

Nanoparticles as a Technology Platform for Biomedical Imaging

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Imaging and therapeutic delivery is increasingly relying on nanoparticles as a key technology platform. This common technology interface affords new opportunities to combine the diagnosis and treatment into a “unified” one-step theranostic approach. Nanoparticles are now emerging as a main innovation driver in developing novel imaging applications, especially in nanomedicine.

1 Origins of Nanoparticles in Biomedical Imaging

The use of nanoparticles dates back to ancient history with clay minerals providing color in pottery [1], with gold and silver particles being incorporated in opulent ceramics by Mesopotamians [2]. The word “tattoo” comes from the Polynesian word “tatau,” where the Pacific Islanders have used nanoparticles for thousands of years to mark one’s genealogy, societal hierarchy, and personal achievements. These visual properties of nanoparticles were also documented by Michael Faraday, who was experimenting with different metal particles and their effects on light [3]. These nanoparticles are natural products from organic (e.g., polysaccharides), as well as inorganic elements (iron oxides). These specific applications revealed their unique

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properties that led to detailed investigations to more systematically produce particles exhibiting the desired characteristics.

A major characteristic of particles of <100 nm is their ability to form colloids (i.e., lack of sedimentation when suspended in a liquid phase) [4]. To account for size, nanoparticles were initially termed ultrafine particles (1–100 nm in size) to contrast these with fine (100–2500 nm) and coarse particles (2500–10,000 nm). The term *nano* is derived from the Greek language, meaning “dwarf.” It was only added in the 1990s to provide further emphasis on size as being a key characteristic that distinguishes these ultrafine particles from larger ones. This is reflected in the definition of the International Union of Pure and Applied Chemistry (IUPAC), which determines a size between 1 and 100 nm as the key characteristic, although under certain circumstances particles larger than 100 nm can also behave like nanoparticles [5].

Nanoparticles have a long-standing tradition in biomedical imaging. The first contrast agent was used in 1905 for X-ray imaging by Walter Cannon. For this, naturally occurring high-density metal salts, notably bismuth- or barium-based nanoparticles, were mixed with food to noninvasively visualize the mechanics of the digestive tract [6]. The generation of novel radioactive particles was a by-product of the nuclear arms’ development that in 1946 was declassified as part of the Atomic Energy Act for the civilian development of radioactive-based therapies and imaging [7]. Imaging of ^{198}Au colloids was subsequently used to investigate its organ distribution, revealing an accumulation in the kidneys, spleen, and liver [8]. This provided the first imaging of the reticuloendothelial system (RES). The first specific nanoparticle preparations for electron microscopy consisted of natural horse spleen ferritin that afforded the specific detection of antigen [9]. With the development of liposomes in the 1960s, a new era was heralded in nanoparticle design in which controlled delivery of pharmaceutical compounds [10, 11] and the incorporation of imaging agents, such as ^{131}I -labeled albumin, became feasible [12].

The 1970s saw a rapid expansion of the use of nanoparticles with their first use for biomedical imaging of myocardial perfusion using single-photon emission tomography (SPECT) [13], as well as adaptation to other imaging modalities, such as near-infrared (NIR) optical imaging [14]. The rapid adaptation of computer tomography (CT) in hospitals and the requirement of contrast material, such as iodine [15], further stimulated nanoparticle research with evidence of their major impact in diagnostic radiology. The emergence of positron emission tomography (PET) was dependent on the generation of new radioligands that did not provide anatomical images per se, but were geared towards molecular targets [16]. One of the first such developments visualized staphylococcal abscesses using $^{99\text{m}}\text{Tc}$ -technetium liposomes [17]. In contrast to CT and PET, the emergence of magnetic resonance imaging (MRI) was not dependent on contrast materials or tracer agents, as the magnetic relaxation properties of ^1H provided the signal for image construction. Nevertheless, in the late 1970s, it was discovered that small metallic particles can influence this relaxation rate [18] and could be used to image the liver and spleen [19], as well as specific antigens [20]. In the mid-1990s, magnetic nanoparticles were approved by the FDA and have seen a plethora of uses in MRI [21], including clinical cell tracking [22].

2 The Emergence of a Synergy Between Therapeutics and Imaging

These developments provided not only the foundation for the rapid development of nanoparticle-based clinical imaging during the 1990s, but also new tools for basic scientists. Indeed, it marked the emergence of an interdisciplinary field, where physicists were driving the advances in image acquisition, biochemists were engineering new imaging agents, and biologists/clinicians were exploiting new frontiers of what could be visualized in living subjects [23]. Easy access routes of administration through ingestion or intravenous delivery sufficed for most imaging requirements, such as the gastrointestinal tract and the RES. However, this afforded a limited penetration into tissue (and cells), where many pathological targets are found, especially in the brain where we have the blood-brain barrier and access through other methods is very limited. The pharmaceutical sciences faced a similar issue in terms of delivery of drugs and hence novel means were sought that could cross the vascular wall and permeate into tissues [24], as well as approaches to block uptake by the RES in order to prolong nanoparticle blood half-life, which is necessary for specific antigen-based targeting applications.

Originally, Paul Ehrlich conceived of this approach as a “magic bullet” that will only affect those cells that are targeted [25]. Liposomes developed in the 1960s suited this nanoscopic vision, but apart of the development of polymeric nanoparticles little progress was seen in the development of nanoparticles for drug delivery until the 1990s, when several developments overcame fundamental challenges [24]. Foremost of all, a significant obstacle for targeting of nanocarriers (i.e., material carrying drug for delivery), such as nanoparticles, was escaping the rapid uptake through the RES. A size of <200 nm facilitated retention in the bloodstream, but was insufficient to provide adequate circulating time for extravasation into target tissues. Non-covalent attachment or amalgamation of polyethylene glycol (PEG), so-called PEGylation [26], and its widespread adaptation were the first major advances in targeting by creating a “stealth” mode for molecules to evade the host’s immune system and afforded the prolonged circulation of nanoparticles [27]. Active (e.g., antibodies) and passive (e.g., enhanced permeability retention) targeting approaches provided the second component to ensure that nanoparticles accumulate in a desired location [28]. Nanoparticles provide key characteristics for drug delivery, notably improved bioavailability through aqueous solubility (i.e., forming a colloid), increased blood circulation time, and potential for tissue and cell targeting [29].

These advances in delivering therapeutics using nanoparticles cumulated in the realization that engineered nanocarriers could carry not only therapeutic drugs, but also contrast agents that would afford a localization and potential monitoring of such delivery [30]. This conceptual advance of therapeutics and diagnosis led to the formulation of the portmanteau word *theranostic* at the start of the new millennium [31, 32]. As with most nanoparticle drug delivery and imaging systems, macrophages constituted the first easy target [33], due to their natural properties to rapidly phagocytose particulate material. Further synergies also became apparent in that certain

drugs could be tagged with a radioligand [34, 35] and nanoparticles based on elements, such as gold [36, 37], could provide a core technology platform for creating multicomponent, multimodal, and multifunctional agents [38]. Increasingly complex possibilities are emerging with multiple imaging moieties, stealth and targeting functionalities, as well as multiple timed release of therapeutic drugs [39, 40].

3 An Outlook on Challenges and Future Opportunities

One of the most significant advances has been the rapid development of optical and ultrasound nanoparticles [41]. Especially the introduction of quantum dots, as well as the use of near-infrared probes and highly sensitive detectors, have now enabled imaging of deeply seated tissue structures [42], allowing clinical optical imaging [43]. The availability of calcium-sensitive agents, for instance, allows an *in vivo* imaging approach that bridges the gap between conventional single-cell electrophysiological recording and macroscopic activity recording, such as functional MRI [44]. Light-sensitive theranostic nanoparticles can also be used to monitor reaching a treatment site, with a specific light wavelength triggering the release of drug in just this area, hence providing a very targeted treatment [45]. These approaches further lend inspiration to the development of probes for other modalities, such as MRI, that currently still dominate the clinical arena. However, optical imaging is currently seeing a more rapid development of nanoparticles than any other biomedical imaging modality. The shift beyond near infrared reduces tissue light scatter and greater organ coverage will eventually dominate biomedical imaging in smaller species to drive a deeper understanding of biology. Still, it remains unclear if optical imaging can indeed deliver on whole-organ imaging in larger species, such as primates and humans. Modalities, such as MRI and SPECT, might hence still remain the dominating nanoparticle-based clinical imaging techniques.

Further challenges to clinical applications are the growing considerations for toxic side effects of nanoparticles, the so-called nanotoxicity [46]. Many of the constituent parts of nanoparticles do not exhibit toxicity in their bulk form, but due to the emergent properties at the nanoscale (e.g., increased cell membrane permeation), cytotoxic effects can become apparent [47]. However, there is also support to indicate that the nanosize by itself is insufficient to determine toxicity and that a more detailed general consideration of particle toxicity is needed [48, 49]. The combination of nanoparticles with biologicals, such as stem cells, further raises concerns as to their potential to induce unwanted side effects that might only become apparent over time [50, 51]. An unanswered question remains if materials should be biodegradable and cleared over time or if biological inertness is more desirable [52]. Indeed, these issues raise concern regarding a premature clinical translation and what framework of evidence is needed to ensure safety [53]. Beyond the regulatory framework, the potential for scale-up and cost-efficient production at an industrial scale will also require further investment and might refine quality control procedures, especially in relation to monitoring potential adverse effects [54].

To conclude, nanoparticles are hence a powerful technology platform that affords the integration of imaging and drug delivery. Their increasing sophistication delivers exciting new opportunities to disentangle complex biological questions at the systems level [55], but also constitutes a major step forward to the concept of a “magic bullet,” where a drug can be delivered to a very focused area, and potentially even to specific single cells [56]. With the increasing number and versatility of probes for the various imaging modalities, the future for biomedical imaging promises to be exciting [57]. These multimodal and -functional nanoparticles are also likely to be the catalyst for an eventual unification of diagnostic medicine and imaging based on more specific and sensitive tissue- and fluid-based biomarkers that improve early disease detection and classification.

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