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"Molecular Imaging in Nanotechnology and Theranostics" (MINT) Interest Group

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Abstract

The "Molecular Imaging in Nanotechnology and Theranostics" (MINT) Interest Group of the World Molecular Imaging Society (WMIS) was founded in 2015 and was officially inaugurated during the 2016 World Molecular Imaging Conference (WMIC). The MINT interest group was created in response to the exponential growth of the fields of Nanotechnology and Theranostics in recent years, and the resulting need to provide a more organized and focused forum on these topics at the WMIS and the WMIC. The overarching goal of MINT is to bring together the many scientists who work on molecular imaging approaches using nanotechnology, and those that work on theranostic agents. MINT therefore represents scientists, labs, and institutes that are very diverse in their scientific backgrounds and areas of expertise, reflecting the wide array of materials and approaches that drive these fields. In this short review, we attempt to provide a condensed overview over some of the key areas covered by MINT. Given the breadth of the fields and the given space constraints, we have limited the coverage to the realm of nano-constructs, although theranostics is certainly not limited to this domain. We will also focus only on the most recent developments of the last 3-5 years, in order to provide the reader with an intuition of what is "in the pipeline" and has potential for clinical translation in the near future.

Introduction

With unique properties endowed by their size, modular structure, and functionalization abilities, biomedical nanoparticles are being unremittingly developed and used in biomedicine. In medical imaging, they serve as contrast agents—detectable with multiple modalities simultaneously—and give rise to new techniques for the ever-richer acquisition of molecular information. Some are already employed clinically as therapeutics, or delivery vehicles for pharmaceuticals, since they serve to reduce systemic side effects [1]. Targeted

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Conflicts of Interest: M.F.K. is an inventor on several pending patents related to Raman nanoparticles, Raman detection and theranostic hardware, as well as radiolabeling of silica particles, and is a co-founder of RIO Imaging, Inc., a startup company that has licensed several of these patents.

drug- and gene-delivery strategies and stimuli-responsive nanoparticle therapies are in clinical trials [2]. Modular and versatile, unifying imaging with therapy, nanoparticles are becoming true theranostic agents.

Compared to small molecules, nanoparticles feature notable advantages as theranostic agents, summarized in Figure 1: (1) their modular structure and surface modifications enable multiple functionalities (decreased immunogenicity, targeting, multimodal imaging, therapy, and controlled pharmacokinetics); (2) specific tissues can be targeted passively (e.g. reticuloendothelial system or kidneys), as can many tumors through the 'enhanced permeability and retention' (EPR) effect; (3) Nanoparticles can respond to their microenvironment or to external stimuli to provide therapy and contrast only where needed [3]; and (4) different types of therapy can be elicited by the Nanoparticles. These features render Nanoparticles as peerless imaging agents using traditional medical imaging, and enable the development of new modalities and theranostic applications. Many strategies have been reported for creating biomedical imaging nanoparticles using a variety of materials, and this has generated a virtual cornucopia of easily obtainable nanoparticle agents, schematically depicted in Figure 2. A non-exhaustive selection of references, tabulated by material, imaging modality, and therapy is presented in Table 1.

Imaging

Among the first nanoparticle structures to allow molecular imaging were superparamagnetic iron oxide nanoparticles (SPIONs), used for contrast generation with magnetic resonance imaging (**MRI**) [4-5]. The current emphasis lies on their clinical translation, especially given the renaissance spurred by Ferumoxytol, which is now FDA-approved for systemic injection as an iron replacement therapy (trade name Feraheme). As a member of the family of ultrasmall superparamagnetic iron oxide nanoparticles (USPIOs), ferumoxytol causes regional T1 and T2* shortening in vivo, leading to signal enhancement or loss on conventional MR pulse sequences [6]. Ferumoxytol has shown promise in diverse areas such as noninvasive identification of Type 1 Diabetes [7], determining the severity of neurological diseases [8], imaging of tumor-associated macrophages (TAMs) [9], cell tracking [10], or whole-body cancer staging [11]. A recent and very exciting discovery was the finding that ferumoxytol may have an intrinsic, anti-cancer therapeutic effect [12]: intravenous ferumoxytol administration was shown to prevent metastases to the liver. This phenomenon is thought to be due to pro-inflammatory macrophage (M1) polarization in tumor tissues [12]. Such discoveries bear the hope that other nanoparticle agents may also harbor such unexpected theranostic effects.

Positron emission tomography (**PET**) and single-photon emission computed tomography (**SPECT**) are noninvasive imaging modalities frequently used in clinical settings for oncology, neuroimaging, cardiology, etc. [13-14] using radioactive nuclides conjugated to small molecules (e.g. ^{18}F-fluorodeoxyglucose (^{18}F-FDG)) or antibodies. Recently, nanoparticles labeled with radiotracers were found to be very promising – particularly in cancer imaging – in preclinical studies because of three major advantages: (1) the EPR effect; (2) high surface-to-volume ratio of the nanoparticles allowing high density radiolabeling either using chelators (such as DOTA), chelator-free strategies, or intrinsic

labeling during synthesis [15]; and (3) complementary multimodal imaging. Many different radionuclide-nanoparticle combinations have been reported; but smaller, rapidly clearable nanoparticles with fast decaying radiolabels are ideal for potential clinical translation. Nanoparticles with ^{64}Cu ($t_{1/2}$ = 12.7 hours) were shown to allow in vivo imaging up to 48 hours [16-21]. Ultra-small chelator-free renally clearable ^{64}Cu-labeled Cu nanoclusters were reported for imaging in orthotopic lung cancer mouse models [22]. In another study, ^{64}Cu based liposomes were used to assess the EPR effect in canine cancer models, suggesting high intertumoral heterogeneity of EPR-based uptake [23]. Other radioisotope-nanoparticle combinations have been employed for different imaging purposes, including ^{68}Ga ($t_{1/2}$ = 68 minutes), ^{89}Zr ($t_{1/2}$ = 3.3 days), ^{111}In ($t_{1/2}$ = 2.8 days), ^{198}Au ($t_{1/2}$ = 2.69 days) [24-30]. Recently, ^{89}Zr was used to label soft, polymeric and lipoprotein nanoparticles for imaging of TAMs [31-33]. Important steps towards clinical translation of PET nanoparticles are being carried out using “Cornell dots” (C-dots) labeled with ^{124}I ($t_{1/2}$ = 4.18 days), showing excellent localization and no toxicity in metastatic melanoma patients [34-35].

Fluorescent nanoparticles (**FNPs**), with intrinsic fluorescence or loaded with fluorescent dyes, are being investigated as imaging agents due to their advantages over small molecule dyes, namely: improved specificity (by active or passive targeting [36-37]), increased circulation time (by evading immune detection and renal clearance), and smart activation (by pH dependency or enzymatic activity) as well as increased signal intensity [36, 38]. FNPs have been reportedly used for sentinel lymph node (SLN) and solid tumor detection, image-guided tumor surgery with real-time feedback, and monitoring of drug delivery [36, 39]. Also fluorescent, quantum dots (q-dots) and gold nanoparticles (passivated with polyethylene glycol (PEG) or silica) [36, 39] can be combined with complementary imaging agents like gadolinium [39-40], organic dyes [39], polymeric p-dots [39, 41], or fluorescent proteins [39, 42-43]. Q-dots are of particular interest due to their broad absorption and size-tunable emission spectra, making them suitable for multiplexing [37, 44] and less susceptible to photobleaching compared to broadly used organic dyes [37].

A new generation of fluorogens has been introduced to bioimaging with FNPs, exhibiting aggregation-induced emission (AIE) [45]. AIE overcomes aggregation-induced quenching and allows for higher concentration of fluorogens on the NP surface while also reducing photobleaching [45]. However, due to the fluorogens' broad emission spectra, it is less suitable for multiplexing, instigating some groups to work on narrowing the emission spectra via Förster resonance energy transfer [46]. Although fluorescence imaging is complicated by high false-positive rates [47], improvements in specificity have been reported, leading to higher levels of complete tumor resection [48].

Raman imaging – a spectroscopic optical imaging technique – with surface enhanced (resonance) Raman scattering nanoparticles (**SE(R)RS NPs)** shows much potential for in vivo imaging of cancer [49]. Unlike fluorescent agents, SERS NPs do not suffer from significant background from endogenous molecules or photobleaching [50]. In fact, the endogenous Raman signals can be used by the detection hardware to generate surface topology on which the specific signals can be mapped without interference [51]. With their low detection threshold and high signal specificity SERRS NPs were shown to delineate tumors – and even premalignant lesions – passively through the EPR effect [52].

Nanoparticle sequestration by the RES allows for imaging of SLNs [53] and tumors in the liver and spleen [54]. When combined with active targeting via antibodies, peptides, or aptamers SERRS NPs were reported to delineate tumors preoperatively and intraoperatively [55], as well as detecting microscopic tumors and metastatic foci in glioblastoma, ovarian cancer, and lung metastases [56-59, 60]. Given their potential significance in tumor imaging and non-toxic composition, the timely translation of SERS NPs into the clinic could represent a fundamental improvement in patient morbidity and mortality.

Nanoparticles can be engineered to allow “hybrid” imaging methods, where excitation and detection occur through distinct physical processes. For example, in photoacoustic imaging (**PAI**), pulses of light excite the contrast agent, which in turn produces a mechanical response, detected as ultrasound [61]. Images are obtained noninvasively, deeper within tissues and with higher spatial resolution compared to purely optical imaging techniques. Nanoparticles based on plasmonic [62-67], polymeric [68-73], and other materials [74-88] have all shown great potential in preclinical studies, combining photoacoustic detection with photothermal and photodynamic therapies (PTT and PDT). However, nanoparticles based on iron oxide [89-91] or silica [92] have a higher likelihood for clinical translation as similar materials are already approved for use in humans. Magnetically actuated photoacoustically-active nanoparticles are of particular interest, as they allow more specific detection through magnetic actuation [93].

Some charged particles produced by radionuclide decay emit visible light, referred to as Cerenkov luminescence (**CL**) [94], already demonstrated for cancer imaging in humans using ^{18}F-FDG [95]. Nanoparticle-based agents bring great new potential to this emerging modality, allowing for more specific imaging [96-98] and therapy [99-101], while active or passive targeting [102] can map receptors [103] or enzymes [104] of interest. As nanoparticles for PET imaging are translated to the clinic, CL will undoubtedly follow suit, providing additional, complementary information to the benefit of the patient.

Therapy

Nanoparticles have great potential as therapeutic agents, delivering drugs, genes, or other forms of therapy, with many examples of clinical success [1]. In the paradigm set by Doxil, nanoparticles can be engineered to encapsulate pharmaceuticals (such as doxorubicin (DOX)) and release them at targeted sites, reducing systemic toxicity and improving pharmacokinetic profiles. In a newer scheme, DOX-conjugated poly(lactic-co-glycolic acid) (PLGA) was loaded into an injectable nanoparticle generator spontaneously releasing nanoparticles upon pH stimulation, which are later cleaved into DOX within the cell to avoid drug efflux pumps, showing enhanced efficacy in metastatic breast cancer models over free DOX [105]. Ultrasmall ^{64}Cu-PEG-melanin nanoparticles loaded with FDA-approved multikinase inhibitor sorafenib provide PET-PAI image-guided chemotherapy in liver xenograft models [106]. Recently, siRNA-loaded nanoparticles were employed in various settings, such as gene delivery into lung cancer cells – but not normal cells – without targeting ligands [107]; transdermal application for suppressing EGFR expression and downstream ERK signaling in mice and humans with no clinical or histological

toxicity [108]; and increasing progression-free survival in murine acute kidney injury models and nonhuman primates [109].

Photothermal therapy (**PTT**) employs heat to destroy cancer cells and nanomedicine can substantially facilitate this process. AuroShell is the first-demonstrated exogenous vis-NIR light absorbing nanoparticle for photothermal tumor ablation and optical coherence tomography (OCT) [110] and was extensively investigated in murine and canine models of various cancer types [111-113]. Pilot clinical studies are being conducted in head and neck cancer (NCT00848042), lung cancer (NCT01679470) and prostate cancer (NCT02680535). Gold nanoparticles with radiofrequency waves can also induce PTT [114-115]. For photodynamic (**PDT**) therapy, Cerenkov luminescence can activate transferrin-coated TiO_2 photosensitizer nanoparticles and mediate tumor remission by generating free radicals and immune cell infiltration [116]. NIR PDT is achievable using photosensitizing silica-coated upconversion nanoparticles for deeper tissue penetration than visible light [117]. Aminosilane-coated iron oxide (NanoTherm), significantly polarized under external magnetic fields to selectively ablate tumors by heat generation, is undergoing clinical trials in the USA [118-120]. FDA-approved SPIONs were also found to inhibit tumor growth by hyperthermia under magnetic fields at preclinical levels [121-123]. The integration of multiple energies and modalities is a unique characteristic of nanoparticles that will make them invaluable for detection and therapy in a wide variety of diseases.

Ultrasound (**US**) can promote nanoparticle accumulation and drug release in tumors through cavitation and is reported to mediate nanoparticles crossing even intact blood-brain barriers [124] — see minireview on US molecular imaging by Caskey in this issue. Nanoparticles as a sonoporation enhancer are advantageous over microbubbles (MBs) for their extravasation in capillaries and sustained activity. PEG-PDLA nanoparticles were used to overcome aqueous solubility barriers of paclitaxel under US guidance [125]. Polymer nanoparticle-stabilized MBs with embedded SPIONs provide MRI/US imaging and pulse-activated nanoparticle release [126]. Gas-generating docetaxel (DTX) and Cy5.5 dye-loaded poly(CBL-PO) nanoparticles in MBs offer fluorescence/US signal and are released at tumor sites upon ultrasound irradiation through bubble burst, with much higher contrast than clinically-used Sonovue® and Definity® and higher therapeutic effects than free DTX or without US activation [127].

Besides the aforementioned hyperthermia effects, SPIONs were recently found to intrinsically inhibit tumor growth as a potential macrophage-modulating immunotherapy [12]. Adjuvant drug labeled liposome- and lipid-based nanoparticles covalently attached to cell surface for adoptive T-cell therapy can markedly decrease tumor burden at preclinical setups [128]. PEG-PLGA nanoparticles encapsulated with indocyanine green (ICG) and TLR7 agonist R837 can generate tumor-associated antigens during PTT and its combination therapy with anti-CTLA4 antibodies can significantly inhibit metastasis in a 4T1 orthotopic model [129]. Carbon nanotube-PLGA nanocomplexes with high surface area were functionalized with T-cell stimulating antigens for delivery of IL-2 at a dose much lower than clinically used to overcome adverse reactions. These nanocomplexes generate a large number of cytotoxic T-cells and delay tumor growth in murine melanoma models [130].

PET-based nanoparticles are being perused as an alternative to traditional internal radiotherapy or brachytherapy as they allow even distribution within the tumor volume. Alpha emitters with long half-life like ^{225}Ac ($t_{1/2}$ = 10 days) are the preferred radionuclides for the formulation of nanoparticles [131-132]. However, there is concern about the radioactivity of downstream decay processes. Recently, ^{131}I ($t_{1/2}$ = 8 days), often used for the treatment of thyroid cancer, has been integrated with iron oxide nanoparticles and polymeric nanoparticles for targeted therapy of hepatocellular carcinoma in mouse models [133-134]. ^{177}Lu ($t_{1/2}$ = 6.6 days) has been utilized in lipid-calcium phosphate nanoparticles showing significant growth inhibition in subcutaneous xenograft tumor models [135]. There is also great deal of interest in using a nonradioactive module as a therapeutic partner in the formulation of PET nanoparticles. In a recent study, a ^{99m}Tc-labeled ($t_{1/2}$ = 6 hours), folic acid targeted, multiwalled CNT nanoprobe has been developed using Methotrexate as a therapeutic module showing an augmentation of the therapeutic efficacy of the drug in the presence of ^{99m}Tc [136].

Metal nanoparticles can act as radiosensitizers, enhancing the efficacy of radiotherapy, e.g. renally clearable ultrasmall gold nanoclusters with high tumor uptake [137], or polymeric nanoparticles loaded with gold nanoparticles [138]. Gold nanoparticles in glioma models boosted overall survival in mice [139], as well as in head and neck cancer models [140], while silver nanoparticles produced similar results in glioma-bearing rats [141]. Therapeutic ^{103}Pd-Au nanoseeds offer SPECT signal along with a radiotherapeutic effect of >80% tumor shrinkage [142]. ^{131}I-doped CuS nanoparticles provide combined PTT and radiotherapy together with CT and gamma image-guidance to treat 4T1 subcutaneous and metastatic tumors [143].

Future Directions

Nanoparticles are quickly becoming universal imaging agents, taking multimodal imaging to new heights [144-145]. Multiple treatments can be packaged within the same nanoparticle agent, for example, a prophylactic hydrogel patch containing fluorescently-labeled targeted gold nanoparticles locally implanted into a tumor makes a triple combination therapy of siRNA against *Kras*, VEGF inhibitor delivery, and PTT available at the same time for colon cancer treatments [146]. Monitoring the nanoparticle distribution in the body, but also the therapeutic load delivery via imaging is possible, for example via MRI [147-148]. The next crucial step will be predicting their distribution even before administration, especially given the high variability of the EPR effect. Such prediction may take the form of “companion-nanoparticles”[149] or computational models [150]. Bioderived nanoparticles, synthesized using “green chemistry” or cells [151-153] can expand the limits of biocompatibility and immune evasion through biomimicry [154]. Such biocompatible synthesis approaches could soon enable chemical manipulation of nanoparticles in vivo [155]. As nanoparticles transition to the clinic, they are investigated more deeply and new effects are discovered. For example, besides their role in intraoperative image-guided oncosurgeries, C-dots were recently observed to induce ferroptosis of cancer cells both in vitro and in vivo [156], and iron oxide nanoparticles were shown to reprogram TAMs to attack tumors [12].

Conclusion

With many examples of successful nanoparticle theranostic agents already employed clinically, several undergoing clinical trials, and countless others emerging from preclinical studies, we are ushering in the era of nanomedicine. Smart, specific, and customizable, theranostic nanoparticles will soon—pending FDA approval—detect, treat, and prevent disease. MINT has been established to create a forum to discuss these advances and better integrate disciplines that develop and use nanoparticles for imaging and therapy.

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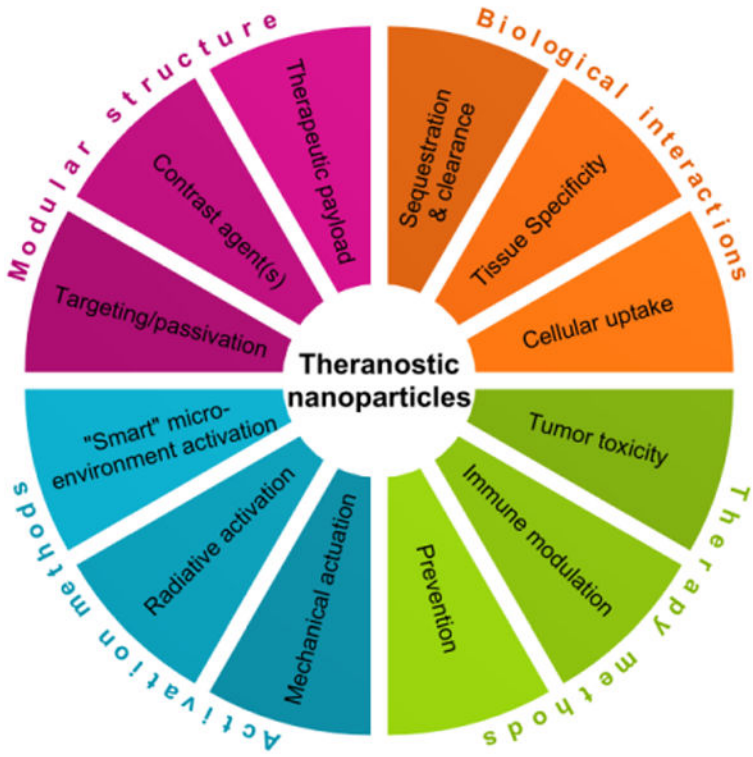

Fig. 1.

Through their modular structure, nanoparticles can incur specific biological interactions and deliver targeted therapy using intrinsic markers or external stimuli.

Fig. 2.
Nanoparticles of different materials, with many applications, are available at our fingertips.

Table 1

Biomedical nanoparticles developed from a wide variety of materials recently reported for theranostic applications. Nanoparticles with multiple functionalities are listed multiple times.

		Noble metals	Other metals	Metal oxides	Semiconductors	Silica	Carbon	Polymers / Liposomes	Proteins	Other materials
Imaging	MRI	[40, 55, 157]	[26, 28, 40, 88, 133, 158-161]	[6-12, 26, 28, 40, 118, 121, 123, 133, 158-160, 162-168]	[39-40]	[55]	[40]	[126, 165]		[82, 169-170]
	PET/SPECT	[16-17, 25, 29-30, 40, 101-102, 142, 171]	[24, 26, 28, 40, 158-159, 172-174]	[24, 26, 28, 40, 158-159, 162, 172-175]	[18, 40]	[20, 27, 34-35]	[40, 109, 136]	[21, 23, 99, 102, 106, 134-135]	[32, 176]	[22, 33, 131-132, 135, 145, 169]
	CT	[17, 30, 62, 65, 137-139, 142, 171]		[80, 118-120]	[18]	[20, 27, 35]		[62, 80, 138]		[135, 143, 145]
	Optical	[36, 49-50, 52, 55-60, 146, 177]	[36, 108, 117]	[36, 78, 116]	[19, 39]	[34-35, 49-50, 52, 55-60, 156, 177]	[109]	[38, 43, 78, 105, 107, 126-127, 129, 146, 178]	[116, 176]	[145, 169]
	Photo-acoustic	[62-67]	[79, 88]	[78, 80, 90-91, 93]	[72-73, 83-85]	[92]	[87, 151]	[43, 62, 67-69, 71-73, 75, 78-80, 83-85, 93, 106]	[76]	[74, 77, 81-82, 86, 145]
	Ultrasound			[78, 165]				[78, 126-127, 165]		
	Cerenkov	[30, 101-102, 104, 171]	[24]	[24, 98, 103, 162, 175]	[18-19]	[100]		[99, 102, 135]	[98]	[145, 179-180]
Therapy	Drug delivery	[66]		[166]		[92]	[136]	[105-106, 125, 127]		
	Gene/siRNA delivery	[146]	[108]				[109]	[99, 105, 107, 146, 178]		
	Immuno-therapy	[101]		[12]			[130]	[129-130]	[181]	
	PTT/PDT	[16, 63, 65, 67, 110-113, 146, 157]	[88, 117, 174]	[78, 80, 98, 116, 174]	[73, 83-84]	[100]		[67, 73, 75, 78, 80, 83-84, 129, 146]	[76, 98, 116]	[82, 86, 143]
	Radio-therapy	[137-142]	[133]	[116, 118, 133]				[135, 138]	[116]	[143]
	Externally actuated	[114-115]		[118-121, 123]						