**Progress of multicompartmental particles for medical applications**

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**Abstract**

Particulate materials are becoming increasingly used in the literature for medical applications, but translation to the clinical setting has remained challenging as many particle systems face challenges from *in vivo* barriers. Multicompartmental particles that can incorporate several materials in an individual particle may allow for more intricate control and addressing of issues that otherwise standard particles have been unable to. Here we briefly described some the advances made in the use of multicompartmental particles for medical applications.

## 1. Introduction

Micro- and nanometer scale particulate carriers are considered to have great potential to address challenges in the treatment refractory diseases via their use in multiple areas including drug delivery and tissue engineering.[1-3] In attempting to address large-scale, reproducible fabrication of carriers with superior efficacy or potency, many different carriers have been made from a variety of materials. Despite advances in the design and fabrication of intricate particulate carriers, they have not realized their full potential in a clinical setting.

Many of the barriers to effective therapy may be attributed to complex interaction between particles and various physiological, and pathophysiological, processes. It is particularly difficult to obtain long circulation times for particulate carriers due primarily to the immune system's effectiveness in removing them form circulation. The reticuloendothelial system is especially adept at nonspecifically phagocytosing foreign particulate material, and several different materials of various shapes, mechanical properties, and surface properties have been developed to help prolong circulation times.[1,3-7] Additionally, while some imrpovements have been made, targeted therapy continues to remain a challenge. Biodistribution studies of targeted drug-loaded particles have shown, at best, 1-2% of total therapeutic administered reaching the desired target.[8,9]

Certain classes of particles may be effective in addressing one particular type of interactions or barriers, but none have addressed all barriers. Inorganic particles are arguably the most well defined carrier systems, usually having exceptional monodispersity with resepect to size and shape.[2] They therefore can have some of the most reproducible *in vivo* results, and the ability to produce extremely small nanoparticles (less than around 5-6 nm in diameter) allows for renal clearance.[10] However, larger inorganic particles, which are not clearable renally or biodegradable, and can therefore accumulate in various tissues – although some studies show that there may be little acute toxicity, the long-term effects are unknown.[2,11,12] Liposomes have excellent biocompatibility, but can be rather ineffective, have difficulty achieving adequate circulation and targeting, and be less stable than other classes of particles.[2,13] Polymer based particles have the potentially for highly selective targeting, but also have short circulation times and, depending on the polymer, can be highly biocompatible or quite cytotoxic.[14,15] On the other hand, the diverse range of polymers available affords particles made from them with a high degree of functionality.[16]

Incorporating multiple materials with different functionalities into a multicompartmental particle may better address the barriers to effective therapy. Multicompartmental particles may afford multiple functionalities, theoretically addressing multiple barriers and thereby allowing for more effective therapy. Here we review some of the recent progress with the use of multicompartmental particles for medical applications, focusing on the areas of drug delivery, tissue engineering, and diagnostics.

## 2. Manufacturing of multicompartmental particles

Multicompartmental particulate carriers may be considered a class of anisotropic particles, the fabrication and study of which have become of great interest for numerous applications as well as a fundamental science. A number of methods have been developed for producing such particles. These methods may be broadly classified as sequential or simultaneous.

Sequential strategies involve step-wise fabrication of each individual compartment. Arguably the most common method involves beginning with the standard fabrication of an organic or inorganic particle, followed by modulation of their surface properties to selectively induce formation of subsequent compartments in particular locations on the seed particle, forming core-shell particles or other anisotropic particles (**Figure 1a-c**).[17-28] This process can then be repeated to add additional compartments.[29] Another traditional method that is still used involves the swelling of polymeric particles with another monomer, followed by polymerization – this process results in phase separation of the resultant polymerized phase, resulting in bicompartmental (Janus) particles.[30,31] Layer-by-layer (LbL) fabrication of particles is also a common method for making multicompartmental particles.[32-34]

More novel sequential methods have also emerged, including a modification of the PRINT (Particle Replication in Non-Wetting Templates) method developed by the DeSimeone group, in which multicompartmental particles are made by sequential partial filling and curing in the photolithographed mold (**Figure 1d**); a similar method is described by Lee et al. but incorporates a dewetting solution before each curing step, allowing for the production of more spherically shaped multicompartmental particles.[35,36] Another unique method employs sequential electrospinning of layers of fibers, followed by controlled deposition of photopolymer and crosslinking, and subsequent etching of exposed fibers.[37]

Simultaneous strategies generally are able to manufacture multicompartmenal particles in a single step, and tend to be more continuous processes whereas sequential strategies are often batch processed. A vast majority of these strategies employ microfluidics. One set of these fabrication methods involves the use of multiple immiscible phases containing different materials to generate droplets with multiple compartments.[38-43] The Weitz group in particular has expanded on this concept to develop a number of unique multicompartmental architectures (**Figure 2a**).[40,41,43-48] These particles tend to have sizes on the order of 1-100 microns in diameter.

Another set of microfluidic-based exploits the advantage of minimal diffusion across parallel streams, containing various materials, in a laminar flow regime. Stop flow lithography employs spatially focused UV photopolymerization of these streams to form multicompartmental particles (**Figure 2b**).[49-53] Another microfluidic method, developed by our group, is a modified electrospraying process called electrohydrodynamic (EHD) co-jetting (**Figure 2c**).[54-58] Multiple solutions are extruded in parallel under a laminar flow regime and a DC voltage is applied, forming a jet that rapidly evaporates leaving solid multicompartmental particles or fibers (that may be further cryosectioned to make particles), mirroring the arrangement of the input streams.[56,59-61]

One other unique method of fabricating multicompartmental particles has been developed by the Muller group and others that employs the self-assembly of multiblock copolymers (**Figure 2d**).[62-68] Well-controlled synthesis of multiblock copolymers are capable of predictably self-assembling into particles such that different blocks of individual polymers associate with one another to form separate phases within an individual particle.[62] Of note, these formulations are exquisitely dependent on the hydrophilic/hydrophobic balance between the polymer co-arms as well as the solvent they are dispersed in.

## 3. Medical Applications

### 3.1 Drug Delivery

#### *3.1.1 Temporal control of drug release*

Multiple compartments allow for more intricate control of drug release from a particle. Our group has incorporated multiple different functional materials to allow for varying measures of stimuli-controlled release. We have developed multicompartmental particles incorporating poly(lactic-co-glycolic acid) (PLGA) and polyethyleneimine (PEI) that allow for pH-dependent release of small interfering RNA (siRNA) such that it is released after endocytosis.[69] Via the secondary and ternary

amines, the PEI compartment of individual particles can expand under acidic conditions of an endosome and ultimately results in the rupture of the endosome either physically or osmotically, known as the "proton sponge" effect.[70,71]

We have similarly shown pH-dependent release of irinotecan using PLGA/acetal-modified dextran multicompartmental particles.[72] The hydrophobic acetal-modified dextran allows for loading of irinotecan – under acidic conditions, the acetal groups are cleaved resulting in water soluble dextran and release of the drug. We have also demonstrated light-responsive drug release by incorporating a photoacid generator into the same compartment as the acetal-modified dextran allows for ultraviolet (UV) light controlled release.[73] Additionally, near-infrared (NIR) light responsive particles have been developed by He et al. that consist of doxorubicin loaded LbL particles modified with a gold half shell that releases the chemotherapeutic agent on exposure to a 808-nm laser.[74]

Sequential release of multiple drugs has been shown by Weitz et al. via the use of fluorescent dyes loaded in multicompartmental polymersomes, consisting of a polymersome within a polymersome using poly(lactic acid)-co-poly(ethylene glycol) (PLA-PEG). Two distinct dyes are loaded, one within the inner polymersome compartment and another in the outer polymersome – the outer polymersome is mechanically ruptured first, releasing one dye, and the inner polymersome ruptures after hydrolytic degradation releasing the second dye.[48] They also show the potential for multiple dye release by incorporating multiple inner polymersome compartments into the outer polymersome.

*3.1.2 Multiple drug release*

Simultaneous release of two or more drugs is another area of research avidly explored. Multicompartmental particles may have a potential advantage for this application by allowing for decoupling of the release of different drugs. For example, Bong et al. fabricate bicompartmental

particles consisting of hydrolysable polymers (ketal containing) one of which is more crosslinked and thus has a longer half life – these compartments are loaded with fluorescent beads as a surrogate for drugs and release is shown to be slower and more prolonged from the crosslinked compartment (**Figure 3a**).[51]

Multicompartmental particles with a core-shell architecture have particularly been explored for releasing two distinct drugs. Vandamme et al. developed a core-shell polyacrylamide particle with ketoprofen loaded in the core and ranitidine in the shell via a microfluidic approach similar to that developed by the Weitz group.[75] Bahadur et al. showed release of doxorubicin and paclitaxel from iron oxide ($Fe_3O_4$)/lipid core-shell nanoaprticles; made by a sequential approach, doxorubicin was loaded into $Fe_3O_4$ nanoparticles that were subsequently modified with a lipid shell containing paclitaxel.[76] Similarly, Loo et al. also showed release of doxorubicin and paclitaxel but from poly(lactic acid) (PLA)/PLGA core-shell microparticle system (**Figure 3b**) – these particles were synthesized uniquely by oil-in-water emulsification where the PLA and PLGA dissolved in dichloromethane (DCM) phase-segregate as DCM evaporates.[77]

### 3.1.3 Combined drug delivery and imaging

Multicompartmental particles are well suited for multifunctional capabilities, and have specifically been used in simultaneous drug delivery and imaging applications. Incorporating inorganic materials often allow for facile fluorescence and/or MR-based imaging. For example, Zink et al. made core-shell iron oxide/silica nanoparticles loaded with camptothecin or paclitaxel, and demonstrated *in vitro* fluoresce imaging and delivery of these drugs – they additional demonstrated the potential for MR imaging by *ex vivo* validation in a clinically used MRI instrument.[78] Similarly, Sahu et al. developed $Fe_3O_4$-metal organic framework (MOF) core-shell particles loaded with paclitaxel, and showed *in vitro* efficacy against HeLa cells.[79] Other groups have similarly made multicompartmental particles that incorporate iron oxide to allow for imaging in addition to drug delivery.[80-85]

Our group has employed EHD co-jetting to manufacture multicompartmental particles capable of simultaneous drug delivery and imaging. As discussed before, we developed PLGA/PEI bicompartmental particles that are capable of delivering siRNA – these particles also incorporate a fluorescent dye in the PLGA compartment, allowing for *in vitro* imaging as well as gene silencing.[69,86] We have also used acetal-modified dextran/PLGA bicompartmental particles to incorporate piribedil and glial cell derived neurotrophic factor (GDNF) for delivery to cochlea for applications to hearing loss (**Figure 3c-e**).[87]

These classes of multifunctional, multicompartmental particles are starting to be validated in *in vivo* models.[88-91] For example, Hammond et al. made a core-shell nanoparticle with a doxorubicin-loaded liposome, and an LbL shell containing siRNA and poly-L-arginine, with the last LbL layer using hyaluronic acid to improve the *in vivo* circulating half-life (**Figure 4**).[91] They show efficacy, by measure of tumor volume, of these multicompartment particles in a mouse model of triple negative breast cancer. Of note, they demonstrate combined use of a chemotherapeutic with siRNA – the siRNA was against MRP1, a multidrug resistance protein; using this siRNA showed improved efficacy compared to multicompartmental particles loaded with doxorubicin and a scrambled control siRNA.

**3.2 Tissue Engineering**

Multicompartmental particles are also increasingly used in tissue engineering applications. By having cells associate with a specific compartment, these particles may be able to develop novel tissues that more accurately mimic the anisotropic architecture seen in native tissues and organs. Maeda et al. fabricates multicompartmental microparticles using a microfluidic approach where parallel streams of alginate solutions are extruded using centrifugal force into a calcium chloride solution, allowing for rapid crosslinking – this approach allows for the inclusion of cells in one of the streams, shown by the incorporation of viable Jurkat cells in one compartment of alginate based bicompartmental microparticles.[92] Our group has also developed, by EHD co-jetting, core-shell

microparticles with a viable mammalian cell (NIH3T3) as the core.[93] These particles demonstrate the ability for cells to remain viable despite exposure to high DC voltages and high velocity jets.

Multicompartmental particles allow for the incorporation of chemically functional materials and therefore may display different surface properties over different corresponding compartments. Using this principle, our group fabricated bioactuators using bicompartmenal cylinder-shaped microparticles that display PEG on the surface of one compartment, and fibronectin on the other (**Figure 5**).[94] Primary rat cardiomyocytes were seeded onto these particles, selectively adhering to the fibronectin-displayed surface of the microcylinders. Autonomous contractions of the cardiomyocytes transduced mechanical displacement of the microcylinders.

### 3.3 Diagnostics

Multicompartmental particles have also started to be used in diagnostic applications. Several proof of concept studies have been published demonstrating their use in prototype enzymatic reactions.[95-98] Skirtach et al. fabricated core-shell microparticles, with a calcium carbonate ($CaCO_3$) core with peroxidase and liposomal shell containing Amplex Red.[99] Application of ultrasonic energy results in the rupture of the liposomes and release of Amplex Red, which reacts with hydrogen peroxidase ($H_2O_2$) via catalysis by peroxidase to produce the fluorescent product resofurin.

Georgieva et al. expands upon this, developing multicompartmental particles that contain three enzymes for coupled enzymatic reactions (**Figure 6**).[100] In their particles, a $CaCO_3$ contains $Fe_3O_4$ and horse radish peroxidase (HRP), glucose oxidase in an inner shell, and β-glucosidase in an outer shell. On exposure of these particles to a substrate for β-glucosidase, fluorescein-di-glucopyranoside, free fluorescein and glucose are produced; the glucose in turn serves as a substrate for glucose oxidase, producing $H_2O_2$, which with Amplex Red can produce resorufin via HRP.

Another potential emerging area is pathogen sensing. Kim et al. shows the ability to detect Staphylococcus (S.) aureus in milk using core-shell iron oxide/Au nanoparticles.[101] The particles display antibodies against S. aureus, causing aggregation of bacterial cells and particles if S. aureus is present in solution. Quantification of bacterial load is determined by degree of aggregation, which corresponds to a color change reflective of effective size of the aggregated Au compartments. While this is shown for identifying S. aureus in milk, this system may readily translated to determining bacterial load in biological specimens such as blood to determine bacteremia.

## 4. Conclusions

Here we have briefly reviewed a few of the advances in the use of multicompartmental particles for medical applications. The manufacturing of particles with more sophisticated and complex architectures have been made possible with the development of more intricate and precise materials processing techniques. The use of photolithography and microfluidics have particularly allowed for such advancements, as shown for example by the PRINT, stop-flow lithography, and EHD co-jetting techniques.

Many of the studies involving these particles have focused on drug delivery and imaging. Multicompartmental particles allow for facile incorporation of both imaging contrast agents, especially for MRI and fluorescent imaging. Incorporation of functional materials, such as pH or light responsive ones, can be used to provide particles with methods for controlled release of therapeutics including small molecule drugs and siRNA.

Other studies have shown the potential for multicompartmental particles for applications in tissue engineering and diagnostics as well. Our group has employed them for use as bioactuators, and other have used them to incorporate various standard biological reactions, which may be expanded on in the future for quantification of biological substances.

As current materials processing techniques for the manufacture of multicompartmental particles advance, we may continue to expect to see increasingly intricate particles that may be able to better address the barriers that have prevented particles from achieving their full potential in drug delivery and more.

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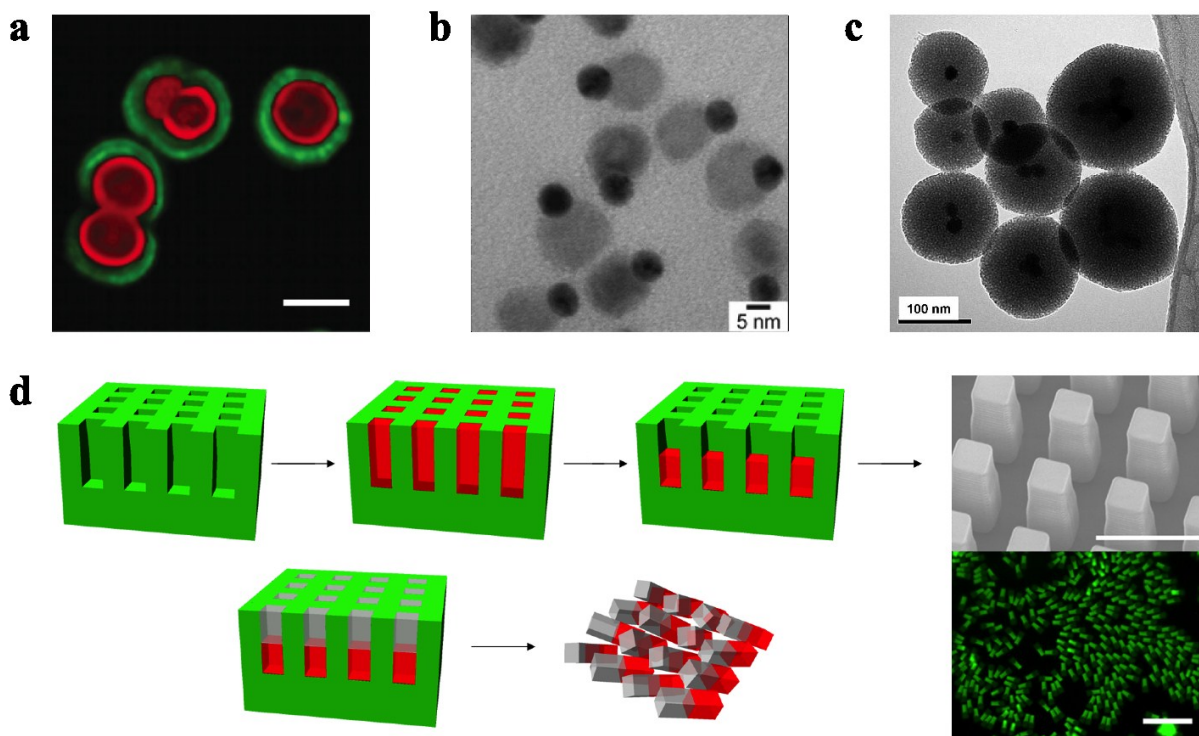Published online: ((will be filled in by the editorial staff))

**Figure 1.** Examples of multicompartmental particles made by sequential processes. (a) Core-shell CaCO$_3$ microparticles. Scale bar 5 µm Adapted with permission rom ref.[28] Copyright 2010, Wiley. (b) Bicompartmental Au/MnO nanoparticles. Adapted with permission from ref.[29] Copyright 2014, American Chemical Society. (c) Core-shell iron oxide/silica nanoparticles. Adapted with permission from ref.[78] Copyright 2008, American Chemical Society. (d) Polymeric bicompartmental particles fabricated using Particle Replication In Nonwetting Templates (PRINT). Scale bars – SEM 5 µm, fluorescence micrograph 20 µm. Adapted from ref.[35] Copyright 2009, Institute of Physics.
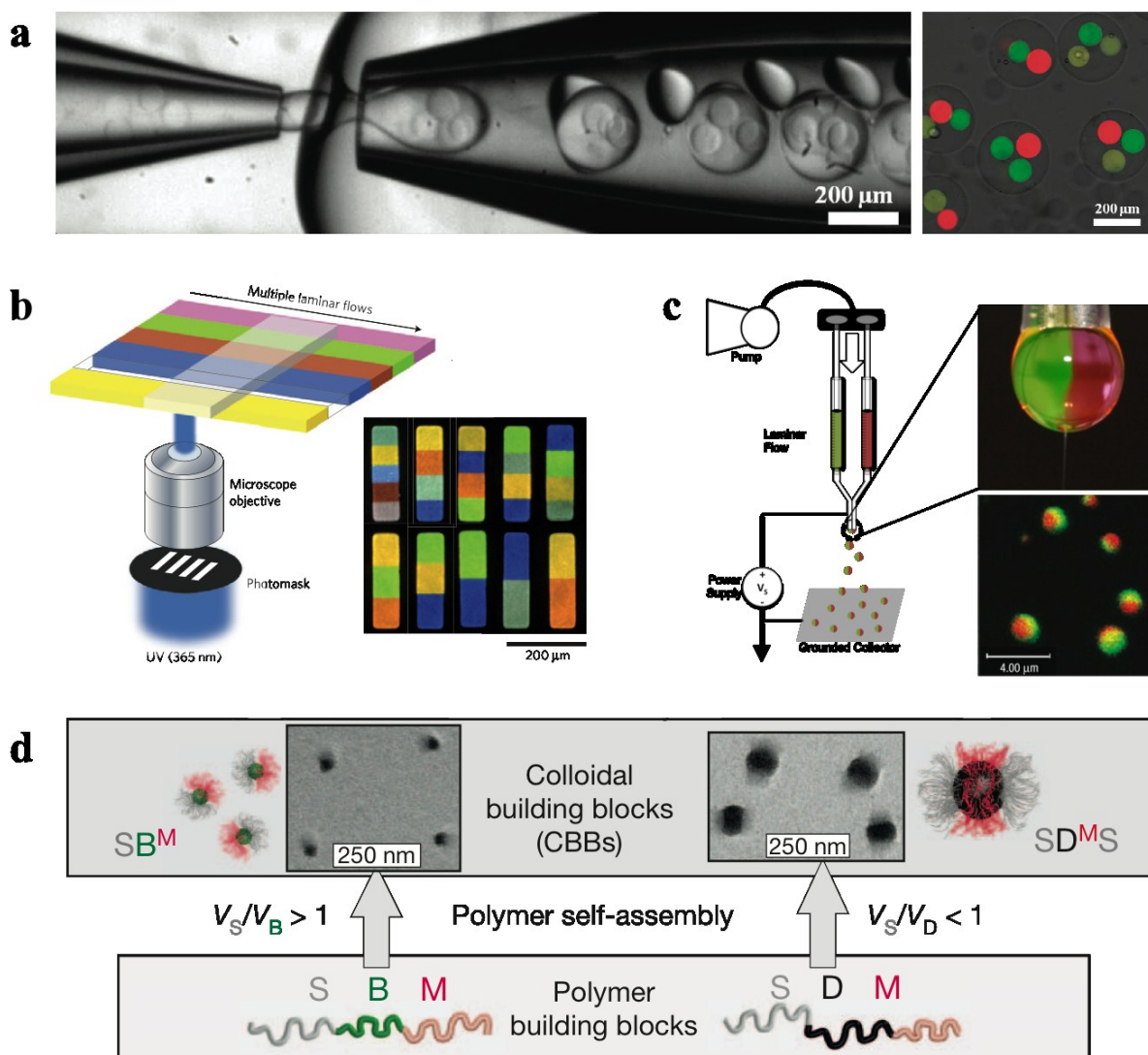
**Figure 2.** Examples of simultaneous fabrication processes. (a) Multicompartmental particles via immiscible phases. Adapted with permission from ref.[48] Copyright 2011, American Chemical Society. (b) Stop flow lithography. Adapted with permission from ref.[53] Copyright 2014, Nature Publishing Group. (c) EHD co-jetting. Adapted with permission from ref.[54] Copyright 2005, Nature Publishing Group. (d) Self-assembly of multiblock copolymers. Adapted with permission from ref.[62] Copyright 2013, Nature Publishing Group.
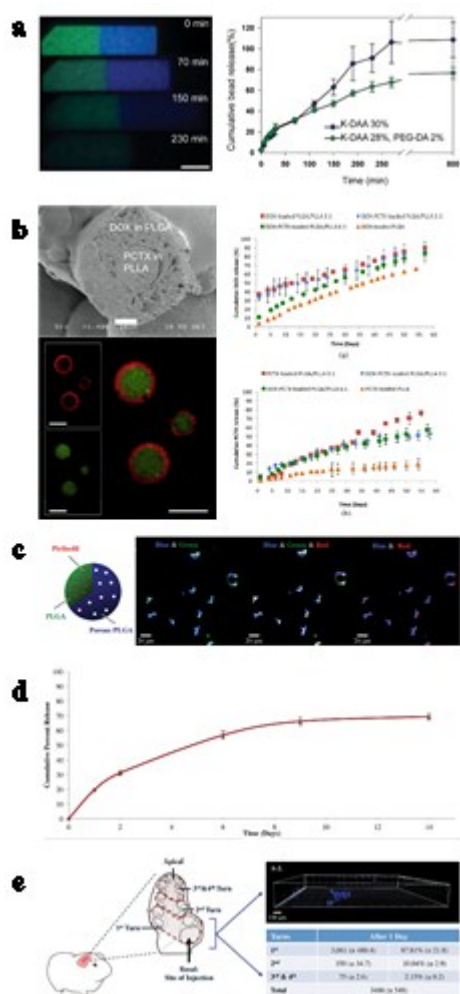
**Figure 3.** (a) Release of fluorescent beads from bicompartmental hydrolysable particles with one compartment crosslinked. Scale bar 50 μm. Adapted with permission from ref.[51] Copyright 2016, Wiley. (b) Release of doxorubicin and paclitaxel from core-shell PLA/PLGA microparticles. Scale bar 30 μm. Adapted with permission from ref.[77] Copyright 2015, Elsevier. (c) – (e) Bicompartmental particles for cochlear imaging and drug delivery, with representative confocal imaging (c), release of piribedil (d), and imaging of cochlea after intracochlear delivery (e). Adapted with permission from ref.[87] Copyright 2016, Wiley.
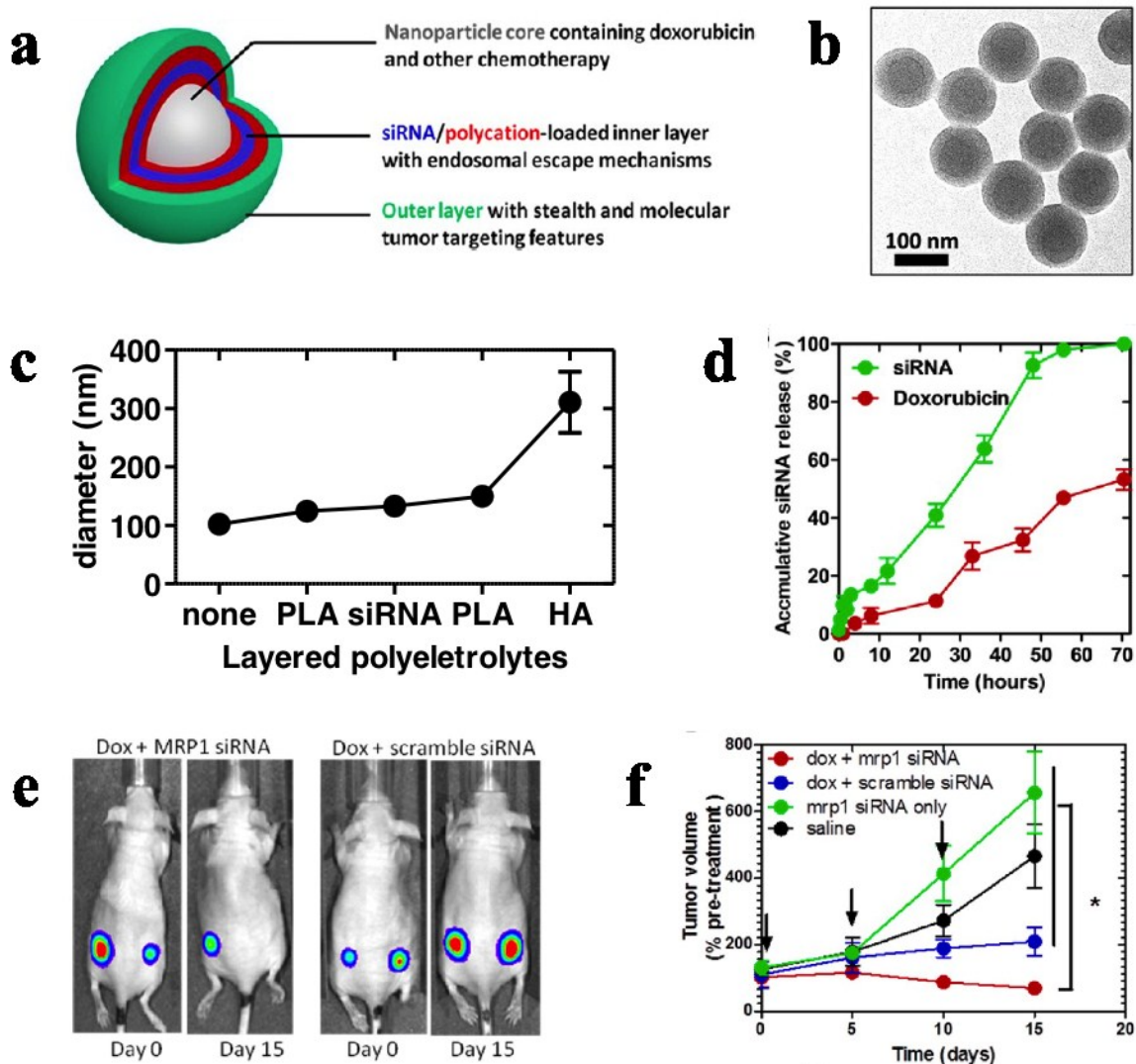
**Figure 4.** Multicompartmental nanoparticles with core-shell and LbL architectures made by Hammond et al. for simultaneous drug and siRNA delivery for triple negative breast cancer (TNBC). (a) Design of multicompartmental particle. (b) Multicompartmental particles with polystyrene core. (c) Size of multicompartmental particles with liposome core at each LbL step. (d) Release of doxorubicin and siRNA from particles. (e) IV administration of particles in mouse model of TNBC, showing localization to tumors, and interval decrease in signal. (f) Quantitative measure of tumor volume over time for various formulations of particles with ones loaded with both doxorubicin and siRNA against MRP1 associated with least increase in tumor volume over time. Adapted with permission from ref.[91] Copyright 2013, American Chemical Society.
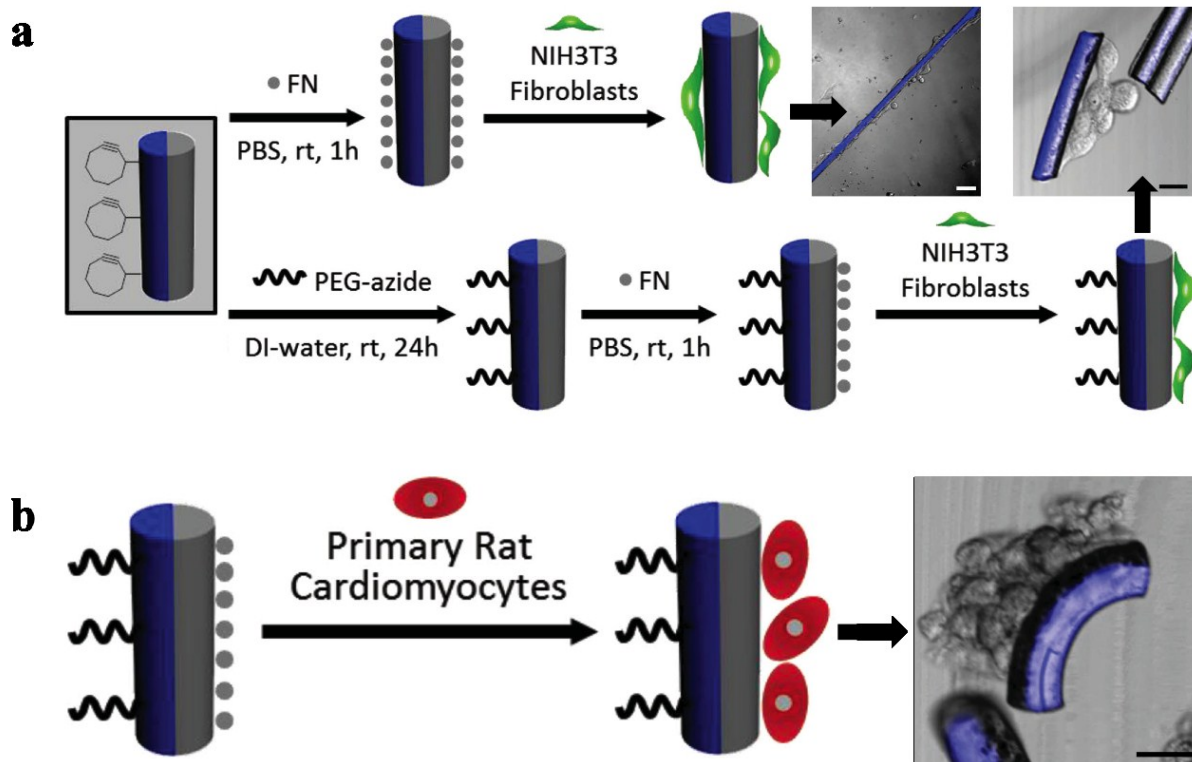
**Figure 5**. Bioacuators made using EHD co-jetting. (a) Demonstration of selective binding of NIH3T3 cells to fibronectin (FN) adsorbed surfaces. Left confocal scale bar 50 μm, right confocal scale bar 20 μm. (b) Selective binding of primary rat cardiomyocytes to one compartment with FN adsorbed to surface, and actuation of particle by contraction of cardiomyocytes. Scale bar 20 μm. Adapted with permission from ref.[94] Copyright 2015, Wiley.
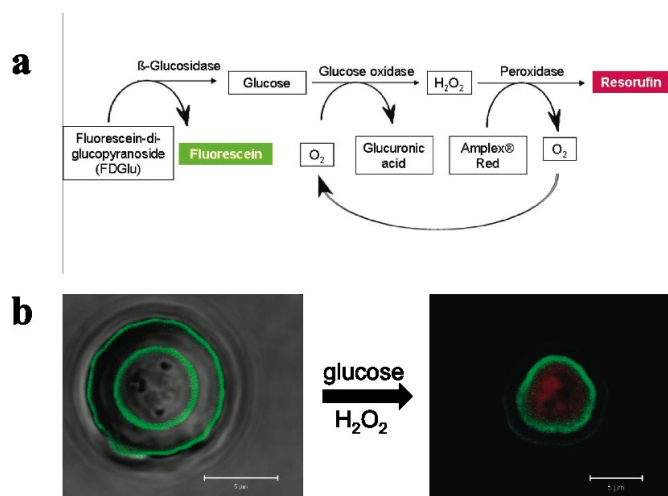
**Figure 6.** Coupled enzymatic reaction within CaCO$_3$-based core-shell microparticles. (a) Diagram of enzyme cascade. (b) Green fluorescent compartments containing enzymes per above diagram, with production of resorufin in core after addition of glucose and H$_2$O$_2$. Adapted with permission from ref.[100] Copyright 2010, American Chemical Society

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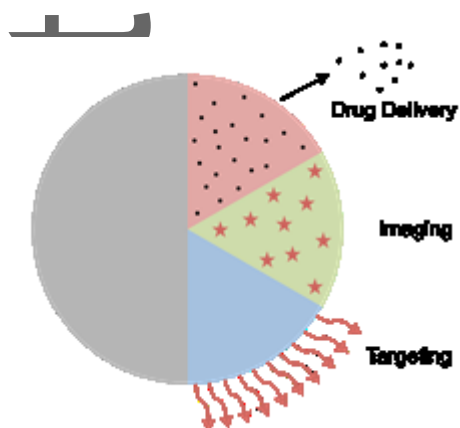


**Multicompartmental particles comprise a broad class of anisotropic particles** that have become of interest in a variety of applications. As more sophisticated materials processing techniques have been developed to more reliably produce such particles on a large scale, increasingly robust data has been published demonstrating their potential, particularly in medical applications. Here we review recent progress in the development of multicompartmental particles in medicine.

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**Progress with multicompartmental particles for medical applications**

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