Expert View

IMPROVING RNA THERAPEUTIC TARGETING BEYOND DELIVERY

Dr Fiona McLaughlin and **Dr Mark Edbrooke** of N4 Pharma discuss the possibilities for developing novel cancer treatments using functionalised nanoparticles, in order to transport a variety of therapies into the tumour microenvironment.

In oncology, the low therapeutic index of traditional chemotherapy drugs poses a persistent barrier – achieving cytotoxic concentrations in tumour cells often results in systemic toxicity that limits efficacy. The rise of ribonucleic acid (RNA) therapeutics, comprising antisense oligonucleotides (ASOs), small interfering RNA (siRNA) and microRNA, offers a route to greater precision. Over the past five years, the number of US FDA-approved RNA therapeutics has risen sharply, yet all currently approved drugs of this class involve either "local" delivery to the central nervous system or only target a single organ – the liver – because no clinically validated platform has yet achieved safe, targeted delivery elsewhere in the body.[1]

The "genome era" has enabled researchers to map disease-causing mutations, spurring the development of personalised nucleic acid drugs capable of silencing or modulating these mutations. The challenge now is to direct these powerful molecules accurately to their intended cellular targets beyond the liver, particularly in complex solid tumours.

BEYOND SINGLE-TARGET DELIVERY

Recent research emphasises that multi-targeting and dual loading are the next transformative steps in cancer treatment.[2,3] If RNA therapeutics can be delivered selectively not only to tumour cells, but also to the cells of the surrounding tumour microenvironment (TME), such as

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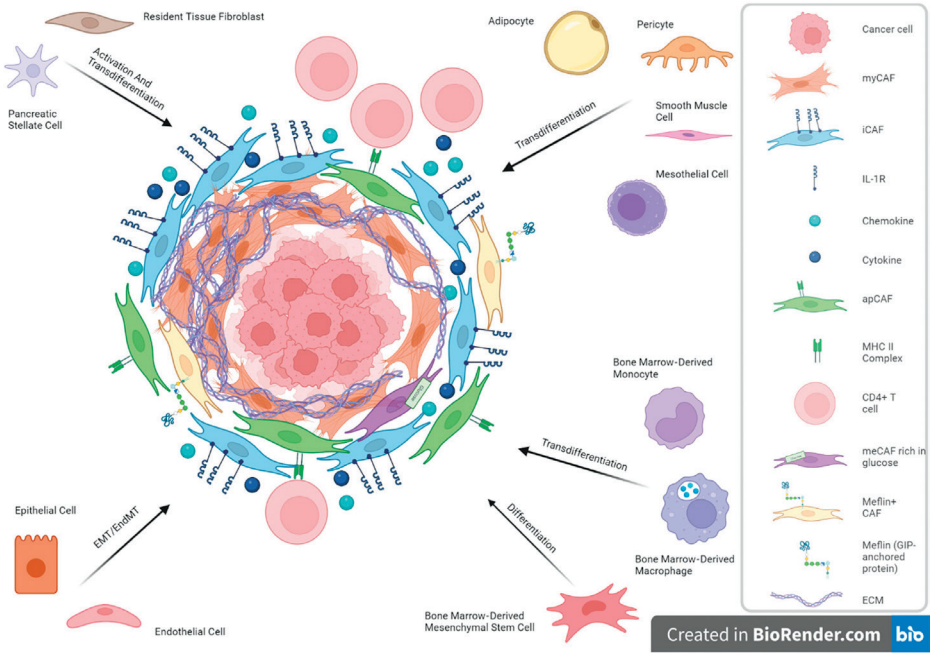

Epithelial-mesenchymal transition / endothelial-mesenchymal transition (EMT/EndMT), myofibroblastic CAF (myCAF), inflammatory CAF (iCAF), interleukin-1 receptor (IL-1R), antigen-presenting CAF (apCAF), major histocompatibility complex Class II (MHC II), metabolic CAF (meCAF), extracellular matrix (ECM).

Figure 1: A diagram illustrating CAFs and cellular origin heterogeneity in pancreatic ductal adenocarcinoma.[4]

fibroblasts, macrophages or T-cells, then multiple disease pathways could be modulated simultaneously. Furthermore, co-delivering two distinct cargos (for example dual siRNAs or an siRNA with a chemotherapeutic) could notably increase therapeutic precision and overcome resistance mechanisms.

Nanoparticle-mediated active targeting strategies, such as arginyl-glycyl-aspartic acid (RGD)-functionalised particles that recognise integrins overexpressed in the TME, offer substantial improvements to therapeutic index and delivery accuracy. These targeted systems overcome the limitations of relying on passive accumulation via the enhanced permeability and retention effect, and enable selective delivery to stromal and immune cells within tumours. Functionalised nanoparticles also exhibit stimuli-responsive features, such as pH-triggered release in the acidic TME, enhancing localised cargo delivery and minimising systemic exposure.

OVERCOMING CURRENT CHALLENGES

An example of the challenge of drug delivery is illustrated by pancreatic carcinoma where up to 90% of the tumour mass consists of cancer-associated fibroblasts (CAFs) and only 10% of malignant epithelial cells (Figure 1).[5] The dense extracellular matrix produced by activated CAFs acts as a physical barrier to conventional drug penetration, whether they are small molecules or biologics. Similarly, immunotherapies struggle because the fibrotic and hypoxic microenvironment restricts immune cell infiltration. Overcoming this requires systems that can target both tumour cells and stromal elements, ideally delivering distinct but complementary cargos.

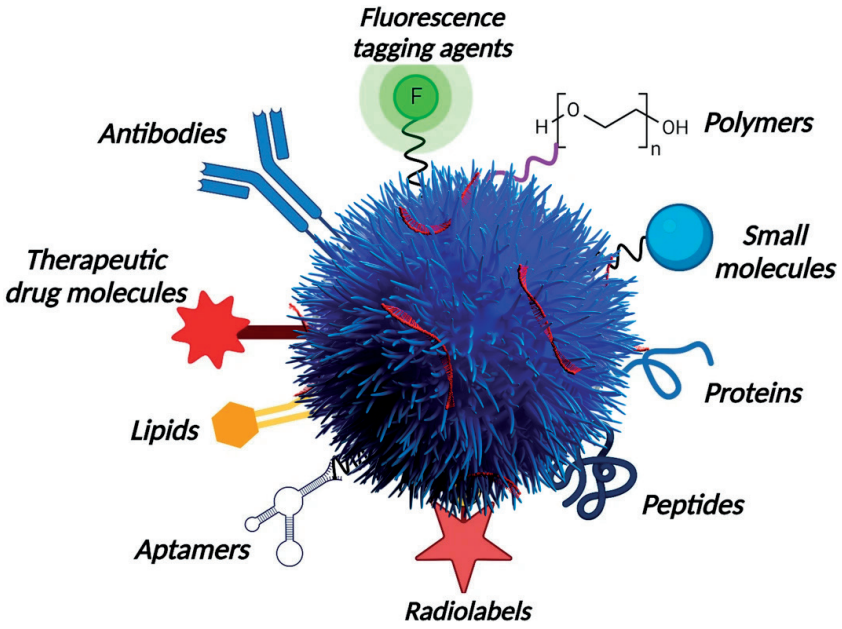

Figure 2: A diagram illustrating how Nuvec® (N4 Pharma) silica nanoparticles can be functionalised to deliver multiple therapeutic and diagnostic agents.

Beyond chemical modifications to improve nanoparticle stability, the use of bispecific ligands targeting both CAF-associated proteins and integrins significantly enhances tumour uptake and therapeutic efficacy. This dual-targeting approach is central to tackling stromal barriers, which traditional drugs cannot cross efficiently. Early preclinical platforms such as silica-based nanoparticles are now being engineered specifically for this multifaceted targeting, providing a sophisticated bridge between nanotechnology and tumour biology.

ONE PAYLOAD IS NOT ENOUGH

Tumour heterogeneity and adaptive resistance limit the long-term efficacy of single-agent therapies. Combination or multi-drug delivery systems allow simultaneous modulation of different cancer pathways and phenotypes.[3]

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For instance, systems that can carry multiple cargos, such as siRNAs targeting both epidermal growth factor receptor and polo-like kinase 1 in non-small cell lung cancer, have demonstrated improved inhibition and reduced compensatory resistance.[6] Similarly, co-loading chemotherapeutic and RNA agents within a single carrier enables synergistic control of tumour growth and immune modulation. PEGylation and surface functionalisation further improve circulation and protect therapeutic cargo from proteolytic degradation en route to their targets.

DIFFERENTIATING TARGETS IN ONCOLOGY

Recent studies using silica nanoparticle-based delivery systems demonstrate how scalable, precision-engineered platforms can be fine-tuned for multi-target approaches. Advances in surface functionalisation, including the attachment of antibodies, ligands or aptamers, enable nanoparticles to recognise specific receptor patterns across tumour and non-tumour cells in the TME (Figure 2).

A mesoporous silica-based nanoparticle can deliver siRNAs or small molecules to multiple cell types simultaneously, ensuring deeper tissue penetration and balanced modulation of tumour biology.

For example, functionalisation with an αvβ6 ligand achieved precise RNA delivery into epithelial tumour cells, including lung, breast, prostate and pancreatic adenocarcinomas. These targeted systems can achieve selective uptake, confirming that they can be steered to specific cancer subtypes, a major advance over non-functionalised platforms. This multi-receptor approach offers a translational pathway to address tumour heterogeneity, validated by significant progress in the development of preclinical lung and pancreatic models.

AMPLIFYING SUCCESS

The promise of dual-cargo, multi-target nanoparticle therapies lies in their modularity. In principle, delivery platforms can:

- Load different modalities (small molecules, oligonucleotides or peptides) tuned for specific release profiles
- Target multiple cell types, whether malignant, stromal or immune, by incorporating diverse ligands on its surface
- Exhibit environment-sensitive release, responding to the acidity, redox conditions or enzyme composition of the TME to ensure localised administration for systemic use.

These attributes align directly with the evolving commercial need for precision RNA therapeutics. With scalable manufacturing and predictable safety profiles, silica nanoparticle carriers could enable precise delivery of siRNA or ASO drugs to previously inaccessible tissues, extending the use of RNA therapeutics beyond hepatic models to complex cancers. Notably, studies from Lorenzoni *et al* stress the need for harmonised physico-chemical characterisation, toxicity evaluation and manufacturing standards to ensure clinical translation of such advanced nanoparticles.[2] Collaborative frameworks between researchers, clinicians and regulatory bodies will be vital for success.

CONCLUSION

The convergence of dual loading and multi-targeting provide a practical pathway towards overcoming the two greatest obstacles in oncology therapeutics: tumour heterogeneity and microenvironmental resistance. As highlighted by the emerging literature on RGD-functionalised systems, precision nanoparticle delivery can orchestrate simultaneous engagement of multiple pathways across the tumour ecosystem, transforming how efficacy, safety and resistance of these therapies are balanced.

Silica nanoparticle carriers exemplify the next evolutionary step towards

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scalable, precise and adaptable delivery systems for RNA and combination oncology therapeutics. While technical and translational challenges remain, such as protein corona formation and patient-specific microenvironment variability, the strategic integration of targeting ligands and multiplexed cargos offers a roadmap towards more effective, less toxic cancer treatments, redefining the therapeutic landscape for complex malignancies such as pancreatic and lung cancer.

By integrating adaptive design principles from nanotechnology with precision targets derived from molecular oncology, silica nanoparticle systems can transform how RNA and combination therapies are deployed.

"BY INTEGRATING ADAPTIVE DESIGN PRINCIPLES FROM NANOTECHNOLOGY WITH PRECISION TARGETS DERIVED FROM MOLECULAR ONCOLOGY, SILICA NANOPARTICLE SYSTEMS CAN TRANSFORM HOW RNA AND COMBINATION THERAPIES ARE DEPLOYED."

Dr Fiona McLaughlin

Fiona McLaughlin, PhD, Head of Research and Development at N4 Pharma, is an experienced oncology drug developer and independent consultant, bringing over 25 years of experience in research and translational drug development in the pharmaceutical and biotech sectors, having led teams from early research through to clinical development. Dr McLaughlin started her career at GSK and has held leadership positions in biotech companies including Avacta Therapeutics, Algeta ASA (now Bayer), Antisoma plc and BTG plc (now part of Boston Scientific). She is also a non-executive director of Hox Therapeutics. Dr McLaughlin received a PhD from the Haematology Department at Cambridge University (UK) and has a BSc in Biochemistry from Glasgow University (UK).

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ABOUT THE COMPANY

N4 Pharma is a preclinical biotech company developing Nuvec®, its proprietary gene delivery system, to enable advanced therapies for cancer and other diseases. RNA therapeutics are set to impact the treatment of a wide range of diseases and Nuvec® has several key advantages for RNA gene delivery, including the ability to deliver multiple RNA therapies in a single particle, ease of manufacturing, protection of the RNA payload to allow for oral delivery, no unwanted immune response and excellent stability and storage.

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