targeted drug delivery achieved with nanoparticle-aptamer bioconjugates

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Ground-breaking results from researchers at Harvard Medical School and Massachusetts Institute of Technology (MIT), USA, disclosed at the 13th European Cancer Conference (ECCO) have shown for the first time that targeted drug delivery is possible using nanoparticle-apatamer conjugates.

Nucleic acid ligands (referred to as aptamers) are short DNA or RNA fragments that can bind to target antigens with high specificity and affinity; analogous to monoclonal antibodies. In the field of cancer nanotechnology, aptamers have the potential to act as targeting molecules – directing the delivery of nanoparticles to tumour-antigens, present on the surface of cancer cells.

In general terms, therapeutic nanoparticles (~50 – ~250 nanometer) are specially designed delivery vehicles that can encapsulate a drug within them and release the drug in a pre-determined and regulated manner which can vary from a sudden release to a slow release over a period of several years. Using prostate cancer as a model disease, proof of concept nanoscale targeted drug delivery vehicles were developed, which can target prostate cancer cells with high specificity and efficiency. Once bound to prostate cancer cells, the nanoparticle/aptamer bioconjugates were internalised making it possible for their cytotoxic payload to get released directly inside the cancer cells. The combination of targeted delivery and controlled release of drugs at the site of cancer will likely result in "smart therapeutics" that are more effective, yet safer than what is available today.

As the initial step, researchers synthesised nanoparticles for controlled drug release made from a biocompatible and biodegradable PLA polymer system and encapsulated a fluorescently labeled model drug within them, in order to visualise nanoparticle uptake into target cells. The nanoparticles in question were designed for attachment to aptamers so that the binding properties of aptamers for targeting could be preserved. Additional design criteria consisted of the development of nanoparticles that demonstrated a long circulating half-life (meaning that they are not readily cleared by the body's immune system) and nanoparticles that exhibited a strong preferential binding to targeted cancer cells.

In what marked the first-ever synthesis of a nanoparticle-aptamer bioconjugate, the nanoparticles were conjugated to RNA aptamers that bind to the prostate specific membrane antigen (PSMA) – a well known marker for prostate cancer which is over-expressed on certain prostate epithelial cells. Experimental results described at ECCO 13 show that these bioconjugates successfully and selectively adhered to PSMA-positive prostate cancer cells, while PSMA-negative cells were not targeted. This prostate cancer targeting was modeled using a microfluidic device and shown to occur under physiological fluid flow conditions that are present in systemic microvasculature, making their use after intravenous administration therapeutically relevant. The investigators also used high magnification microscopy and 3-D image reconstruction to study the localisation of the bioconjugates after incubation with the prostate cancer cells and confirmed that the particles were rapidly internalised into the targeted cells – an important fact since the payload of nanoparticles may be released inside the cancer cells in a regulated manner over an extended period of time.

The study principle investigator Dr Omid Farokhzad from Harvard Medical School, USA, commented, "Our tumour reduction data in mice using bioconjugates which have the chemotherapeutic agent, docetaxel,

encapsulated within the nanoparticles are remarkably promising. In close collaboration with Dr. Robert Langer at MIT, we are continuing to test and optimise our vehicles in larger animal models of prostate cancer with the goal of one day using them on patients with hormone refractory prostate cancer where the current therapeutic modalities are far from adequate."

These results mark the first ever example of targeted drug delivery using nanoparticle-aptamer bioconjugates. Significantly, the drug delivery was highly specific. Uptake of particles was not seen to be enhanced in cells which did not express the PSMA protein, indicating a selective tumour-targeting action.

"These bioconjugates represent an exciting prospect in the advancing field of cancer nanotechonology and hold significant promise for future cancer treatment," remarked Dr Farokhzad. "Through modification of the controlled-release polymer system or tweaks to the aptamer targeting group it may be possible to produce a diverse range of specific and selective bioconjugates. In this way, drug delivery 'vehicles' can be made to target a myriad of important human cancers. The application of nanotechnology to cancer therapy is expected to result in future therapeutic modalities that are superior to our current approach. Importantly, this is no longer a farfetched science. Nanoscale drug delivery vehicles are getting closer to clinical realisation."

About Prostate Cancer

The prostate is a small gland about the size and shape of a walnut situated just below the bladder and surrounding the urethra. The prostate produces the seminal fluid in which sperm is transported. Prostate cancer begins with small changes in size and shape of the prostate gland cells which can develop into an uncontrolled growth of cells.

Prostate cancer predominantly affects Western populations although the black population has a significantly higher rate than the white population. The lowest incidence is seen in Asian populations. There are just under 238,000 cases of prostate cancer in Europe each year and it is the cause of 85,000 deaths annually.

Risk factors associated with prostate cancer include family history of the disease, age (predominantly men over 50 years of age) and a diet high in red meat and dairy products.

Once the cancer has been diagnosed it is graded and staged to assess the aggressiveness of the tumour and how far it has spread, and for evaluating the type of treatment required. Treatment can involve surgery, radiotherapy, hormonal treatments and chemotherapy (severe cases). Prostate cancer diagnosed at an early stage is usually treated by a combination of surgery and radiotherapy; more advanced cases are treated with radiotherapy and hormonal therapies such as the anti-androgens. In patients with metastatic disease where the cancer has spread to other parts of the body, a multi-disciplinary approach which could include chemotherapy is implicated.

Source: Federation of European Cancer Societies