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Mini-Symposium: Nanoparticles and Children's Lungs

Imaging the paediatric lung: what does nanotechnology have to offer?

K.L. Ordidge [1,2], B.A. Duffy [2], J.A. Wells [2], T.L. Kalber [1,2], S.M. Janes [1,a,b,*], M.F. Lythgoe [2,b,*]

[1] The Centre for Respiratory Research, The Department of Medicine, UCL
[2] UCL Centre for Advanced Biomedical Imaging

EDUCATIONAL AIMS

- To provide an overview of the potential, limitations and difficulties of using nanoparticles in various imaging modalities.
- To discuss the use of nanoparticles as both diagnostic and therapeutic agents.
- To understand that nanoparticles can be actively or passively targeted, or used as intracellular agents to track living cells.

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SUMMARY

This review will provide an overview of current research into lung imaging with nanoparticles, with a focus on the use of nanoparticles as molecular imaging agents to observe pathological processes and to monitor the effectiveness of nanoparticulate drug delivery systems. Various imaging modalities together with their advantages and limitations for lung imaging will be discussed. We will also explore the range of nanoparticles used, as well as active or passive targeting of nanoparticles.

INTRODUCTION

Nanoparticles can act as a contrast agent in medical imaging in order to enhance the difference between normal and diseased tissue. Over the past decade, research into nanoparticles for imaging and drug delivery has increased rapidly.[1] This may be partly due to improvements in sensitivity of imaging instrumentation but also due to increasing appreciation of their potential utility. A nanoparticle is described by the National Nanotechnology Initiative as being any material having one or more dimension in the nanoscale (0–100 nm). The advantage of using nanoparticles over small molecular weight contrast agents is their ability to deliver a large payload of contrast material, targeting moieties, drugs or nucleic acids per particle. Nanoparticles may also have significantly different pharmacokinetics and pharmacodynamics to low molecular weight compounds, and altering their physicochemical properties can tailor biodistribution for tissue specific targeting.

This review will discuss recent advances in the field of imaging nanoparticles for the investigation of pathology and monitoring drug delivery. Although the development of nanoparticulate contrast agents for pulmonary imaging is very much in its infancy, imaging lung disease in the clinic or in preclinical models can be achieved through various modalities, for example, nuclear medicine, CT (computed tomography), optical imaging or MRI (magnetic resonance imaging).

The only nanoparticle with FDA approval for clinical use in imaging is the superparamagnetic iron oxide nanoparticle (SPIO) Endorem™, used in MRI diagnosis of liver tumours and metastases, although this is no longer manufactured.[2] However, there are many different types of nanoparticles in development for imaging. These include superparamagentic or paramagnetic nanoparticles,[3] liposomes,[4] carbon nanotubes,[5] micelles[6] and quantum dots.[7]

Lung Imaging

Delivering contrast agents to pulmonary tissue can be achieved by inhalation or by intravenous injection. Delivering agents though the airways may offer advantages when the aim is to target lung tissue. The alveoli provide a large surface area for drug absorption, and the single cell layer of the epithelium allows easier penetration of compounds into the vasculature.[8,9] Conversely, clearance of agents from the lungs can be rapid due to its high vascularity,[10]

* Corresponding authors. UCL Centre for Advanced Biomedical Imaging, Paul O'Gorman Building, 72 Huntley Street, London, WC1E 6DD.
E-mail addresses: s.janes@ucl.ac.uk (S.M. Janes), m.lythgoe@ucl.ac.uk (M.F. Lythgoe).
[a] UCL Centre for Respiratory Research, Rayne Building, University College London, 5 University Street, London, WC1E 6JJ.
[b] Joint senior authors.

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meaning that the requirements of nanoparticles for imaging will be retention rather than absorption of nanoparticle.

Yet the challenges do not just lie with the design of the nanoparticles. Respiratory and cardiac motion leads to imaging artefacts and corruption of the images. To overcome these problems images can be acquired during a breath hold, although this technique is impractical for very young children. Another method is to use respiration image gating, where images are acquired at specific points in the breathing cycle.[11]

Despite these problems, which are applicable to all imaging modalities, each method has its own specific qualities. MRI offers distinct advantages over the nuclear imaging modalities in terms of the achievable spatial resolution, and over both CT and nuclear imaging as it uses non-ionising radiation, although its sensitivity is limited. This is especially important in paediatric patients and those needing repeated follow-up scans. The use of nanoparticulate contrast agents for imaging modalities holds much potential for the early detection of various diseases in the lung including obstructive lung diseases, cystic fibrosis and cancer.

MAGNETIC RESONANCE IMAGING

Imaging the lung using proton magnetic resonance imaging is notoriously difficult. Multiple airspaces restrict the tissue density within a MRI voxel, dramatically reducing the signal intensity. This is further exacerbated by rapid dephasing of magnetisation; shortening T2, the MRI transverse relaxation time of the tissue. This rapid dephasing of magnetisation is a result of multiple air-tissue interfaces (there is a very high surface area to volume ratio of the lung tissue). Therefore conventional MRI sequences may have very limited sensitivity to contrast agents that employ negative contrast (i.e. reduce the measured signal) due to the very low baseline signal. There have been considerable efforts to improve lung MRI to overcome these challenges.

Lung MRI Advances

In order to increase the measured signal, specialised MRI techniques have been developed. An important example is ultra-short echo-time (UTE) imaging.[12] This is a specialised pulse sequence that detects signal rapidly, before it quickly decays due to T2 and has recently become possible due to advances in MRI gradient hardware and MRI physics innovations.[13] The increase in signal enables visualisation of lung parenchyma, allowing assessment of lung architecture and possible diagnosis of pathology.[12,14] An alternative approach to improving image quality is balanced steady-state free precession (SSFP), however lung imaging using this technique has primarily been employed using low field MRI scanners (0.2T),[15] which are not typically found in the most hospitals. Importantly, by employing UTE or SSFP to enhance the signal, contrast agents that produce local decreases in signal can be detected.

Hyperpolarised gas MRI can provide a ten thousand to one hundred thousand fold increase in signal[16] and has produced impressive images of lungs in patients.[17] This can provide accurate information on lung function that global spirometry measures cannot. For a detailed recent review on the subject of estimating functional parameters such as perfusion and ventilation using imaging techniques see Ohno et al.[18]

As previously mentioned, there is limited use of nanoparticles in MRI in the adult population, let alone the paediatric arena. However, nanotechnology has been increasingly developed and applied in preclinical medical imaging over the past decade. In–icular, superparamagnetic iron oxide nanoparticles (SPIO) are well suited as an MRI contrast agent and thus will be the focus of this section.

Superparamagnetic Iron Oxide Nanoparticles (SPIO)

Magnetic nanoparticles offer attractive possibilities in biomedicine as an MRI contrast agent and also for other applications, such as magnetic separation, hyperthermia therapy for cancer and drug delivery.[19] A key advantage of SPIOs is that their sizes can be accurately controlled during manufacture over a wide range, to reflect dimensions that are smaller than or comparable to those of a cell (10–100 μm), a virus (20-450 nm), a protein (5–50 nm) or a gene (2 nm wide and 10–100 nm long).[19] Thus, they can be incorporated into cells affording a controllable means of 'tagging'. Importantly, MRI relaxation times are shortened by the use of magnetic contrast agents, which enables imaging of these particles.

The most common MRI contrast agents currently used are the paramagnetic gadolinium ion complexes, although agents based on superparamagnetic nanoparticles have been commercially available. The superparamagnetic iron oxide (SPIO) particles are magnetically saturated in the normal range of magnetic field strengths used in MRI scanners, thereby establishing a substantial locally perturbing dipolar field which leads to a marked shortening of T2, leading to local hypointensities in an image and the possibility of imaging the localisation of these particles. However, given the extremely short T2 in the lung, the use of superparamagnetic contrast agents to enhance this further may be less applicable in the lung than it is to other organs.

Actively Targeted Nanoparticles for MRI

In order to overcome the problem of short T2 in the lung, hyperpolarised helium gas MRI has been used in conjunction with actively targeted iron oxide nanoparticles. The hyperpolarised helium increases the signal strength in the lung[20] and enhances the detection of the signal hypointensity caused by the nanoparticles. SPIOs functionalized with luteinizing hormone–releasing hormone (LHRH) have been used with hyperpolarised helium gas MRI to specifically target pulmonary micro-metastases which, due to their size, could not be imaged by PET or SPECT[21]. The micrometastases were visible after SPIO injection due to the signal voids they created in the hyperpolarised helium gas.

Passive Targeting of Nanoparticles

Despite the limited use of targeted nanoparticles, SPIOs are readily used to image preclinical models of cancer, taking advantage of the *passive* targeting to tumours that can be achieved with systemic injection. Once tumours reach a certain size, new blood vessel formation, or angiogenesis is required for further growth. These new vessels are poorly structured and irregular, allowing leakage of blood plasma components, including nanoparticles, into the tumour. Once inside the tumour, they are retained for longer periods of time due to poor lymphatic and venous drainage. This phenomenon is known as the enhanced permeability and retention effect (EPR) and allows passive targeting of nanoparticles into tumours.[22] Once inside the tumour, the nanoparticles produce signal loss and hence, contrast between tumour and normal tissue. This has lead to preclinical applications of SPIO for imaging tumours and metastases. For example, Jain et al. have developed pluronic coated nanoparticles that enhance contrast in the tumour, and could also be loaded with anti-cancer agents.[23]

Cell tracking and therapies

Another interesting property of SPIOs is their ability to label cells for MRI tracking. Mesenchymal stem cells (MSCs) can be easily extracted from a patient with a bone marrow biopsy, and expanded in culture for injection back into the body as an

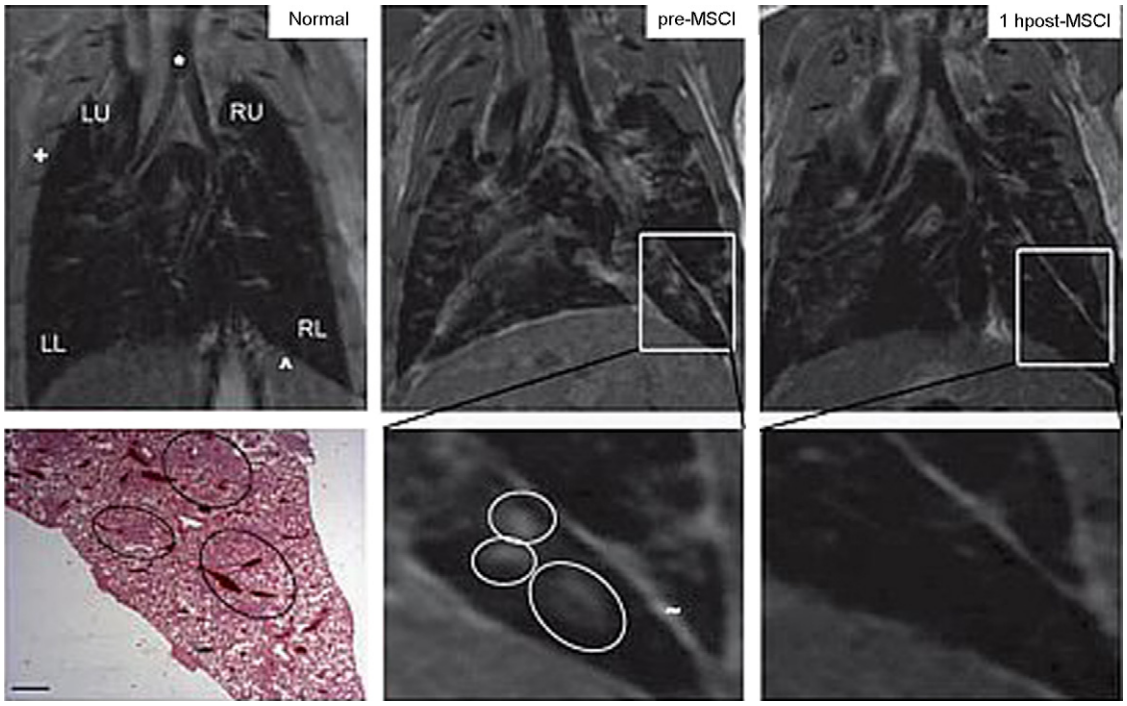

Figure 1. High-resolution lung MR images showing lung metastases (circled) pre- and post-MSC delivery. The MSCs contain SPIO, therefore after MSC delivery the metastases become dark. Adapted and reprinted by permission from the American Association for Cancer Research. Loebinger et al. Magnetic resonance imaging of mesenchymal stem cells homing to pulmonary metastases using biocompatible magnetic nanoparticles. Cancer Research, 69(23); 8862-8867.

autogenic transplant. MSCs are readily labelled with SPIO through endocytosis, with little effect on cell survival or proliferation.[24] It is well known that MSCs have the ability to home to and incorporate into areas of inflammation and injury within the body.[25] Therefore, SPIO can be utilised to track these labelled MSCs using MRI.

In a recent preclinical study, SPIO labelled MSCs have been tracked homing to pulmonary metastases using MRI (Figure 1).[26] This ability to visualise both primary tumours and metastases using SPIO labelled MSCs and MRI is obviously of great benefit for cancer staging and diagnosis. MSCs are also being used as vectors to carry anti-cancer therapies to tumours.[27] Combining these applications will allow MRI tracking of cell therapies being delivered to tumours. Although much of this work has been done in lung cancer models, it may also be applicable to any disease process inducing inflammation within the lung.

There is currently a lot of interest in using stem cells for the repair of airway injury[28] and as vectors for the delivery of drugs or therapeutic genes into a targeted area.[29] Labelling these engineered MSCs with SPIO before injection would allow tracking to the site of interest and quantification of the efficiency of cell delivery.[30] Combined with MR imaging, this developing field could see MRI tracked cell therapy aimed at common respiratory diseases in childhood, for example gene therapy for cystic fibrosis.

Summary

Preclinical MR imaging with nanoparticles is a rapidly expanding field. SPIO nanoparticles are becoming ever more complex, functionalised with therapeutic or targeting agents. However, it could take many years before these experimental nanoparticles are translated into paediatric clinical applications.

NUCLEAR MEDICINE

The nuclear imaging modalities do not suffer from the same sensitivity problems as MRI. The major issue in the nuclear modalities is background signal caused by non-specific organ uptake or prolonged circulation of the radiotracer in blood. There is therefore much interest in designing high-affinity radiotracers with improved biodistribution, targeted to markers of angiogenesis or inflammation as this could enable earlier detection of pathology.[31] Nanoparticles are attractive for this purpose as they can be modified to carry radioisotopes on their surface coatings. Although there are currently no nanoparticulate radiotracers in clinical use, radiolabelled nanoparticles are being increasingly used in preclinical studies of inflammation and cancer.

Targeted imaging agents for nuclear medicine

The use of coated nanoparticles with a targeting ligand or antibody can provide enhanced tissue targeting and specificity. For example, integrins such as $\alpha_v\beta_3$, $\alpha_v\beta_5$, and $\alpha_5\beta_1$ are often highly expressed on tumour vasculature and have a low background expression in normal tissue, rendering them ideal targets for molecular imaging probes. For example, Lee et al. have demonstrated the possibility of using combined PET/MR imaging of bifunctional iron oxide nanoparticles labelled with radioactivity and tumour targeting integrin $\alpha_v\beta_3$[32]. This bimodal approach could be advantageous due to the recent commercialisation of dual modality PET/MRI scanners.

Latex nanoparticles conjugated to monoclonal antibodies specific to intercellular adhesion molecule 1 (ICAM-1) have been radiolabelled for PET imaging appear to be specific to the lung endothelium[33]. In this study a systemic lipopolysaccharide (LPS) insult led to increased nanoparticle retention in pulmonary tissue at 24 hours post injection, probably due to the high vascularity of lung tissue compared with other organs, leading to favourable pharmokinetics. The authors suggest that the nanoparticles could be used to monitor inflammation of lung disease, because ICAM-1 is upregulated by pathological processes.

Radiolabelled nanoparticles can be administered intravenously, or via inhalation. In order to specifically deliver drugs and imaging agents to the lungs it is possible to deliver them via an aerosol. This method can improve the efficacy of anti-cancer drugs in models of

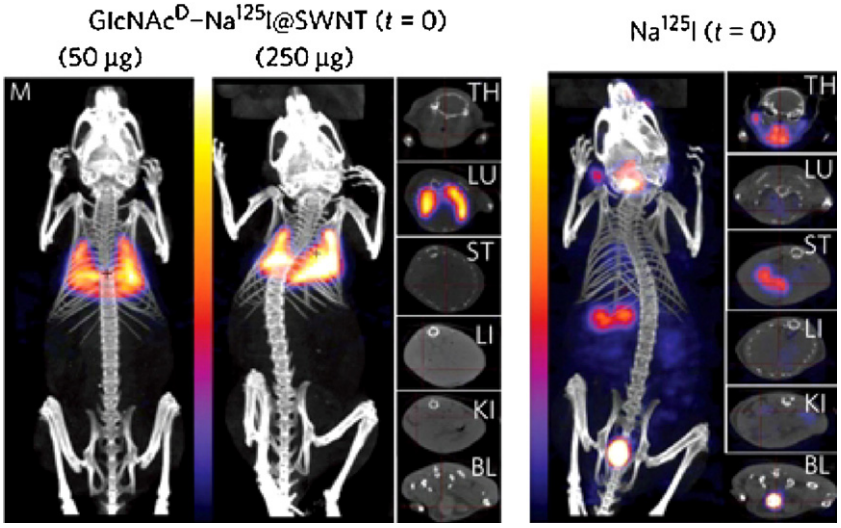

Figure 2. Whole-body SPECT/CT carried out immediately after tail-vein injection of glycosylated $Na^{125}I$ carbon nanotubes compared to injection of $Na^{125}I$. These functionalised carbon nanotubes show remarkably specific lung accumulation. Reprinted by permission from Macmillan Publishers Ltd: [Nature Materials 2010;9(6):485–90], copyright 2010.

pulmonary metastases. Koshkina et al. have reported a 75% reduction in tumour volume using a paclitaxel aerosol in mice.[34] Targeting the lungs directly via inhalation can result in much better delivery and retention of nanoparticles.[35] Videira et al. have used solid lipid radiolabeled nanoparticles to track delivery and clearance within the lungs of rats using a SPECT system.[36] Inhaled nanoparticles were delivered to small airways, where they were taken up by the lymphatic system through the alveolar spaces. They proposed the use of radiolabelled solid lipid nanoparticles for lymphoscintigraphy or for monitoring drug delivery.

Carbon nanotubes

Single-walled carbon nanotubes (SWNTs) consist of a single atomic layer of graphite rolled into a cylinder and consequently they have unusual physical properties, such as electrical conductance, thermal conductivity and luminescence.[5] Recently, there has been interest in using them for imaging applications as radioemitting atoms or paramagnetic ions can be encapsulated into SWNTs. Glycosylated nanotubes encapsulating Na ^{125}I radioactive atoms have been shown to accumulate in lungs with remarkable specificity and stability in mice (Figure 2).[37] Tissue histology 30 days after dose showed no necrosis or fibrosis in the lung, or any other organ, but there are still concerns about the safety of using such materials in patients.[38] Carbon nanotubes longer than 20 μm are expected to cause fibrosis, pleural thickening and mesothelioma (similar to asbestos fibres), while shorter nanotubes may be phagocytosed and cleared by macrophages, although the specific relationship between nanotube length and toxicity has not yet been fully investigated.[39]

Monitoring drug delivery

Nanoparticles can be labelled with a radioactive probe in order to track their progress *in vivo*. This can be done with direct labelling techniques, or by using a ligand to attach the radioactive molecule to the nanoparticle. The advantage of using radiolabelled nanoparticles for SPECT or PET, is that they allow quantitative assessment of nanoparticle delivery, with a high sensitivity.[31] In preclinical systems concentrations of radiotracer in the picomolar range can be imaged at resolutions below 1 mm. This can be measured repeatedly over a defined period of time, depending on the biodistribution and clearance of the nanoparticle, and the radioactive half-life of the radiolabel. It is also possible to achieve high activities of radiolabeled nanoparticles by attaching more than one molecule of radioactive isotope to the nanoparticle, which means they can be given at lower doses.[40] This allows quantitative assessment of nanoparticle delivery, and can be used to monitor delivery of 'theranostic' drug-nanoparticle complexes, which can be used for diagnosis and therapeutics. Chang et al. have successfully shown delivery and therapeutic efficacy of their ^{188}Re labelled Doxirubicin liposome for SPECT imaging and treatment of murine colorectal carcinomas.[41]

COMPUTED TOMOGRAPHY (CT)

X-ray CT uses multiple x-ray projections to form a single 3D image. Endogenous contrast is provided by the different x-ray attenuation properties of air, tissue and bone. Exogenous contrast agents include barium and iodinated compounds. These commonly used contrast agents have high densities and are hence radioopaque in CT images. However, there are no nanoparticles in clinical use as contrast agents for CT imaging and very few preclinical studies exploring this.

The most commonly used nanoparticle in preclinical CT studies are gold particles. They have a high atomic number and density, which provides a 3-fold improvement in contrast over conventional iodine contrast agents.[42] These particles have been shown to accumulate in tumours due to the enhanced permeability and retention effect, indicating a potential use in tumour imaging.[42] In a different approach, Aillon et al. have used aerosolized nanoparticles in a preclinical CT imaging study to increase contrast in the lungs.[43] These nanoparticles were formulated from a derivative of diatrizoic acid, an iodinated compound, and agglomerated to produce nanoclusters of diameter 1-5 μm, suitable for deposition in the lung periphery. They observed good enhancement of the airways, with no acute toxic effects on lung tissue (no alveolar tissue damage or inflammation within the lungs 2 hours after dosing).

CONCLUSION

Nanoparticles show great potential as contrast agents to enhance diagnostic imaging of the lungs. Nanoparticles are already

used for drug delivery applications and for MR imaging. They are also extensively used in preclinical studies with both MR imaging and nuclear imaging. Nanoparticles for multimodal imaging, and for combined diagnosis and therapy, is a rapidly developing area. Combining this imaging expertise with nanoparticle based drug or gene delivery systems will allow monitoring of therapies *in vivo*.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest are reported in the writing of this review.

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