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REVIEW

Target, Treat, and Track: Superparamagnetic Iron Oxide Nanoparticles (SPION) Driven Theranostic Delivery of Antimicrobials to the Lungs

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Abstract: This review explores the emerging potential of theranostic approaches in the pulmonary delivery of antimicrobial agents, with particular attention to recent FDA warnings concerning inhaled antifungal therapies. Pulmonary infections remain difficult to treat effectively due to the limitations of systemic drug delivery, anatomical and physiological barriers within the lungs, and microbial strategies that promote colonization. Inhaled drug delivery offers a targeted alternative but faces significant challenges, including the inherent variability of lung anatomy, disease-induced pulmonary alterations, and host defence mechanisms. We examine the crucial role of lung imaging in enabling theranostic applications, emphasizing magnetic resonance imaging (MRI) as the most promising modality due to its ability to provide non-invasive, radiation-free, and repeatable assessments of drug deposition. Within this context, the use of superparamagnetic iron oxide nanoparticles (SPIONs) as MRI contrast agents is critically assessed. SPIONs offer a safer alternative to gadolinium-based agents and hold considerable promise for improving the precision of imaging and treatment monitoring in the lungs. The article also outlines the significant regulatory barriers to the development and clinical adoption of inhaled antimicrobial therapies. These include the lack of standardized patient selection criteria, poorly defined clinical endpoints, and the inherent complexity of trial design for heterogeneous patient populations. To address these issues, we propose a conceptual framework for translating inhaled theranostic formulations into personalized antimicrobial therapies. This includes individualized dose adjustments based on imaging data and real-time monitoring of drug concentrations at the infection site. Such a tailored approach could significantly enhance treatment outcomes and meet the urgent clinical need for safer, more effective inhaled antimicrobial treatments.

Keywords: theranostic, pulmonary delivery, inhaled antibiotics, inhaled antifungals, SPIONs, MRI

Introduction

The term *Theranostic* merges two words, therapy and diagnostic, and was first used by John Funkhouser in 1998 to highlight the shift toward more specific, individualised treatments by integrating diagnostics and therapeutics into a single agent. This approach enables simultaneous diagnosis, drug delivery, and treatment monitoring.[1] However, the origins of the theranostic concept dates to the mid-1950s, when Saul Hertz's research on radioactive iodine (^{131}I) for hyperthyroidism led to its clinical adoption for both diagnostic scintigraphy and thyroid cancer treatment.[2,3] Another widely used example is the combined introduction of Herceptin (Trastuzumab) and HER-2 receptor testing for advanced breast cancer treatment, approved by the FDA (Food and Drug Administration) in 1998,[4] which some consider the beginning of modern theranostics.

Since then, cancer theranostics has made significant progress.[5] While the concept is primarily applied in oncology, integrating drug delivery, immunotherapy, radiotherapy, phototherapy, thermal therapy, and imaging,[6] its use with antimicrobial drugs is crucial for improving treatment efficacy and reducing drug resistance. This need is especially

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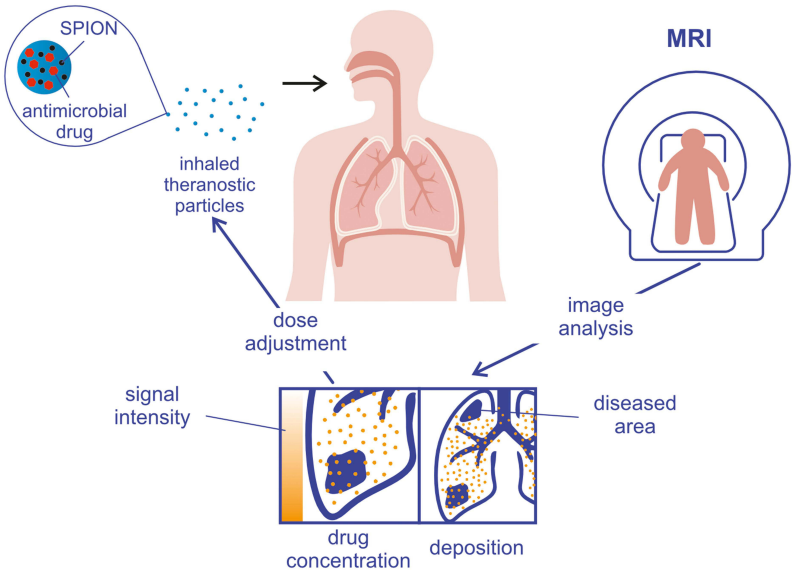
Graphical Abstract



critical for lung infections, where traditional pharmacokinetic studies measuring plasma drug levels do not accurately reflect local drug concentrations at the infection site. Real-time monitoring of therapeutic outcomes can help adjust drug doses to maintain optimal concentrations within the therapeutic window.[7]

This theranostic approach requires repeated lung imaging, making a safe and effective imaging method crucial for its success. Among available techniques, magnetic resonance imaging (MRI) is unmatched for its non-invasive and precise imaging of organs and tissues.[8] The use of superparamagnetic iron oxide-based nanoparticles (SPIONs) for contrast enhancement, instead of gadolinium chelates that can cause side effects, enables MRI to be used in inhaled theranostics for antimicrobial drugs.

In this review, we address the challenges faced by scientists in designing inhaled formulations, including the physiological defence mechanisms of the lungs and disease-induced changes in lung physiology, as well as the defence mechanisms of microorganisms that facilitate lung colonisation. We also explore regulatory issues, which are a key factor in the limited availability of inhaled antimicrobial therapies and the difficulties associated with their approval. We explore the potential of lung imaging, with MRI emerging as the most suitable option for theranostics, especially given the need for repeated imaging to determine the optimal dose for patients. Additionally, we review the use and modification of superparamagnetic iron oxide nanoparticles (SPIONs) as a contrast agent and evaluate their safety. Finally, we present the concept of translating inhaled theranostic formulations containing antimicrobials into personalised therapy, aimed at selecting the appropriate drug dose and determining its concentration at the site of action.

Challenges in Inhaled Antimicrobial Drug Delivery

Pulmonary infections are challenging as microorganisms (bacteria, fungi, mycobacteria, viruses) penetrate deep into the small airways. Current therapy relies on oral or intravenous antimicrobial administration, but systemic delivery results in poor lung distribution, suboptimal drug levels, and resistance development. Antimicrobial drugs require high doses, increasing the risk of systemic toxicity and serious side effects. The pulmonary route enables targeted delivery to the deep lung while reducing systemic exposure.

While inhalation is common for bronchodilators and corticosteroids in COPD and asthma, currently few inhaled antibiotics and antivirals are FDA- or EMA-approved, with no antifungals (in clinical trials) or tuberculosis drugs available (Table 1). In their absence, nebulised intravenous antimicrobials are often used off-label.[9]

Table 1 Inhaled Antibacterials, Antifungals and Antivirals Currently Used or in Development

API	Brand Name	Dosage Form	Indication	Status	Ref
Antibacterials					
Tobramycin	TOBI Podhaler	Dry powder for inhalation	Lung infection due to Pseudomonas aeruginosa in CF	On the market	[10]
Vancomycin	AeroVanc	Dry powder for inhalation	MRSA lung infection in CF	Development halted	[11]
Aztreonam	Cayston	Dry powder for reconstitution and nebulisation	Lung infection due to Pseudomonas aeruginosa in CF	On the market	[10]
Colistimethate sodium	Generic drug	Lyophilisate for reconstitution for injection and nebulisation*(i)	Lung infection due to Pseudomonas aeruginosa in CF	On the market	[10,12]
Colistimethate sodium	Colobreathe	Dry powder for inhalation	Lung infection due to Pseudomonas aeruginosa in CF	On the market	[13]
Colistimethate sodium	Colistin Cyclops	Dry powder for inhalation	Lung infection due to Pseudomonas aeruginosa in CF	Orphan drug status, in development	[10,13,14]
Levofloxacin	Quinsair	Solution for nebulisation	Lung infection due to Pseudomonas aeruginosa in CF	On the market	[13]
Antifungals					
Itraconazole	PUR 1900	Dry powder for inhalation	Allergic bronchopulmonary aspergillosis	In development	[15]
Voriconazole	TFF VORI	Dry powder for inhalation	Pulmonary Aspergillosis	Terminated*(ii)	[16]
Opelconazole	PC945	Dry powder for inhalation	Pulmonary Aspergillosis	In development	[17]
Amphotericin B	N/A*(iii)	Nebulised liposomal amphotericin B	Pulmonary Aspergillosis	Off-label use*(iii)	[18,19]
Antivirals					
Ribavirin	Virazole	Lyophilisate for reconstitution and nebulisation	Respiratory syncytial virus (RSV)	On the market	[10]
Laninamivir	Inavir	Dry powder for inhalation	Influenza A & B	On the market (Japan only)	[20]
Zanamivir	Relenza	Dry powder for inhalation	Influenza A & B	On the market	[10]

Notes: *(i) Reconstituted colistimethate sodium nebulisation is done off-label in the US, approved in Poland by URPL. *(ii) TFF Pharmaceuticals has been liquidated. *(iii) Nebulised liposomal amphotericin B is used off-label.

The efficacy of inhaled antimicrobials depends on lung deposition, which is influenced by formulation performance and pathophysiology.[21] Aerodynamic diameter, density, crystallinity, shape and molecular size are some of the factors that must be considered to target the particles to specific regions of the respiratory tract. For optimal treatment outcomes, drug deposition in the deeper alveolar regions of the lungs at an adequate topical concentration is desired,[22] especially in the case of pulmonary infection, where ensuring effective drug levels in the affected areas of the lung is crucial for preventing resistance development. Pulmonary drug delivery must overcome lung defences, including filtration, immune response, and rapid exhalation.[23] A thick mucus layer traps and clears foreign particles,[24,25] with clearance regulated by the number of cilia and ciliary beat frequency,[26] alveolar macrophages and tight junctions in alveolar epithelium.[27] Infections further hinder inhaled drugs by causing mucosal swelling, excess mucus, and airflow turbulence, leading to improper deposition in central airways instead of deep lungs.[28,29] Moreover, different infectious microorganisms have

various defence mechanisms against the immune system and drug penetration. These include antimicrobial entrapment in a dense mucus layer, surface proteins, carbohydrates, extracellular proteases; exopolysaccharide galactosaminogalactan (in fungi), and granuloma formation (eg, *Mycobacterium tuberculosis*), which aids immune evasion, inhibits immune responses, and facilitates adherence to host tissue.[30–33]

Drug formulation is crucial for effective inhaled therapy in infected lungs. Inhaled particles should range from 1 to 5 μm in aerodynamic diameter to effectively reach the deep lung. Particles smaller than 1 μm are often exhaled, while those larger than 5 μm tend to deposit in the upper respiratory tract (nose, throat, trachea). However, very small particles (<200 nm), including nanoparticles (<100 nm), can enhance mucus penetration and evade mucociliary clearance, allowing them to remain in the lung lining fluid until they dissolve.[34,35] Despite optimised formulations, airway impairments can hinder drug delivery, leading to suboptimal antimicrobial levels and resistance risks.[36,37] Additionally, often neglected individual lung variability further challenges treatment success.[38] Poorly aerated lung regions often go undetected, as healthy airways can compensate, masking ventilation issues in standard tests like spirometry.[39]

Lung Imaging

The assessment of infection-related lung function alterations is a priority to establish proper countermeasures enabling effective drug deposition within the lungs.[38] To discriminate between the effect of the delivery mechanism and the pharmacological action, it is crucial to (i) properly assess the effectiveness of the treatment, (ii) adjust the appropriate dose, and (iii) prevent false negative treatment results.[40] From this perspective, the development of functional lung imaging methods may help to discriminate between drug and pathophysiological effects, as well as quantify the local drug concentration.[41]

These techniques may enable treatment personalisation, and thus, maximizing therapeutic outcomes by granting control over lung deposition and local drug levels.[38] Although theoretically feasible, inhalation treatment personalisation through imaging techniques is not an easy task and requires the development of proper tools to record a patient's conditions and inhalation behaviour. In this regard, the concept of theranostic is in the spotlight in personalised medicine.

Currently, chest radiography (X-ray) and computed tomography (CT) are most prevalent when it comes to lung imaging,[42] MRI however is becoming a popular alternative method thanks to its reduced radiation dose.[43] Methods such as ultrasonography (USG) or chest X-ray have disparate indications due to the different nature of resulting images. A general breakdown of the different methods' indications, advantages, disadvantages and mechanisms of action is illustrated in Figure 1. A USG mainly showcases vertical pleura artefacts, consolidation and pleural effusion, which are associated with increased amounts of fluid in the lungs, increased lung density and decreased lung aeration.[44] This information may be important for assessing disease progression but will offer limited information on drug deposition. X-ray can visualise changes caused by pulmonary fungal infections, described as lesions lying within a cavity,[45] however it also offers limited information on drug deposition. CT, which offers high-resolution 3D cross-sectional images, allows for the imaging of contrast agents; currently, the most used CT contrast agent being iodinated contrast agents (ICAs) such as Iohexol. However, ICAs have a short biological half-life, requiring high doses that can cause nephrotoxicity, thyroid-disruption, occasional immunogenicity, and on top of that, they are able to cross the placental barrier, and may pose a risk to developing foetuses. Metallic nanoparticles are a promising alternative to current CT contrast agents; gold, silver, bismuth, and several lanthanides being extensively investigated.[46] On top of this, the radiation dose resulting from CT is too large to consider repeated imaging of the lungs in a theranostic approach, with a conventional chest CT emitting 6.1 mSv on average, which is equal to around 70 chest X-rays or 2 years of natural background radiation.[44,47] Positron emission tomography (PET) could also allow for the imaging of contrast agent within the drug formulation, however the radiation dose which depends on the radioisotope used, is also too large to consider repeated imaging in a theranostic approach, also averaging around 7 mSv.[44] The method is based on detecting emitted positrons, requiring radiopharmaceutical agents containing a radioactive isotope used for diagnostic or therapeutic purposes to be administered to the patient[48] eg radiolabelled glucose analogue 18-fluorodeoxyglucose[29] (F-FDG)) which also limits the exploration/use of safer alternatives of contrast.[48] Similarly, single-photon emission computed tomography (SPECT) which offers valuable information on organ function, also utilises radiopharmaceuticals containing radioisotopes such as ^{99m}Tc.[49] While the

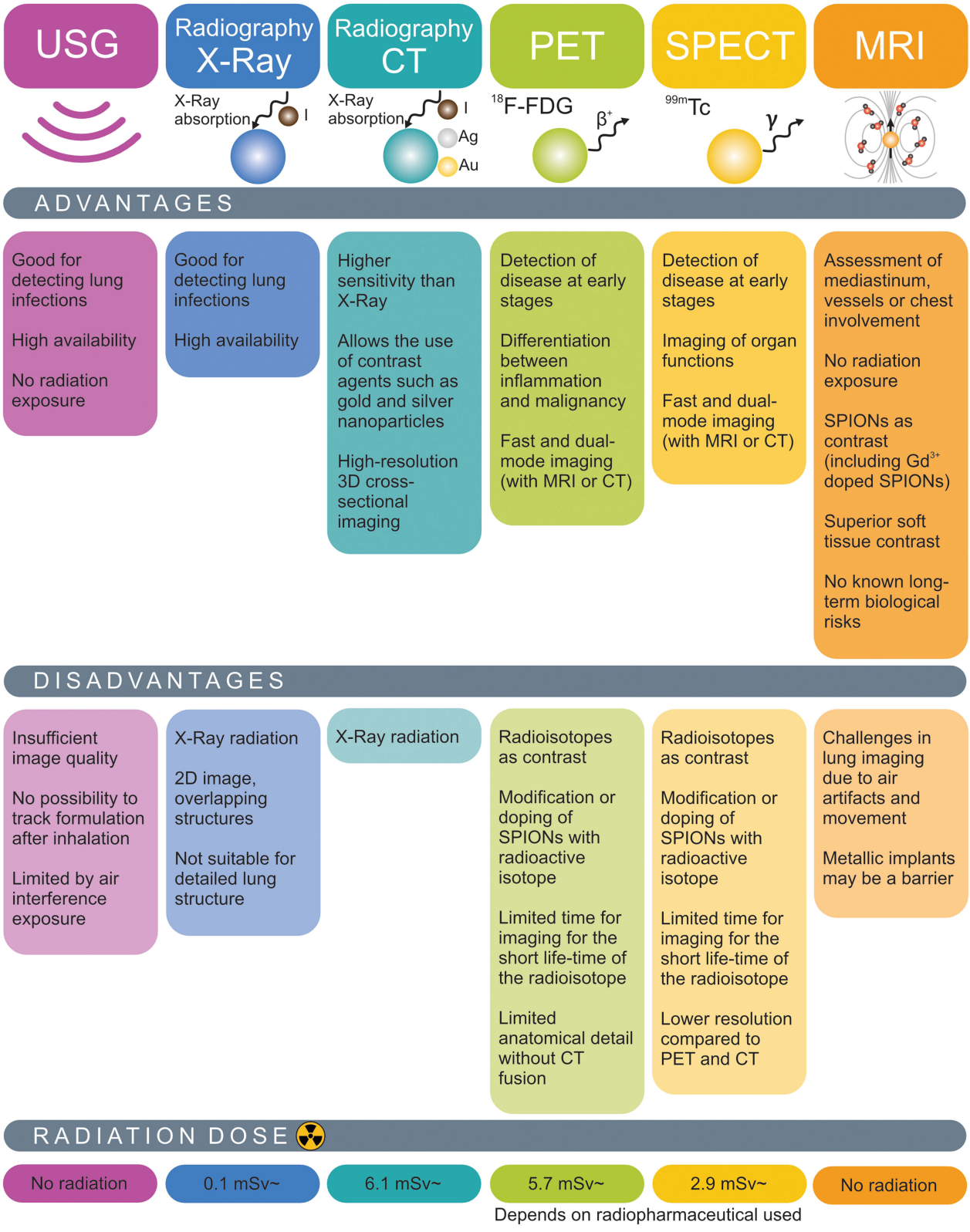


Figure 1 Comparison of available lung imaging methods about their potential use in theranostics of inhaled antimicrobial drugs.[44,55–57]

doses of radiopharmaceuticals used in both techniques are relatively low and adverse reactions are rare, a wide range of different adverse effects have been reported, including cases of anaphylaxis, bronchospasm, and respiratory failure, as well as cardiac arrhythmias and pulmonary oedema, in a few cases even leading to the death of the patient.[48,50–52]

For these reasons, MRI may become the procedure of choice for patients which require multiple examinations.[53] It significantly contributes to lowering the cumulative radiation dose and provides excellent soft tissue contrast and functional information.[54] For the above reasons MRI becomes feasible in a theranostic approach, where repeated imaging of the lungs is required.

MRI as the Method of Choice and Its Contrast Agents

The advantage of MRI is its high sensitivity to soft tissues and the flexibility of selecting the contrast mechanism of MRI images depending on the purpose of the medical examination. Contrast agents are used to increase imaging sensitivity delivering more precise images. Usually, MRI imaging protocols can be classified into molecular diffusion-weighted imaging, proton density, spin-lattice longitudinal (T_1) or spin-spin transverse (T_2) relaxation times.[58] The mechanism of action of MRI contrast agents involves altering magnetisation relaxation in the T_1 and T_2 planes. T_1 contrast agents produce bright contrast in conventional images, by shortening the T_1 relaxation time. These agents usually include paramagnetic molecules which are chelating metals or organic radicals.[59] In turn, T_2 contrast agents provide dark contrast in the T_2 image and are usually composed of superparamagnetic nanoparticles (eg Fe_3O_4, FeC_x).[60]

Choosing the contrast inducing agent for this approach poses a challenge, as both its potential toxicity and clearance mechanism must be carefully considered. Currently, most MRI contrast agents are Gadolinium Based Contrast Agents (GBCAs) which consist of the paramagnetic gadolinium ion (Gd^{3+}) complexed with a chelating ligand, with GBCAs being administered in 35% of all MRI examinations.[61,62] The chelates purpose is to remain bound to the gadolinium ion until it is excreted, preventing its deposition in soft tissues. Unfortunately, there are various factors that negatively affect the binding of the Gd^{3+} ion, including chelating ligands exchange through the transmetalation process that causes the release of $Gd^{3+,}$ not only affecting the imaging effectiveness but also leading to buildup in tissues, resulting in safety concerns. Subsequently, GBCAs have been identified as the key factor in the development of nephrogenic systemic fibrosis (NSF), and the FDA mandated a black box warning on all GBCAs.[62] While NSF mainly occurs in patients with significant renal disease, safer alternatives for traditional GBCAs are sought for. Additional drawbacks of clinically used Gd^{3+} chelates are the short circulation time in the body and the relatively low efficiency of proton relaxation, necessitating the use of high doses for effective imaging.[63] A safer alternative to GBCAs are SPIONs, which are functioning in clinical practice.

While outside the scope of this paper, it is worth mentioning that recent research on nanodiamonds (NDs) showcases their potential for diverse applications due to their biocompatibility, non-toxicity, and versatile functionalization.[64] Most importantly, as reported by Lazovic et al, the occurrence of paramagnetic centres within the diamagnetic nanoparticle presents the unique property of NDs, leading to efficient T_1-signal enhancement without a significant reduction in transverse relaxation time T_2 due to much lower magnetisation of NDs. The sparse paramagnetic centres contribute to low transverse over longitudinal relaxivity (r_2/r_1) ratio, making ND particles suitable as a T_1-contrast agent in MRI.[65] Moore et al[66] reports that the administration of NDs to rats and non-human primates showed no apparent adverse effects, even with multidose subacute and chronic exposure, indicating that NDs are well-tolerated. Furthermore, while NDs and other nanoparticles tend to accumulate in the liver, they did not induce any apparent systemic inflammation, liver damage or impaired function. Pilot studies show particle clearance from blood indicating 50% clearance 33 min following the end of particle infusion, as well as proving urine excretion of NDs through urine analysis with a Transmission Electron Microscope (TEM) or assessing ND urine content.[67–69] However, the exact mechanisms of ND accumulation/distribution/excretion have not been thoroughly explored. Nevertheless, NDs are a high-potential alternative to current T_1 signal enhancing contrast agents such as GBCAs.

SPIONs as Contrast Agents

SPIONs are mainly based on the Fe_3O_4 and/or Fe_2O_3 sized below 15 nm offer superparamagnetic behaviour and biocompatibility which make them usable for many different biomedical and bioengineering applications, including use as MRI contrast agent. To meet the MRI requirements, a contrast agent must enhance image contrast by reducing T_1, leading to bright-weighted images (positive contrast agent) or T_2 resulting in dark-weighted images (negative contrast agent). SPIONs, due to their small size, have a very low magnetic moment and a long T_2 and are mostly used as T_2

contrast agents.[8] However, depending on their size and shape, SPIONs can act as dual-mode contrast agents, functioning both as T_1 (positive) and T_2 (negative) agents[70] and enhancing MRI imaging, including MRI angiography.[71]

Unlike GBCAs, which are widely used in clinical practice as T_1 contrast agents, SPIONs can be easily doped with various metals that change their physicochemical characteristics including magnetic properties and functionalised with organic molecules on their surface.[72,73] Compared to pure iron oxide, lanthanide ions (eg Gd^{3+}) doped iron oxide nanoparticles as MRI contrast agents have advantages since lanthanide ions have larger effective magnetic moment (7.9 μ_B for Gd^{3+} and 5.9 μ_B for Fe^{3+}) and a shorter relaxation time, making them promising candidates for both T_1 and T_2 MRI contrast agents. These modifications enhance imaging effectiveness while maintaining biocompatibility, thereby broadening their potential clinical applications, such as magnetic hyperthermia.[74] SPIONs doped with Gd^{3+} offer a promising alternative to traditional GBCAs demonstrating superior MRI performance at clinical fields (1.5 or 3 T) compared to conventional GBCAs.[75,76] Pre-clinical studies also highlight the potential for dual mode MRI-PET imaging using iron oxide-doped with Gd^{3+} and labelled with the[77] Ga radioisotope, without the need for chelators.[78]

Recent clinical applications of bare SPIONs in MRI include inflammation imaging, vascular imaging, cell tracking, lymph node imaging, and tumor imaging.[79,80] Contemporary clinical trials involve Phase I/II studies to assess the efficacy and safety of SPIONs, primarily as imaging agents.[77,81,82] The FDA has approved iron oxide nanoparticle-based contrast agents Resovist® (with a particle size of about 60 nm) and Feridex® (with a particle size 120–180 nm) as commercial MRI T_2 contrast agents for clinical diagnostic use.[83] Moreover, Ferumoxytol (Feraheme®) which is a ultrasmall superparamagnetic iron oxide (particle size 17–31 nm)[10] approved by the FDA for iron replacement therapy is widely used off-label as an MRI T_1 and T_2 contrast by clinicians and researchers.[84] Wei et al[85] have shown that small SPIONs (consisting of ~3 nm inorganic cores and ~1 nm ultrathin hydrophilic shells) can be created with limited T_2 activity, making them potential T_1 contrast agents. The agents developed are qualitatively different from existing T_2 contrast SPIONs and closely approach the performance characteristics of gadolinium-based contrast agents.

Biological Considerations

A wide range of applications of SPIONs in biomedicine undeniably require a deeper understanding of their impact on cellular metabolism and safety. Recent studies emphasise the potential of magnetic nanoparticles as a therapeutic tool in cancer treatment, where their properties facilitate the targeted destruction of cancer cells.[86] SPIONs have the capacity to produce highly reactive oxygen species (ROS), either through direct interaction with iron oxide or after exposure to UV radiation, thereby contributing to the destructive effects on tumour tissue.[87] Furthermore, SPIONs can host photosensitisers to generate heat under NIR radiation, leading to cancer cell destruction through various mechanisms, including disruption of the cell membrane, DNA damage, and protein denaturation. Iron oxide nanoparticles can generate heat when exposed to an alternating magnetic field (AMF), which was first proposed by Gilchrist et al in 1957 as a method to treat lymphoma tumours in dogs.[88] The first clinical trial on magnetic hyperthermia, also known as magnetic fluid hyperthermia (MFH), took place in 2006 at Charité Hospital in Berlin, Germany. This trial focused on treating prostate carcinoma using aminosilane-coated SPIONs, where the colloidal suspension was injected transperineally.[89]

On the other hand, the ability to track and quantify SPION tracers, particularly in drug inhaled delivery applications or image-guided therapies, represents a significant advancement in lung imaging quality and therapy. However, the successful implementation of this technology requires addressing and mitigating the potential drawbacks and risks associated with its possible widespread distribution in the human body.[90]

The critical considerations of inhaled particles in lung theranostics concern appropriate lung deposition, local and systemic safety, and elimination from the body. The first challenge in assessing inhalation toxicity is understanding the biological fate of nanoparticles once they enter the respiratory system (Figure 2). The size of nanoparticles plays a critical role in their behaviour once inhaled. Particles larger than 5 μm are more likely to be deposited in upper airways and are more susceptible to rapid pulmonary clearance. Particles smaller than 5 μm are particularly effective at reaching the deep lungs. However, these smaller particles can also enter the systemic circulation, raising concerns about potential unintended effects on other organs and tissues.[91] This opens the second consideration. Once particles are delivered to the lungs, they can be easily incorporated into the cells, inducing local adverse effects such as inflammatory response,

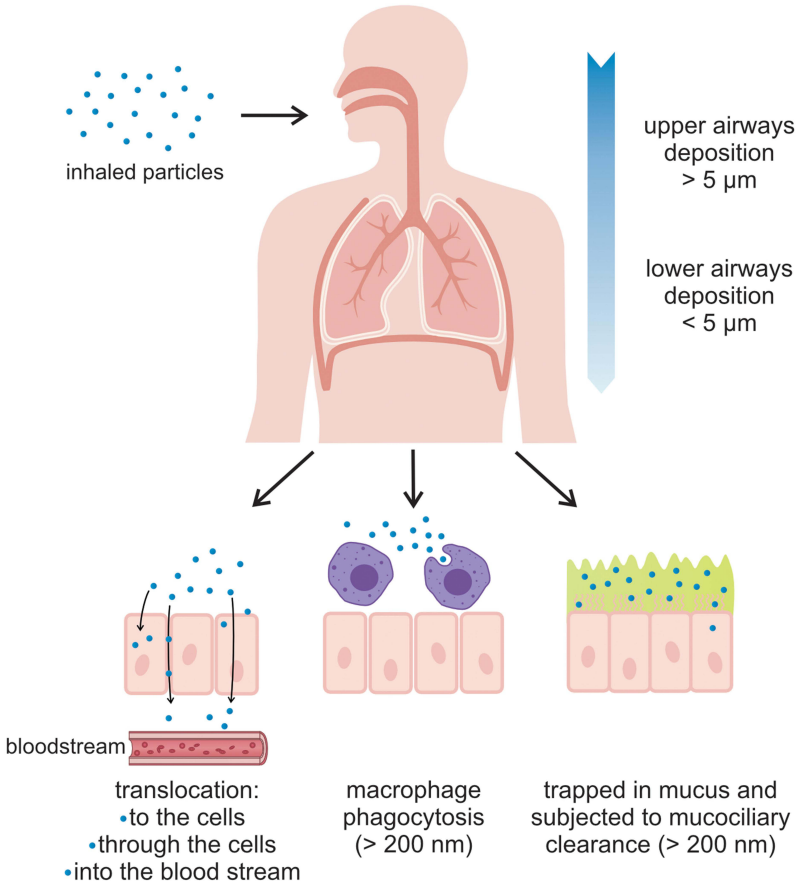


Figure 2 The biological fate of inhaled nanoparticles depends on their size. Particles larger than 5 µm are more likely to be deposited in upper airways where they are either swallowed or cleared by mucociliary action. Smaller particles can be deposited in the upper and lower airways. The mucus layer and macrophages are the main barriers eliminating larger nanoparticles. The smallest nanoparticles can avoid the clearance by macrophages and reach respiratory epithelial cells or pass through respiratory epithelia towards the systemic circulation.

oxidative stress or DNA damage; or they can be removed by alveolar macrophages or excreted through mucociliary motion which eventually moves the particles to the oropharynx, where they become swallowed.[90]

Tay et al[92] used a combination of the drug doxorubicin hydrochloride and SPIONs as an imaging agent for inhaled therapeutics in rat lungs. To monitor mucociliary clearance of inhaled aerosols, Magnetic Particle Imaging (MPI) scans were conducted at intervals. The aerosols, containing SPIONs with a hydrodynamic diameter of 130 nm, were tracked over a period of 13 days. The results revealed that the lung signal gradually faded over time. Initially, the signal was most prominent in the trachea and in the gastrointestinal tract, indicating that the particles were mainly excreted from the body in faeces. In conclusion, to reach the epithelial layer, the delivered particles must avoid mucociliary clearance and, in the deeper lungs, must also evade pulmonary surfactants and alveolar macrophages.

In vitro research on Fe_3O_4 toxicity indicates none or negligible effect on cell viability at lower doses (<200 µg/mL), suggesting that the toxicity of iron nanomaterials depends on concentration and chemical composition.[93,94] The Resovist (ferucarbotran) is a liver-specific MRI contrast agent composed of magnetite (Fe_3O_4) and maghemite (Fe_2O_3), coated with carboxydextran in a 1:1 ratio of iron. It efficiently accumulates primarily in the liver, with approximately 80% of the injected dose taken up within minutes after administration. Human tissues contain iron in the forms of hemosiderin, ferritin, and transferrin. The normal liver contains about 0.2 mg of iron per gram of wet weight, with total iron stores in the body amounting to approximately 3.5 g. For clinical MRI imaging with ferucarbotran, the required amount of iron oxide is typically between 0.2 and 0.8 mg of iron per kilogram of body weight. For a 75-kg individual, this would equate to approximately 15–60 mg of iron, which is relatively small compared to the body's normal iron stores.[95] The previously

mentioned ferumoxytol (Feraheme®) composed of SPIONs, at a dose of 2 x 510 mg injected intravenously (IV), displayed a similar overall safety profile to other IV iron products. Severe hypersensitivity reactions, hypotension, increased risk for infections and risk iron deposit are known risks for all IV iron products and were reported at low rates according to FDA documentation on Feraheme®.[10]

SPIONs can be coated with citric acid, a non-toxic, biodegradable organic compound that forms a stable shell and prevents oxidation and aggregation. Such a combination has already been tested as a possible contrast candidate in MRI.[96] Gadolinium-doped Carbon dots (Gd@CDs), designed for the treatment of triple-negative breast cancer (TNBC), demonstrated good in vitro blood compatibility and had minimal impact on the viability of human embryonic *293T* kidney cells, even at a concentration of 1 mg/mL after 24 h of incubation.[97] While GBCAs have been extensively characterised for their toxicity in humans and animals,[98] the use of gadolinium to dope iron oxide nanoparticles (Gd-IONPs) still requires further investigation regarding their biocompatibility and potential toxicity.

Regulatory Concerns

Nanotechnology holds promise for overcoming antimicrobial colony forming challenges through micron-sized dry powder formulations that exert microbicidal effects and treat lung infections. However, achieving controlled release remains a challenge for micron-sized drug particles.[34] While numerous factors must be considered when designing inhalation formulations, such as inter-individual variability, disease-induced pathological changes, and pathogen-specific defence mechanisms, the primary obstacle to their approval lies in the design and execution of clinical trials.

The growing interest in developing inhaled antifungal agents is exemplified by a workshop organized by the FDA in 2020, which addressed the existing barriers to their development.[99] Additionally, the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD pathway), enacted in 2016, aims to facilitate the development of drugs intended to treat serious or life-threatening infections.[100] Such programs may follow a streamlined approach, involving smaller, shorter, or fewer clinical trials. Patients with pulmonary fungal diseases represent a heterogeneous population characterized by impaired immunity and diverse underlying conditions. This heterogeneity, along with varying disease severity, poses challenges in designing clinical trials and selecting appropriate endpoints for inhaled antifungals.[101] Eligibility criteria, including the use of prohibited medications (eg, long-term oral corticosteroids and immunomodulators commonly administered to this population), complicate patient recruitment efforts.

Determining appropriate endpoints is challenging due to the difficulty in achieving and/or measuring adequate drug concentrations in the lungs and other sites of infection. As a result, several primary endpoints have been adopted in studies evaluating lung efficacy in fungal asthma, including assessments of lung function (eg, walking distance), patient-reported outcomes related to quality of life, and clinical outcomes such as the frequency of exacerbations. Owing to the lack of clinically validated instruments, many randomized controlled trials have employed composite endpoints that integrate pulmonary function, radiological findings, and reductions in biomarker levels (eg, serum total IgE and sputum eosinophils). However, diverse treatment-response patterns observed across patient subgroups make it difficult to establish a universal "one-size-fits-all" endpoint for these heterogeneous populations.[101] Therefore, on the one hand defining the target population and outcome measures for patients with active disease is important, but on the other hand too narrow patient qualification factors make it impossible to select a group for clinical trials. During the workshops, no clear solutions were found to address the uncertainties related to patient eligibility, clinical trial endpoints, duration of therapy, and resistant pathogens.

The need to develop robust animal models that more accurately reflect specific disease entities and affected patient populations was also emphasized, as such models are essential for optimizing and streamlining clinical trial designs. Animal models can support the identification of relevant pharmacokinetic–pharmacodynamic (PK–PD) targets in the development of inhaled therapeutics. Furthermore, nonclinical studies, including both in vitro assays and animal infection models, provide valuable insights into the activity of antimicrobial agents administered either as monotherapies or in combination with other drugs.[101] Despite these advances, there are currently no regulatory requirements or standardized methodologies for dissolution testing of inhaled products, although such testing is essential for tailoring the release characteristics of inhaled particles and ensuring consistent quality control throughout drug development.[102]

These issues are the cause of difficulties in approving inhaled antimicrobial drugs. To our best knowledge, there are only four dry powder drug formulations that are inhaled and are currently approved as medicinal products with antibacterial or antiviral indications (Table 1). Furthermore, there are only a few cases of inhaled antifungals that made it into clinical trials, including ZP-059 (Voriconazole dry powder for inhalation from Zambon SpA) and PUR 1900 (Itraconazole dry powder for inhalation from Pulmatrix), which are both still in clinical trials. Phase II clinical trials were attempted for PUR1900, but were terminated twice, once due to the COVID-19 pandemic[103] and once due to low enrollment;[104] according to the companies website, the company is searching for partnership to advance to Phase II.[105] There was also development of another dry powder for inhalation formulation (TFF VORI) by TFF Pharmaceuticals, but the development ended with the completion of Phase I clinical trials, as the company has been liquidated and no longer exists.[106] The fact that PUR1900 is currently on hold before Phase II, and TFF VORI was terminated before phase II underlines the challenges around defining patient inclusion and exclusion criteria and defining primary endpoints when designing the trial for an inhaled dry-powder formulation. On the contrary, the off-label use of many pharmaceuticals as described in Alves et al[9] and as seen in the clinical trials with off-label nebulised liposomal amphotericin B,[18,19] which were sponsored by hospitals rather than pharmaceutical companies, demonstrates the high clinical demand for inhaled formulations which is unfulfilled by the pharmaceutical industry. This is also evidenced by both EMA and FDA granting orphan drug status to Colistin Cyclops®, which is an antibacterial drug indicated in Cystic Fibrosis that is still under development.

It is crucial to highlight that the currently approved TOBI® PODHALER®, which is one of the few dry powder formulations approved for inhalation, when assessed in the clinical trials, employed radiolabeled tobramycin. All dosed subjects underwent scintigraphic assessments, to allow for lung deposition of delivered tobramycin to be determined.[107]

In our opinion, this emphasises the necessity of being able to image the drug deposited in the lungs after administration, or theranostics, for an inhaled drug formulation to be successfully approved.

Inhaled Contrast Agents and Image Analysis

In vivo Animal Studies

Choosing the right imaging method is an important aspect, however for a theranostic approach to be successful, the obtained images must be adequate for image analysis. We present some examples of successful image analysis, where lung drug deposition was determined in in vivo animal studies.

In a pilot study by Redman et al[108] the authors measured lung deposition of cromoglycate acid loaded with SPIONs in New Zealand White Rabbits using MR. Demonstrating the possibility of administering contrast agent via nebulisation to animals, but more importantly the possibility of analysing the resulting MR images and determination of iron concentrations in the animal lung.

This is also shown in the work by Oakes et al[109] where the authors administered superparamagnetic iron oxide (SPIO) particles and measured their deposition in the lungs of healthy rats and rats treated with elastase using MRI. The authors were able to measure whole lung particle deposition and deposition in each lobe. This work also represented a continuation of previous attempts to characterise the three-dimensional regional distribution of deposited SPIO particles in rat lungs[110] and an improvement of several previous animal MRI studies that reported lung deposition.[111,112]

An innovative approach to assessing the suitability of the Fe-MIL-101-NH_2 metal-organic framework (MOF) as a theranostic carrier of an antituberculosis drug in terms of its functionality was shown in our previous work.[40] Different concentrations of MOF suspensions in water were prepared and utilised to hydrate sponge phantoms which were made to resemble lung structure, and were then imaged using MR. Qualitative and quantitative analysis of MR volume images of sponge phantoms was done with the use of Fiji distribution of ImageJ version 1.44 and the dependence of relative maximum histogram value on MOF concentration in the sponge was determined.[113,114] Thanks to this, we were able to determine that the most probable inhalable therapeutic Isoniazid (INH) concentration, which corresponds to 50% of the INH oral dose, would assure excellent contrast. These contrast possibilities were consequently confirmed on an extracted rat respiratory tract.

Future Steps

While the discussed studies prove the possibility of using MR imaging to carry out image analysis and to determine inhaled contrast agent concentrations in animals; certain aspects of the human lung MRI must be overcome. Human lung MRI may be perceived as challenging due to image noise caused by pulmonary ventilation and heartbeat,[115,116] which is the main differentiator between human and animal lung MRI, as MRI of an animal's lung is usually done after the animal has been sacrificed or sedated.

While this noise may hamper image analysis, specific imaging techniques, MRI sequences and tools, such as breath hold acquisitions or Multivane-XD software have been developed to eliminate as much of this noise and enable meaningful image evaluation.[43,117] Reassuringly, MR images of the lung have already been assessed for pulmonary abnormalities such as pulmonary infiltration or lesions.[118,119] Other approaches to improving image quality are also investigated, such as the use of hyperpolarised gases ^{3}He and ^{57}Xe or pure oxygen for inhalation.[120,121] While these methods provide impressive contrast of the airways and provide substantial feedback on things like ventilation defects or mucus-filled airways, tracing of inhaled drugs is impossible with the use of such gases.

SPIONs have not been administered to humans via the pulmonary tract yet, however we believe that the use of SPIONs as a contrast agent incorporated into the drug formulation will allow for a theranostic application, allowing for the determination of lung deposition of the drug via the signal emitted, which is supported by the already mentioned pilot studies in animals.[108,109]

It is worth to note that the estimation of total iron body content via MR imaging of the liver and measurement of the liver iron concentration (LIC) is a standard clinical practice,[122,123] as LIC is linearly related to total body iron stores.[124,125] The FDA already approved tests such as FerriScan® (Resonance Health, Australia) for the estimation of LIC, which are also reproducible with the use of in-house analysis methods such as parametric MRI software.[126,127]

We further hypothesise that if the estimation of LIC via MRI is possible and a standard clinical practice, and the lung deposition of inhaled SPIONs in animals has been successfully measured, then the estimation of SPION concentration in a patient's lung, as well as the complementary estimation of drug deposited, should also be possible after a theranostic formulation has been administered. Figure 3. Contains a graphical summary of our proposed theranostic treatment.

Concluding Remarks

Theranostics, which has focused on cancer treatment for decades, can now play a new role in inhaled antimicrobial drug therapy. An alarming FDA report[101] highlights the urgent need for the development of inhaled therapies, particularly for fungal infections. This disease primarily affects individuals with weakened immune systems, who often have multiple other health conditions and take corticosteroids and immunomodulators (drugs that typically disqualify patients from participating in clinical trials), creating significant challenges in patient qualification. A similar issue arises with pneumonia and pulmonary tuberculosis. In all these cases, systemic treatment does not ensure therapeutic drug levels in the lungs and contributes to the development of antimicrobial resistance, which is already alarmingly high. The clinical practice of administering intravenous drugs via off-label nebulisation further underscores the urgent need for the development of inhaled antimicrobial therapies.

The imaging method used in theranostics of antimicrobial drugs must be safe for the patient and allow for repeated imaging to determine the appropriate dosage. MRI is the procedure of choice as it enables contrast agent tracking, provides excellent soft tissue contrast, and avoids radiation exposure, with no known long-term biological risks. The ideal MRI contrast is T_1 positive (brightening the image), requiring a low r_2/r_1 ratio. However, traditional gadolinium-based contrast agents (GBCAs), which meet this criterion, have raised safety concerns, leading to black box warnings on all GBCAs. Safer alternatives are essential, as using such controversial agents would contradict the goal of selecting MRI as a non-invasive imaging technique.

We explore SPIONs as a safer alternative for enhancing MRI contrast, useful for tracking drug deposition. In vitro studies have shown no toxic effects of SPIONs on experimental cell line models, particularly when administered at low doses (10–200 μg/mL).[91] The murine PBPK model confirmed that liver and spleen are the primary organs responsible for clearing SPIONs from the bloodstream through macrophages.[128] However, the safety of pulmonary delivery differs from

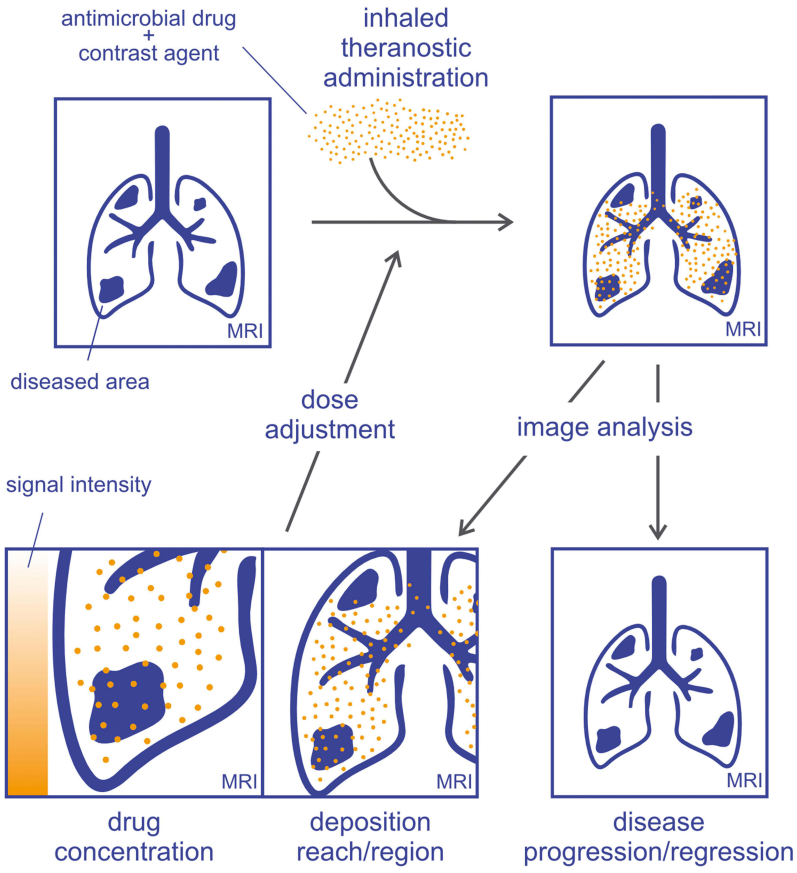


Figure 3 Hypothesised theranostic treatment summary. Patient with invasive microbial pulmonary disease undergoes MRI before treatment initiation to assess pathophysiology. A theranostic enabling formulation containing antimicrobial drug and contrast agent is administered. The patient undergoes MRI once again after administration. Image analysis of before and after formulation administration images allows for the determination of lung deposition of the formulation thanks to the signal produced by the contrast agent. Allowing assessment whether formulation has reached the diseased areas. Measurement of signal intensity allows for estimation of drug concentration, allowing for informed dose adjustment.

intravenous administration. Inhaled particles are mostly cleared by the mucociliary escalator, leading to eventual excretion through faeces.[92] Modifying SPIONs' surface can improve tissue interaction, prevent aggregation, and reduce toxicity. Doping SPIONs with Gd^{3+} enhances contrast without compromising safety. FDA approved SPION based drugs used in clinical practice further demonstrate their safety.[129] Developing robust preclinical models is key for advancing safety assessment and clinical trial design.

The use of SPIONs as a contrast agent in inhaled theranostic enables the estimation of drug concentration in the lungs, and subsequent dose adjustment. Given the limitations of inhaled therapy, tailoring treatment to individual patients appears to be the most viable solution at this stage. This is especially true considering that in clinical trials of approved antibiotics dry powder for inhalation to assess the effectiveness, imaging methods were used to evaluate formulation deposition (radioisotope-labelled formulations for trial purposes only). Moreover, the lack of a unanimous consensus among FDA experts regarding patient qualification, research protocols, and endpoint selection suggests that this issue cannot be addressed within the traditional "one-size-fits-all" paradigm. A shift toward personalised treatment, even in clinical trials, is essential.

Abbreviations

SPIONs, superparamagnetic iron oxide nanoparticles; MRI, magnetic resonance imaging; FDA, food and drug administration; EMA, European medicines agency; CT, computed tomography; PET, positron emission tomography; SPECT, single photon emission computed tomography; USG, ultrasonography; ICAs, iodinated contrast agents; GBCAs,

gadolinium-based contrast agents; NSF, nephrogenic systemic fibrosis; NDs, nanodiamonds; IV, intravenously; TNBC, triple-negative breast cancer; MOF, metal-organic framework; INH, isoniazid; PK–PD, pharmacokinetics–pharmacodynamics; LIC, liver iron concentration; LPAD, limited population pathway for antibacterial and antifungal drugs; MPI, magnetic particle imaging; AMF, alternating magnetic field; MFH, magnetic fluid hyperthermia.

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Disclosure

The authors declare that they have no competing interests.

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