MIDATECH PHARMA

At A Glance

MidaCore™

Smallest Particles In Biomedical Use For Targeted Delivery To Tumour And Disease Sites. And The Immune System

OVERVIEW

The MidaCore™ technology platform is based on ultra-small gold nanoparticle (GNP) drug conjugates, which at 2nm are among the smallest particles in biomedical use. They are composed of a core of gold atoms decorated with a permutation of therapeutic and targeting molecules. The small size and multi-functional arrangement around the gold core underpin the ability to improve biodistribution, and target tumour and/or immune sites providing a new generation of oncology drugs.

THE TECHNOLOGY

Targeted delivery is achieved using our gold nanoparticle technology Midacore™, a leading innovation in 'ultra-small' nanomedicine, enabling improved delivery of therapeutics to tumour cells and the immune system. In oncology treatments Midacore™ provides a nano complex (less than 5nm in size, or 80,000 times smaller than the width of a hair) that carries conventional small molecule chemo-therapeutic payloads and delivers these to the tumour site in high concentrations. In immune-oncology treatments, Midacore™ acts as a nanocarrier complex for synthetic immuno-peptides that stimulate the immune system to seek out and destroy cancer cells via immune mediated vaccine processes. These small complexes can enter immune processing cells to induce T-cell mediated immune responses specifically against tumour cells, viral infected host cells or autoimmune disease.

The Chemistry:
Midacore™ design and synthesis gold nanoparticle (GNP) technology enables the production of 2nm - 5nm medications, which is roughly five- to ten-fold smaller than any other delivery vehicle in clinical trials. MidaCore's therapeutics are comprised of a core of gold atoms (approximately 100 gold atoms per GNP) surrounded by an organic layer of carbohydrates attached via gold-sulfur bonds that stabilizes the metallic core and makes the particle water-soluble and biocompatible. Coupling of API or targeting ligands are via glycol ligands such as PEG-COOH or PEGamine. MidaCore™ therapeutic constructs have a number of key advantages in their use as drug delivery vehicles, driven chiefly by their small size and multivalency attributes:

Multivalency:

- **Targeting:** multivalency - enables binding of several targeting and therapeutic agents to a single nanoparticle
- **Therapeutics:** active payloads conjugated to form small (~5nm) medicines for targeted delivery
- **Solubility:** enable the transport of water insoluble and lipid soluble compounds to disease sites
- **Releasability:** designed to release the active compound inside the cell

Size:

- **Mobility:** small size (~1.5 nm) and defined charge allows transport to disease sites otherwise very difficult to reach
- **Compatibility:** ultra-small gold nanoparticles are bio-inert, non-toxic, and do not generate an immune response
- **Excretability:** small size allows drug conjugates to be eliminated via the kidneys and liver

GNP's nondisruptively penetrate the cell membrane to deliver drugs via endocytosis. Positively charged GNP's exhibit much higher rates of endocytosis than negatively or neutrally charged GNP's, and remain in the cell longer. Intracellular release of payloads is via glutathione (GSH)-mediated release of payloads from the GNP surface. GSH is the major reducing agent in biochemical processes, and intracellular GSH concentration (1-10 mM) is substantially higher than extracellular levels (2 µM in plasma), thus serving as an effective trigger to release a payload from GNP surfaces. In oncology, the difference in GSH concentrations is even more marked between cancer cells and normal cells, an important advantage in GNP cancer therapeutic

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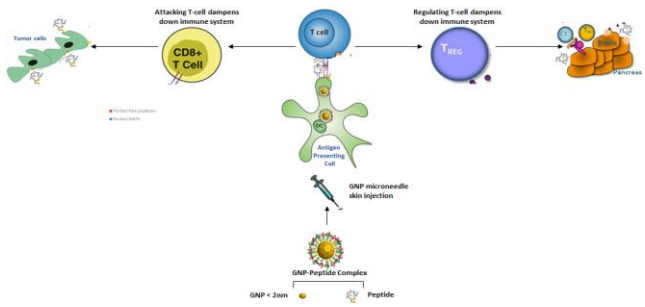
THE VALIDATION

Diseases

MidaCore™ is being developed as an immunotherapeutic as well as a chemotherapeutic platform. Midatech's immunotherapy franchise aims to create commercial vaccines for cancer and auto-immune diseases, that have no or limited treatment options. Midacore™ represents an innovative approach to vaccines whereby gold nanoparticles are designed with antigenic peptides and other immune moieties to either i. activate and enhance the immune response against tumour cells or ii. to suppress the immune response in autoimmune diseases. In oncology there are 14 million cases of cancer worldwide each year, and 8 million cancer related deaths. 'Any drug that meaningfully extends life is likely to generate over $1 billion per year', and multi blockbuster drugs will drive immuno-oncology market to $14bn in 2019, rising to $34bn by 2024. For autoimmune disease, 20% of the population suffer from an autoimmune disease where the body causes disease by attacking itself.

Science

Midacore vaccines are easily injectable and rapidly mobile to lymph nodes and antigen presenting cells (APCs) – the gateway cells of the human immune system. Upon reaching the APC's, the Midacore™ vaccine is processed by the intracellular machinery, and then expressed on the surface of the APC's via MHC class I receptors. In the case of cancer indications this expression is then recognised by CD8+T-lymphocyte **attacking** immune cells, that then proliferate and seek out and attack cancer cells with the same peptide epitope expressed on their surface. In the case of autoimmune disease such as Type 1 Diabetes the T lymphocytes that respond to the beta cell antigen peptide on the gold nanoparticle are CD4 T-regulatory cells that instead of stimulating the immune system actually act to **dampen** down the immune response and stops the body attacking itself.



Thus the same gold nanoparticle concept is common to both cancer and autoimmune applications, but the immune system is stimulated in the former and reduced in the latter depending on the gold nanoparticle peptide combination selected. In addition, this concept is being applied to the development of vaccines for killer viruses such as ebola, dengue, and zika.

Data

Several data readouts are expected in 2018 and 2019. In **autoimmune** indications, MidaCore™ is in clinical development in a first-in-human Phase 1 study for diabetes the most common autoimmune disease worldwide. Data as illustrated below suggests that MidaCore™ can, by normalising the immune system, improve diabetes control by preserving the insulin producing beta cells of the pancreas.

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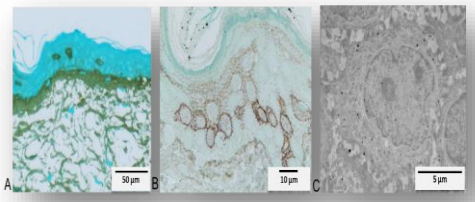
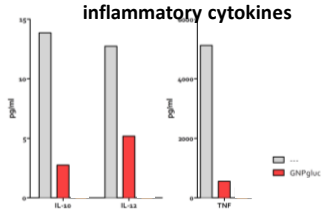
The data below suggest GNP Antigen Specific Immunotherapy (ASI) substantially enhances tolerogenic response, preferentially target specific immune cells, migrates to epidermis immune cells, distribute rapidly to lymphoid tissues and spleen within 3 days, and influences phenotype of immune cells from CD4 vs CD8

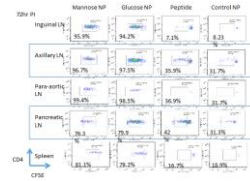
1. GNP in dermis, epidermis, and epidermal cells



2. GNPs inhibits LPS-induced inflammatory cytokines

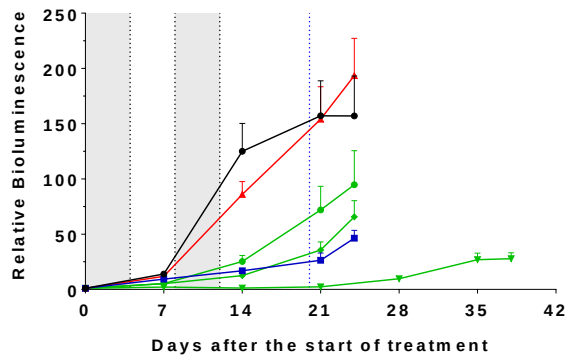


3. Increased T Cell Proliferation In Draining And Distant Lymph Nodes And Spleen At 3 Days



MidaCore™ is also in pre-clinical development for a further autoimmune disease, psoriasis, with a re-engineered version of the immuno-suppressive methotrexate for topical application in psoriasis. This would be a first topical formulation, thus avoiding the need for toxic systemic administration of methotrexate MTX. Data to date suggests that MidaCore™ GNP-MTX returns psoriatic skin to normal non-psoriatic skin. There are over 100 million people who suffer from psoriasis worldwide.

In **oncology**, MidaCore™ is in preclinical development for vaccines for brain cancer in adults and children. Vaccine complexes comprising MidaCore™ gold nanoparticle technology are bound chemically to tumour specific surface-marker peptides, with the objective of enhancing the recognition of tumour cells by the immune system, which then attack and kill the DIPG or GBM tumour cells. For targeted chemotherapeutics, research suggests that conjugation of active payloads such as DM1 with MidaCore™ re-focuses the biodistribution of the compound on the tumour site and enhances uptake of DM1 into tumour cells, which in turn substantially improves the on target efficacy and reduces the off target safety effects. Midacore® drug conjugates such as with DM1 are being developed to repurpose and improve the delivery and efficacy of existing chemotherapeutics for liver cancer and other solid tumours. The preclinical data shows what's possible, with MidaCore-DM1 markedly improving both the safety and efficacy of DMI alone, and having better efficacy than Sorafenib which is the standard of care for liver cancer treatment



PARTNERING

MidaCore™ is a leading edge gold nanoparticle technology used for targeting sites of disease at the nanoscale either for i. chemotherapy - improved and targeted delivery of existing chemotherapeutic agents to tumour sites, as well as ii. immunotherapy - enhanced uptake of new immuno-moieties by immune cells that can then mount an immune attack against cancer cells. Midacore™ products provide opportunities for Midatech to either develop internally or license to pharmaceutical partners. Data to date suggest that the platform could be the next generation in nanomedicine healthcare products. If you are interested to hear more and want to be part of this cutting edge healthcare science, contact …