The development of nanoparticles for diagnosis and therapy is guided by core concepts across an increasingly broad range of scientific disciplines. Indeed, nanotechnology is, by its nature, the most multidisciplinary of sciences and the application of its principles to human health applications demands this to achieve any significant technical advancement. There is no doubt that the complexity of the materials being developed and the need for novel characterization tools, coupled with the inherent complexity of organisms, means that today, there is vastly more potential than actual clinical presence for nanoparticles as targeting and carrying agents. However, it is undeniable that the various sizes, materials, and targeting moieties of nanoscale platforms introduce the possibility of targeting both at the organ and cellular level. The vibrant and increasingly creative activity in this field is evident in the large number of studies using various types of nanoparticles for a myriad of biological and medical applications and the promising results from early stage clinical trials. Indeed, nanoparticles are having an impact on many diseases including cancer, with more than 30 products in clinical use and hundreds more in clinical evaluation. Formulations such as Abraxane®, clearly demonstrate the potential can be converted to reality and many more nanoscale formulations will likely play an increasing role in the treatment of disease and in pain management.

In this themed issue of *J. Mater. Chem. B*, we bring together outstanding original work from the top scientists in the field, from diverse scientific disciplines currently developing a range of nanoparticles, both synthetic and semisynthetic, for diverse biomedical applications. For example, the synthesis of silver nanoparticles (NPs) using a sonochemical approach for the reduction of silver ions with ethylene glycol and simultaneous deposition on TiO₂ powders was demonstrated (DOI: 10.1039/c2tb00337f). These homoge-
neous silver nanoparticles approximately 3 nm in size, strongly attached to the surface of titania. The properties of Ag–TiO₂ were tested against a number of Gram-positive and Gram-negative bacteria and were found to enhance antimicrobial activity opening new avenues for combatting bacterial contamination at interfaces.

Ultrasound superparamagnetic iron oxide (USPIO) nanoparticles are attractive MRI contrast agents due to their negative ($T₂$) contrast enhancement capability and biocompatibility. In a study by the group of Sandre (DOI: 10.1039/c3tb00429e), three different maghemite ($\gamma$-Fe₂O₃) USPIO particles were developed as a series of hybrid copolymer/iron oxide contrast agents, presenting two different geometries (micellar or vesicular). The cluster structure (i.e. micellar or vesicular) appeared to have a mild influence on the transverse relaxivity value. The $r₂$ value was mainly governed by the individual size of the USPIOs, correlated with both the cluster external diameter and the magnetic material volume fraction. This type of morphological tuning of the properties of contrast agents could greatly influence how materials are designed and optimized for in vivo use.

In a departure from purely synthetic nanoparticle systems for tuning relaxivity properties of MR-contrast agents, the group of Marianne Manchester (DOI: 10.1039/c3tb20521e) demonstrated a gadolinium (Gd)-based contrast agent for MRI in a viral nanoparticle format. The plant virus, cowpea mosaic virus (CPMV), is a biocompatible nanoparticle format for imaging applications and Gd is rapidly incorporated into the interior of the CPMV capsid without disrupting particle integrity. These CPMV–Gd particles have relaxivity comparable to gadolinium chelates used clinically. In this study, gadolinium-loaded CPMV particles (CPMV–Gd) were tested as sensitive imaging agents for experimental autoimmune encephalomyelitis (EAE). The in vivo distribution of CPMV-Gd was examined within the periphery and central nervous system (CNS). CPMV accumulated in inflammatory lesions within the brain and spinal cord, and specifically associated with CD11b⁺ and CD11c⁺ cells. These results demonstrate that CPMV is an attractive nanoparticle platform for gadolinium for in vivo applications and may have clinical utility as a contrast agent for the detection of autoimmune demyelinating diseases of the CNS.

A novel strategy for decorating the surface of mesoporous silicon particles with targeting entities, e.g. bacteriophage and gold nanoparticles (AuNP), while maintaining their payload carrying potential, was reported by the groups of Ferrari and Godin (DOI: 10.1039/ c3tb20595a). The resulting Bacteriophage Associated Silicon Particles (BASP) demonstrated efficient encapsulation of macromolecules and therapeutic nanoparticles into the porous structures. In vitro targeting data showed enhanced targeting efficiency with about four orders of magnitude lower concentration of bacteriophage. In vivo targeting data suggest that BASP maintain their integrity following intravenous administration in mice and display up to three fold higher accumulation in the tumor.

Rotello’s group (DOI: 10.1039/ c3tb20377h) showed that two protein isoforms, β-lactoglobulin (BLG) BLGA and BG, can differentiate using electrostatics on cationic gold nanoparticle (GNP). These results show the potential of protein recognition platforms based on enhanced electrostatic interactions.

The success of nanoparticle-based cancer therapies ultimately depends on their ability to selectively and efficiently accumulate in regions of disease. Outfitting nanoparticles to actively target tumor-specific markers has improved specificity, yet it remains a challenge to amass adequate therapy in a selective manner. To help address this challenge, the group of Sangeeta Bhatia (DOI: 10.1039/c3tb20619j) developed a mechanism of nanoparticle amplification based on stigmergic (environment-modifying) signalling, in which a “Signalling” population of gold nanorods induces localized unveiling of cryptic collagen epitopes, which are in turn targeted by “Responding” nanoparticles bearing gelatin-binding fibronectin fragments. They demonstrated that this two-particle system results in significantly increased, selective recruitment of responding particles. Such amplification strategies have the potential to overcome limitations associated with single-particle targeting by leveraging the capacity of nanoparticles to interact with their environment to create abundant new binding motifs.

Gold nanostructures can be incorporated into macroporous scaffolds to increase the matrix conductivity and enhance the electrical signal transfer between cardiac cells. The group of Tal Dvir (DOI: 10.1039/c3tb0584c) reports a simple approach for fabricating 3-dimensional (3D) gold nanoparticle (AuNP)-based fibrous scaffolds, for engineering functional cardiac tissues generating a strong contraction force. A polyacrylate-gelatin mixture was electrosprun to obtain fibrous scaffolds with an average fiber diameter of 250 nm. In a facile method, AuNPs were evaporated on the surface of the fibers, creating nanocomposites with a nominal gold thickness of 2, 4, and 14 nm. Compared to pristine scaffolds, cardiac cells seeded on the nano-gold scaffolds assembled into more elongated and aligned tissues. The AuNPs on the fibers were able to maintain the ratio of cardiomyocytes to fibroblasts in the culture, to encourage the growth of cardiomyocytes with significantly higher aspect ratio, and promote massive cardiac sarcomeric actin expression. Finally, engineering cardiac tissues within gold NP-based scaffolds exhibited significantly higher contraction amplitudes and rates, as compared to scaffolds without gold. Thus, the vision here is that cardiac tissues engineered within these AuNPs scaffolds can be used to improve the function of the infarcted heart.

There is tremendous work using nanoparticles as drug delivery systems. In this themed issue, the review from Dennis Discher and coworkers on filomicelles as ligand-targeted carriers for combination therapy for brain tumors is fascinating (DOI: 10.1039/c3tb0431f). Nanoparticles that are made by self-assembly into non-spherical shapes are promising as drug delivery vehicles. In this review, Discher’s group focuses on flexible and fragmentable filamentous micelles referred to as filomicelles made of degradable block copolymer amphiphiles. They are inspired by filoviruses
and also by tubular proplatelets that break up into smaller platelets in blood flow. The synthesis and assembly of the constituent block copolymers are described together with ligand targeting and fragmentation as well as drug release in therapeutic applications to model tumors and, most recently, brain tumors.

Another feature article that provides an overview of two classes of nanoparticles, namely iron oxide and NaLnF4, and synthesis methods, characterization techniques, study of biocompatibility, toxicity behavior, and applications of iron oxide nanoparticles and NaLnF4 nanoparticles as contrast agents in magnetic resonance imaging and associated applications. Iron oxide nanoparticles show a saturation of magnetization at low field, therefore, the focus will be on MLnF4 (Ln = Dy3+, Ho3+, and Gd3+) paramagnetic nanoparticles as alternative contrast agents which can sustain their magnetization at high field. The reason is that more potent contrast agents are needed at magnetic fields higher than 7 T, where most animal MRI is being done these days. Furthermore, they observe that the extent of cytotoxicity is not fully understood at present, in part because it is dependent on the size, capping materials, dose of nanoparticles, and surface chemistry, and thus needs optimization of the multidimensional phenomenon. Therefore, it needs further careful investigation before being used in clinical applications.

Other interesting papers in this issue include the work of the innovative Bartholomew group on lipid oligonucleotide conjugates as responsive nanomaterials for drug delivery (DOI: 10.1039/c3tb20357c); the work of Paolo Caliceti on novel pH-responsive nanovehicles for controlled release of ionisable drugs (DOI: 10.1039/c3tb20360c); the work of Huangxian Ju (DOI: 10.1039/c3tb20410c) on platinum nanodendrites functionalized graphene nanosheets as non-enzymatic label for electrochemical immunosensing; the work of Yi Lu (DOI: 10.1039/c3tb20412j) on selective delivery of an anticancer drug with aptamer-functionalized liposomes to breach cancer cells in vitro and in vivo; the work of Guangshan Zhu (DOI: 10.1039/c3tb20466a) on magnesium hydroxide nanoplates: a pH-responsive platform for hydrophobic anticancer drug delivery; the work of Carole Aime (DOI: 10.1039/c3tb20499e) on reversible bioresponsive aptamer-based nanocomposites: ATP binding and removal from DNA-grafted silica nanoparticles; the work of Chung-Yuan Mou (DOI: 10.1039/c3tb20529k) on a simple plant gene delivery system using mesoporous silica nanoparticles as a carrier; the work of Malcolm Xing (DOI: 10.1039/c3tb20544d) on polymeric mesoporous silica nanoparticles as a pH-responsive switch to control doxorubicin intracellular delivery; the work of Peng Liu (DOI: 10.1039/c3tb20975j) on folic acid-conjugated temperature and pH dual-responsive yolk/shell microspheres as drug delivery systems and an interesting manuscript by the group of Mahmoud Elsabahy (DOI: 10.1039/c3tb20668h) on shell-crosslinked kandel-like nanoparticles that induce lower immunotoxicity than their non-crosslinked analogs.

Finally, the feature article of Torchilin (DOI: 10.1039/c3tb20990c) on lipidic nanoparticles in cancer research focuses on the solid lipid nanoparticle (SLN) and nanostructured lipid carrier (NLC) with their outstanding properties as controlled release vehicles for drugs and imaging agents and their relatively low to no toxicity.

In summary, the development of nanoparticles for biological and medical applications is at the verge of revolutionizing and transforming medicine. Although numerous nanoparticle-based strategies exist, choosing the appropriate nanoparticle is still not obvious and comparative studies, of which there are few, are difficult to interpret. Indeed, a suitable system which demonstrates optimal characteristics remains elusive.

Determining the optimal nanoparticle system is especially difficult given the numerous factors, which affect biodistribution and targeting. Therefore, successful targeting strategies at present must be found experimentally on a case-by-case basis, although this is not a rare problem when it comes to searching for function from chemical systems where predictable, complex behavior remains an elusive goal. In addition, systemic therapies employing nanoparticles require methods for overcoming the non-specific uptake of nanoparticles by the mononuclear phagocytic cells and non-targeted cells and presently it is not clear to what extent this is possible. This includes efforts to develop universal strategies for stealth particles where pegylation is not necessarily the panacea. Moreover, when any serious attempt is made to move materials into even small mammals, there is a constant demand for simple scale-up methods and high throughput assays for quality assurance. This impacts on how materials are made from the very beginning of their design, and is something that should be part of the thought process when researchers embark on projects of this type. Proof-of-concept is of course a necessary part of research, but cannot be allowed to lead inevitably to materials with limited chance for testing on even a small scale in animal models for human disease.

It is likely that we are entering an era where nanoparticle-based approaches will represent a common modality within therapeutic and diagnostic oncology. With many hurdles to overcome, the type of multidisciplinary efforts exemplified in this issue, will likely form the backbone of those future therapies.

References