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COMMENTARY

Recommendations for clinical translation of nanoparticle-enhanced radiotherapy

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ABSTRACT

A multi-disciplinary cooperative for nanoparticle-enhanced radiotherapy (NERT) has been formed to review the current status of the field and identify key stages towards translation. Supported by the Colorectal Cancer Healthcare Technologies Cooperative, the cooperative comprises a diverse cohort of key contributors along the translation pathway including academics of physics, cancer and radio-biology, chemistry, nanotechnology and clinical trials, clinicians, manufacturers, industry, standards laboratories, policy makers and patients. Our aim was to leverage our combined expertise to devise solutions towards a roadmap for translation and commercialisation of NERT, in order to focus research in the direction of clinical implementation, and streamline the critical pathway from basic science to the clinic. A recent meeting of the group identified barriers to and strategies for accelerated clinical translation. This commentary reports the cooperative's recommendations. Particular emphasis was given to more standardised and cohesive research methods, models and outputs, and reprioritised research drivers including patient quality of life following treatment. Nanoparticle design criteria were outlined to incorporate scalability of manufacture, understanding and optimisation of biological mechanisms of enhancement and *in vivo* fate of nanoparticles, as well as existing design criteria for physical and chemical enhancement. In addition, the group aims to establish a long-term and widespread international community to disseminate key findings and create a much-needed cohesive body of evidence necessary for commercial and clinical translation.

INTRODUCTION

Radiotherapy aims to achieve tumour control by killing cancer cells while simultaneously sparing healthy tissues. However, cancer cells and healthy cells share similar characteristics that limit both the sensitivity of detection and therapeutic ratio of radiation response in tumour and healthy tissue. Tumour-targeted nanoparticles have potential to overcome these fundamental limitations, first

demonstrated in the pioneering study by Hainfeld et al,[1] in which gold nanoparticle-based radiation therapy was used to enhance the therapeutic ratio in mice. A plethora of *in vitro* and *in vivo* studies demonstrate enhancement factors on the order of 10–100% at clinically feasible concentrations.[2] Despite the promising experimental results presented in the literature there has been limited clinical translation of this concept, with only two metal-based nanoformulations currently in NERT clinical trials; gadolinium-based polysiloxanes theranostic particles (AGuIX, NH TherAguix SAS) and hafnium oxide particles (Nanobiotix SA). Lack of translation is largely due to an incohesive set of experimental parameters (unrelated broad spectra of cell lines, nanoparticle properties, nanoparticle coating, radiation characteristics) – each of which impact on radiation enhancement, and also poor consideration of *in vivo* factors. Our cooperative has instead approached the problem from a clinical and commercial angle early on to outline a roadmap to translation that is optimised, streamlined and accelerated. Here we highlight priority research development areas required for translation.

UNDERSTANDING OF UNDERLYING MECHANISMS OF BIOLOGICAL ENHANCEMENT

Understanding of mechanisms driving NERT will inform the correct experimental read-outs to enable comparison and mechanism-driven optimisation of nanosolutions. Monte Carlo simulations can be used to calculate the physical dose enhancement on the microscale stemming from photoelectrons and Auger electrons (the probability of these interactions increasing with atomic number of material, the original reason for using gold).[3,4] However, physical models underestimate the observed biological enhancement in cellular systems.[5] Alternative mechanisms have been suggested including nanoparticle-induced cellular oxidative stress and enhanced production of reactive oxygen species, and modification of the cell cycle to radiosensitive phases.[6] However, there is still no consensus nor significant evidence regarding the fundamental science governing these processes, and additional mechanisms may yet be at play. Therefore, mechanism discovery through introduction of more sophisticated methodologies not currently performed in this field such as genomics or proteomics is required.

Nanoparticle design strategies

It is currently difficult to confirm any relative advantages between different nanoparticle-based therapeutic strategies because nanoparticle design parameters and corresponding read-outs are highly varied throughout the field, and commonly focus on one mechanistic optimisation (*e.g.* physical dose enhancement). Nanoparticle design should be guided by *all* major needs of the nanosystem, including:

- Factors that affect *in vivo* radiation enhancement including; protein corona changes *in vivo*, colloidal stability and aggregation, cellular and nuclear localisation, and toxicity profile and clearance pathway
- High circulation time in order to increase passive uptake
- 3D penetration to ensure required tumour distribution
- Scalability of manufacture
- Environmental impact of the nanoformulation
- Multifunctionality for imaging and drug delivery options

Cohesive and representative pre-clinical testing strategies

Pre-clinical NERT studies reported in the literature are currently diverse in models, methodologies and outcome reporting.

(a) Cohesive methodologies

Implementation of more cohesive methodologies should be prioritised in order to maintain consistency and comparability across this multi-disciplinary community. Results are reported in wide-ranging journals spanning different fields, making consistency in experimental approach more challenging. This highlights the importance of multidisciplinary research to address this issue. More clarity in terminology when referring to nanoparticle dosage, and clear reporting of cellular concentrations and bio-localisation will add value to results. Clearly expressed radiation parameters are essential to understand the impact of radiation on mechanism and enhancement. The formal introduction of metrics and standardisation to include the dual effect of nanoparticles alongside radiation, seeking guidance from standards laboratories such as the National Physical Laboratory, and both the European and US Nanotechnology Characterisation Laboratories, could provide researchers with a more consistent basis upon which to measure and report treatment efficacy.

(b) Standardised set of outcome measures

Unlike pharmaceutical drugs which use IC50 and EC50 as standardised measurements for efficacy and potency respectively, NERT does not have a standard to define efficacy. The underlying mechanisms must be understood in order to identify the correct read-outs to compare different nanoformulations. The classification of nanoparticles in this application – drug or medical device – will determine which testing standards are needed. Researchers should engage with authorities such as the MHRA to assist in defining nanoformulations and shape regulatory thinking, with reporting of enhancement following international standardization practice[7,8] making it easier to report to regulatory bodies.

(c) Representative models

Models should be representative of intra- and inter-tumour heterogeneity. Drug resistant models should be developed to represent patients of unmet need. For reliable precision medicine, increased use of phenotypic screening in patient derived models[9] should also be implemented to allow researchers to test for patients who may derive significant benefit. Models should better represent *in vivo* factors, including human serum proteins and their impact on the protein corona[10] and downstream biodistribution and aggregative instability.

Nanoparticle delivery strategies

The optimal delivery mechanism would give the greatest differential uptake between tumour and healthy tissue, and lowest toxicity. Passive uptake mechanisms through intravenous injection and direct intratumoural injection have been implemented in current clinical trials of AGuIX[11] and Nanobiotix[12] particles respectively; active targeting has so far been resisted by commercial partners due to the manufacturing difficulty associated with personalised coating, and poses practical challenges in terms of keeping the integrity of the functional coating once introduced into an *in vivo* system, with increased size of nanoparticles due

to the hydrodynamic radius of targeting ligands resulting in issues with tumour penetration.[13] There are also a lack of suitable biomarkers and imaging strategies for defining optimal uptake and bioavailability of targeted nanoparticles. Therefore, it was suggested that research is focussed on passive uptake via the enhanced permeability and retention (EPR) effect. There is scope to further optimise nanoparticle size/shape for EPR, and to exploit the interplay between radiation-induced biological/vascular damage and nanoparticle accumulation.[14] Double localisation using focussed radiation may negate less precise targeting offered by the EPR effect.

DISCUSSION

Implementing the combined perspectives from manufacturers, clinicians and patients allows researchers to develop NERT products with more understanding of the efficacy criteria as defined by the priorities of those manufacturing, delivering and receiving treatment. Viewpoints from each group follow.

Manufacturer perspectives

Translation and integration of NERT technologies relies on a consistently homogenous and reproducible end-product. However, the majority of nanoparticles used in preclinical studies implement small batch synthesis strategies, making scale-up for larger quantities impossible in some instances.[15] It follows that large quantity scale-up should be prioritised during the nanoparticle design stage, with the same tools being used at discovery and scale-up stages. Contract manufacturing organisations should be included during the initial design stages, and laboratory plans and procedures should be parallelised to the manufacturer laboratory.

Clinical perspectives

Future use of this concept will particularly benefit tumours where radiotherapy tumour dose is restricted by surrounding normal tissue tolerances, tumours that are targetable and those where current treatment yields unsatisfactory results. In line with recent guidelines to accelerate drug-radiation development,[16] NERT becomes a clinically viable option if it:

- displays lower toxicity than alternatives for similar efficacy (including dose de-escalation)
- displays greater efficacy than current standard of care (including nanoparticle-mediated dose escalation)
- can replace surgery to improve quality of life
- can guide therapies (multifunctional solution: optical fluorescence for intraoperative guidance, MRI or CT contrast to guide radiotherapy)
- offers a pathological response

Implementation of NERT will require modifications to clinical workflow, and a number of research questions remain to be answered which currently act as barriers to clinical translation. The mode of nanoparticle introduction, tumour targeting strategies, frequency and timing of nanoparticle injection prior to irradiation, and biological fate of the nanoparticles must be considered. Platforms to quantify nanoparticle concentration distribution are required, profiting from theranostic nanoparticle solutions with imaging capability. It is imperative that clinical trials are designed to consider the extent to which nanoparticle concentration in both tumour and healthy tissue has an effect on radiation dosimetry and develop strategies to incorporate the expected dose distribution changes into the treatment planning process. This may be particularly important during charged particle therapy, where density changes induced by metallic nanoparticles can have a significant impact on dose distribution and Bragg peak characteristics.[17]

Patient perspectives

Patients and consumer groups should be involved from the clinical trial concept stage onwards for a clear understanding of patient priorities and what strategies they accept. Outcomes of trials must include patient reported outcome measures as well as conventional efficacy and toxicity measures. The physical and psychological impact of treatment must be considered, the latter having longer lasting implications; shifting the focus from prevention of death, to preparation for life.

CONCLUSION

NERT demonstrates great potential to enhance the therapeutic ratio in radiotherapy for improved patient outcomes and reduced side effects. In order to accelerate clinical translation for patient benefit, barriers to translation must be identified in the first instance, and research driven to overcome those barriers. The cooperative recommends that research is prioritised to themes that are on the critical path to translation, including nanoparticle design driven by manufacturer scalability, *in vivo* fate and patient priorities, as well as NERT enhancement mechanisms. Mechanism discovery of NERT and standardisation of appropriate experimental methods is required to enable meaningful comparison of nanoparticle systems throughout the diverse research community. Towards this aim, development of a database platform to deposit this wide-ranging data would make strides towards accelerating clinical translation. The cooperative's future goal is to establish a widespread community representative of all required groups to create a cohesive, clinically and industrially aligned body of evidence required for translation.

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