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Highlighting the Usage of Polymeric Nanoparticles for the Treatment of Traumatic Brain Injury: A Review Study

For Biomaterials in Neuronal Repair

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Highlights

- Polymeric nanoparticle chemistry, shape, corona, and size all impact their behavior
- Targeting microglial and endothelial cells can lead to substantial improvements following TBI
- Targeting peptides can have a role in spite of the limited changes in overall biodistribution in that peptides do lead to an enrichment of nanoparticles in the brain regions
- The vast majority of work to date is targeted towards acute injury, but the findings suggest directions for chronic TBI treatment via nanoparticles as well.

Abstract

There are very limited options for treating traumatic brain injury (TBI). Nanoparticles offer the potential of targeting specific cell types, and, potentially, crossing the BBB under the right conditions making them an area of active research for treating TBI. This review focuses on polymeric nanoparticles and the impact of their chemistry, size, and surface groups on their interactions with the vasculature and cells of the brain following injury. The vast majority of the work in the field focuses on acute injury, and when the work is looked at closely, it suggests that nanoparticles rely on interactions with vascular and immune cells to alter the environment of the brain. Nonetheless, there are promising results from a number of approaches that lead to behavioral improvements coupled with neuroprotection that offer promise for therapeutic outcomes. The majority of approaches have been tested immediately following injury. It is not entirely clear what impact these approaches will have in chronic TBI, but being able to modulate inflammation specifically may have a role both during and after the acute phase of injury.

1. Introduction

The CDC estimates that 214 people died each day in 2014 from traumatic brain injuries (TBIs). TBIs contribute substantially to injury-related deaths from motor vehicle accidents, and traumas more broadly (Wang et al. 2016; Taylor et al. 2017). The lethality can be attributed in no small part to the initial hours of impact, but it has been found through recent studies (Ladak et al. 2019; Oberholzer and Muri 2019) secondary effects can be deadly, or at the very least, cause substantial damage. In TBI, the first observed phenomena following mechanical trauma is the rupture of microvessels (Sandsmark et al. 2019). An injury cascade ensues that includes ischemia, anoxia, free-radical formation, inflammation and excitotoxicity that occur over hours and days following injury (Veenith et al. 2016). To mitigate these secondary effects, multiple methods are being conducted to prevent the neuronal cell death that follows, prominent and promising among them being nanoparticle delivery (Abdal Dayem et al. 2017; Alam Bony and Kievit 2019).

The advent of nanoparticle delivery in TBI patients is a relatively new development but has had far more field testing in cancer-based treatments. Nanoparticles have been shown to be versatile and penetrative transports for pharmaceutical drugs that otherwise could not have accumulated effectively in cancer treatment (Zhang et al. 2011; Park et al. 2017). This translation has allowed

for a number of nanoparticle technologies to be introduced simultaneously into TBI therapeutics, all contributing potentials for repair to brain function (Alam Bony et al. 2019).

The most famous polymeric delivery system used in the brain is the Gliadel wafer (Brem et al. 1995). Used as a polymer implant for continuous carmustine drug introduction to glioma tumors, gliadel wafers have been shown to generally increase survival in tumor patients in greater number than the few other currently approved U.S. Food and Drug Administration delivery methods (Ashby et al. 2016; Doishita et al. 2018). While the Gliadel wafer system is revolutionary, like all interventions, there are challenges. The surgical implant process risks brain edema, and the limited transport of the drug from the wafer limits the long term impact (Kuramitsu et al. 2015). There is hope that a nanoparticle system, particularly a peptide nanoparticle system, if designed thoughtfully, could circumvent some of the limitations associated with implants and be more suited to TBIs (Kwon et al. 2016).

To better understand the potential of nanoparticle delivery as a TBI therapeutic agent, we will present our review primarily on the usage of polymeric nanoparticles in all of their varieties, analyzing their biochemical usages based on factors of penetration, accumulation, and versatility. We also will analyze the corresponding targeting molecules these polymerics may pair with for added benefits, of which primarily corresponds to targetability. Finally, analyzing nanoparticles more holistically to speculate on further nanoparticle delivery systems alongside polymerics and how they may influence the way we target and diagnose TBI altogether.

2. Polymeric nanoparticles

Polymer nanoparticles are used a great deal in TBI research. The ability to combine different surface elements, coronas, and targeting moieties coupled with their ability to deliver drugs and provide contrast in a number of imaging modalities make them extremely attractive as a platform for TBI (Liao et al. 2020). The ability of many of the polymeric systems to degrade and be cleared by the body is also critical to their use.

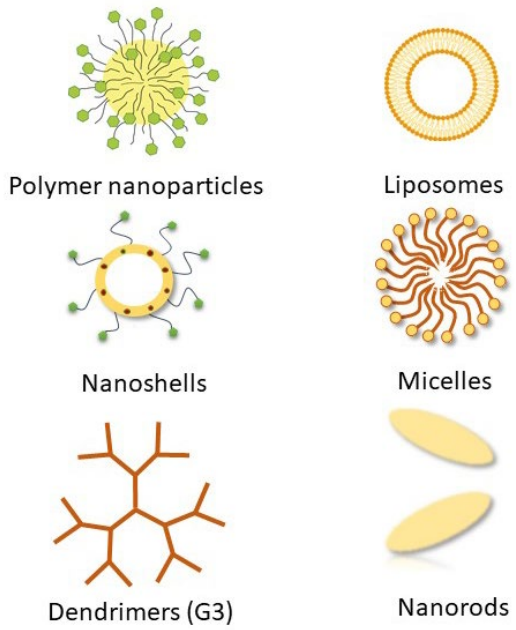

Figure 1: Examples of some of polymeric nanoparticles used in TBI research. Polymer nanoparticles can be made from a range of materials but are often from degradable polymers such as polyesters functionalized with PEG to form a corona to increase circulation time (. Nanoshells are polymer capsules filled with air or gas filled cores. Dendrimers organize into hierarchical particles. Liposomes, based on lipid bilayer systems have drawn a great deal of interest for TBI and have been used in the clinic in a number of applications including for delivery of chemotherapy agents (liposomes delivering doxorubicin, DOXIL, for example.) Micelles are spherical structures based on amphiphilic molecules with hydrophobic cores. A number of groups have looked at altering the shape of nanoparticles to nanorods or other shapes to increase circulation and promote targeting to specific tissues.

Table 1: Examples of Nanoparticles for TBI and their targets

Particles	**Structure**	**Attributes**	**Potential Targets**	**Reference**
Polyester nanoparticles	Range of sizes (100-1000 nm), versatile composition	Large experience with delivery of small and large molecules	Endothelial Cells Microglial Cells Macrophages Astrocytes	(Carroll et al. 2010; Tahara et al. 2010; Khalin et al. 2016)
Nanoshells and nanocapsules	Often air or gas filled, versatile composition Range of sizes (50-900 nm)	Drug delivery, ultrasound contrast, light responsive	Endothelial Cells Sites of degeneration	(Sershen et al. 2000; Patel et al. 2009; Morton et al. 2010; Menikheim et al. 2020)
Dendrimers	Highly-branched, smaller particles on average, organized (5-20 nm for each molecule)	Prodrug potential, endocytosed by immune cells	Microglial Cells Immune Cells more broadly	(Kannan et al. 2017; Sharma et al. 2018; Zhu et al. 2019; Sharma et al. 2020)
Liposomes	Hollow, amphiphilic, bilayer (50 nm-1000 nm)	Long circulation time, potential for cell fusion and internalization	Mitochondria Immune Cells	(Boyd et al. 2015; Kaijzel et al. 2017)
Micelles	Amphiphilic molecules, monolayered	Simple formulations for delivery	Areas of leaky BBB	(Gilmore et al. 2008; Denora et al. 2009)
Nanorods	High aspect ratio, made from a range of polymers	Long circulation, adaptive targeting	Similar to polyester nanoparticles but longer circulation	(Thompson et al. 2013; Karathanasis and Ghaghada 2016)

			time to reach targets	

2.1 Polyester nanoparticles

One of the most common polymers used in nanoparticles for drug delivery applications is the class of degradable polyesters, poly(lactic acid) (PLA), and poly(lactic-co-glycolic acid) (PLGA). These polyesters are favored for their widespread availability and previously established approval and utilization in commercially available products (Tahara et al. 2011; Cruz et al. 2016; Inyang et al. 2020).

The size of polyester nanoparticles has been shown to be critical for penetration into rodent brains (Cruz et al. 2016). PLGA nanoparticles were fabricated in sizes of 100 nm, 200 nm, and 800 nm. The nanoparticles all had a poly(ethylene glycol) PEG corona to facilitate their circulation time, and 800CW, a cyanine dye that binds to necrotic areas, on the surface to target injury (Cruz et al. 2016). When the particles were administered systemically, the majority went to the liver, as is typical with systemically administered nanoparticles. While 800CW improved targeting, smaller particles (100 and 200 nm) were essential to get to the area of injury. A similar impact of particle size has been well documented by others, who found injury areas to be most reduced by polymerics smaller than 200nm, and most effective when less than 100nm (Bharadwaj et al. 2016; Bharadwaj et al. 2018). This effect showed greater accumulation, as well as greater clearance time. Notably, sex plays a role in nanoparticle accumulation with female mice exhibiting greater accumulation of nanoparticles at longer timepoints post injury (Bharadwaj et al. 2020).

One of the major challenges of treating brain injury is the blood-brain barrier (BBB). The BBB is disrupted in the early acute phase of TBI, being the initial catalyst for much of the secondary effects consequently following (Bharadwaj et al. 2018; Cash and Theus 2020). As a part of the increased permeability following injury, polyester nanoparticles can penetrate and accumulate (Miller et al. 2019). While crossing the BBB is one area of active research, there is much that can be achieved by targeting the endothelial cells in the region of TBI. Polyester nanoparticles can interact and deliver drugs to the endothelial cells that improve neurological outcomes, such as delivering drugs that reduce reactive oxygen species and maintain BBB integrity to preserve neural tissue (Table 1, Lutton et al. 2019) as well as other molecules (Inyang et al. 2020). In a related approach, our lab has previously shown polyester nanoparticles designed to reduce bleeding can reduce neurodegeneration after blast TBI and exhibit more expression of a marker for the BBB functionality, highlighting to us the increased rate of reformation in turn (Hubbard et al. 2018). These nanoparticles improved outcomes on their own, but when loaded with dexamethasone, they led to further improvements.

The work looking at polyester nanoparticles and the impact of size and sex on their penetration after TBI is essential for the broader nanoparticle field. Polyester nanoparticles are an attractive system in that they have been used to deliver a wide range of small and large molecules ranging from steroids to Tempol to growth factors like brain-derived neurotrophic factor (BDNF) (Khalin et al. 2016; Gonzalez-Pizarro et al. 2018; Inyang et al. 2020). However, polyester nanoparticles can trigger infusion reactions which must be dealt with if they are to be administered systemically (Onwukwe et al. 2018; Zhou et al. 2018; Maisha et al. 2020) because these infusion reactions can be lethal and can exacerbate outcomes. Infusion reactions generally occur within

minutes of intravenous administration of nanoparticles or biologics and have been documented across nanomaterials ranging from Doxil to iron oxide formulations for MRI, nanoparticle iron infusions for severe anemia (Banda et al. 2014; Rampton et al. 2014), polyester nanoparticles, as well as cellular therapies and biologics (Szebeni 2012). These reactions lead to the need for slow infusions and careful management, and infusion reactions, in a substantial portion of patients, limit the treatments available. For example, in the case of Doxil, even with this slow infusion rate to mitigate the infusion effect, in approximately 10% of patients, the response leads to serious cardiac side effects (Goram and Richmond 2001). These side effects can be lethal and limit translation of promising new therapies to patients.

2.2 PBCU nanoparticles, polyurethane nanoparticles and nanogels

Poly(butyl cyanoacrylates) (PBCU) polymers have been studied for many years for biomedical applications. Poly(butyl cyanoacrylates) are commonly referred to as superglue and have been explored as nanoparticles for crossing the BBB for over a decade (Weiss et al. 2008; Kulkarni et al. 2010; Tian et al. 2011), still continuing to be studied to this day(Chung et al. 2017; Elgattar et al. 2019; Lin et al. 2019). The nanoparticles are easily synthesized, and the chemistry can be tailored by the choice of precursors as well as excipients. The delivery of drugs from PBCU is generally quite fast over a few hours, but the true attraction is their potential to cross the BBB (Weiss et al. 2008; Kulkarni et al. 2010; Tian et al. 2011). The percentage of nanoparticles that cross the BBB is similar to other polymeric nanoparticles including polystyrene nanoparticles (Bharadwaj et al. 2016; Bharadwaj et al. 2020) and polyester nanoparticles (Carroll et al. 2010; Khalin et al. 2016). Like polystyrene nanoparticles, PBCU nanoparticles are not degradable which may raise concern for some applications where their presence may stimulate an undesirable immune response, though over the short term, they are well tolerated (Kolter et al. 2015).

Polyurethane nanoparticles can degrade hydrolytically or enzymatically depending on the chemistry of the particles and the environment (Hung et al. 2009; Feng et al. 2017; Aluri et al. 2018; Pramanik et al. 2018). Like PBCU nanoparticles, the chemistry to synthesize polyurethane nanoparticles is straight forward and flexible. The particles are often made via an interfacial polymerization that leads to hollow nanocapsules (Bouchemal et al. 2004; Johnsen and Schmid 2007; Menikheim et al. 2020). These nanocapsules, in some cases, are ultrasound responsive which can lead to on demand drug release which could be very valuable in the CNS (Menikheim et al. 2020). These materials are being pursued for delivery of molecules to the brain in a number of models (Kim et al. 2015; Patel and Patel 2017).

Nanogels are hydrogel-based nanoparticles that can deliver drugs and have shown promise for delivery to the CNS. These hydrogel nanoparticles consist of crosslinked, water soluble polymers ranging from poly (N-isopropyl acrylamide) grafted with fibrinogen for the delivery of multiple drugs in a tumor model (Rejinold et al. 2014) to amine functionalized PEG nanogels for microglial targeting (Mauri et al. 2020). Because these materials are water swollen, they have historically been challenging to use as drug delivery systems, but with careful molecular design to promote affinity-based interactions, not only are they able to be loaded with drugs, but can be made to be stimuli responsive which opens up new avenues for therapy (Vinogradov 2007; Vashist et al. 2018). Importantly, there is evidence that nanogels can cross the BBB (Patel et al.

2017; Rueda and Cruz 2017; Khan et al. 2018; Harilal et al. 2020), and nanogels have been shown to be suitable for intranasal delivery (Aderibigbe and Naki 2018; Cuggino et al. 2019).

2.3 Dendrimer Nanoparticles

Dendrimer nanoparticles have an organized, hierarchical structure (Table 1). The individual dendrimer molecules are highly branched (Figure 1). The most famous of these molecules is poly(amidoamine) (PAMAM), but dendrimers have been synthesized from a wide range of starting molecules and have been used to deliver a number of drugs (Chauhan 2018). The classic PAMAM polymer has amines throughout the hyperbranched structure which can facilitate very selective delivery of particular drugs (Chauhan 2018). The individual dendrimer molecules organize to form nanoparticles, and the hierarchical organization means that these particles are monodisperse which is something of a rarity in the nanoparticle field. One of the exciting things about dendrimer systems, is that dendrimers can be prodrugs (da Silva Santos et al. 2016) which opens up potentially new therapeutic approaches. Examples of specific dendrimer-based prodrugs, their mechanisms, and applications are summarized beautifully in (da Silva Santos et al. 2016).

Dendrimers have been used in a number of brain injury and disease models (Zhu et al. 2019). One of the exciting components of dendrimers is their ability to be conjugated to drugs to facilitate delivery, and this has been leveraged in the brain. Sinomenine, an anti-inflammatory drug, has been conjugated to PAMAM which promoted delivery of the drug to activated macrophages and microglia in a rabbit model of TBI showing a reduction in inflammatory cytokines compared to the free drug (Sharma et al. 2020). Being able to target inflammatory cells specifically following TBI is essential for limiting the secondary degeneration, and dendrimers seem to be effective in targeting these cells (Sharma et al. 2018; Sharma et al. 2020). Perhaps we should not be surprised at this. Dendrimers have been a very attractive nanoparticle formulation for targeting inflammatory cells more broadly (Katsuki et al. 2017; Qu et al. 2017; Fruchon et al. 2019).

The use of anesthetics can modulate dendrimer nanoparticle uptake. A recent study looked at the impact of pentobarbital following TBI in mice and saw greater activation of microglial cells which correlated with uptake of dendrimer nanoparticles based on PAMAM (Kannan et al. 2017). While the authors noted the work showing BBB alterations by anesthetics, they did not characterize the BBB in the study. Nonetheless, the potential to augment nanoparticle uptake to microglial is an attractive approach for early interventions following TBI that seek to modulate inflammation. Nonetheless, the fact that anesthetics can activate microglial cells needs to be considered carefully in thinking through potential treatments. Being designed to target microglia give dendrimers a great potential in early restoration of acute TBI, but the uncertainty of how best to introduce them in clinical fashion still leaves more research to be done on how to proceed.

A second concern that must be addressed with the use of dendrimers is that many of the chemistries exhibit cytotoxicity requiring careful chemical tuning for applications in the brain (Zhu et al. 2019). This cytotoxicity is likely due to the amines present in the structures (Zhu et al. 2019).

2.4 Liposomal Delivery Systems

Liposomes are spheres of lipid bilayers that initially drew interest as models for cell membranes, but over time have become a cornerstone of nanoparticle drug delivery technologies (Figure 1, Table 1, Weissig 2017). Most recently, they have been in the news as a critical component of a number of the potential COVID-19 vaccines. They are used in the clinic for the delivery of drugs including doxorubicin for cancer therapy (Doxil, a PEGylated liposomal formulation), and Myocet, an unPEGylated liposomal formulation of doxorubicin, as well as analgesics such as Exparel, a liposomal formulation of bupivacaine (Bulbake et al. 2017). It is noted that the preceding names are the names for the approved formulations and are the names under which the majority of publications reference the nanomedicines. In some cases, there are now generics for these formulations that have been approved, with one such generic being for Doxil as an example. They can be formulated with a wide range of sizes from 100 to 1000 nanometers, and their surface charge and surface molecules can be tailored by the choice and ratio of lipids.

Liposomes, to a degree, are mimics of exosomes, and can achieve some of the functions of exosomes, but in a head-to-head study following TBI, they were not able to lead to the same functional improvements over time (Zhang et al. 2017). Nonetheless, they are a robust tool for getting molecules to the brain post injury. These synthetic, lipid-based particle carriers have the unique trait of transporting both hydrophobic and hydrophilic compounds to target sites, which is relatively unique among nanoparticle formulations.

One of the particularly intriguing targets for liposomes are mitochondria. Liposomes have been shown to deliver drugs to mitochondria in cancer studies, and the concept is to apply a similar approach following brain injury to deliver antioxidants and other drugs to mitochondria to mitigate secondary degeneration (Lamade et al. 2019). The principle is that liposomes could be administered during the acute phase of TBI when the BBB is destabilized permitting transport of the liposomes. However, while this is a neat idea, the challenge lies in designing liposomes that can both cross the BBB and interact with mitochondria. The chemistries may not be amenable to collocating in a single system which then opens questions regarding materials design. Nonetheless, the target is an attractive one, and liposomes may lend themselves to multilayered chemistries that could, potentially, address this challenge (Polak et al. 2015; Sironi et al. 2016).

Liposomes, though, are not the only particles with the potential for targeting mitochondria. Peptide-RNA particles infused (with mir-146a specifically?) following TBI targeted mitochondria and alter inflammation following injury (Wang et al. 2021) along with dendrimers which also target mitochondria in the brain (Sharma et al. 2018). Albumin particles modified with red blood cell membranes have been used to target mitochondria of neurons in the brain via intravenous delivery (Gao et al. 2020) and modified lipid particles with red blood cell coatings have also been used (Han et al. 2020). The multilayered chemistry approach makes intravenous administration with targeting mitochondria in the brain possible and is an exciting target for modifying inflammation post injury.

2.5 Polymersome nanoparticles

Similar in origin to liposomes, polymersomes take much of their inspiration from cellular vesicles, and include both hydrophobic and hydrophilic parts. Essentially, they are designed to mimic the lipid bilayer but with polymers rather than lipids which leads to a great deal of chemical flexibility in their design (Leong et al. 2018).

Polymersomes can enter cells via the same methods as liposomes because of their amphipathic nature and are able to carry a variety of compounds to different sites at relatively high loading (Tian et al. 2015; Kim et al. 2020). The ability to be loaded with high amounts of drugs is particularly important for drugs which have more limited potency and require larger amounts for efficacy. Polymersomes have been shown to increase the impact of drugs including a model protein, IgG (Tian et al. 2015) and carnosine (Kim et al. 2020). Notably, in both, the polymersome chemistry was optimized to cross the BBB, and the targeting molecule, LPR-1, was essential for the greatest effect.

In general, polymersomes function in a similar capacity to normal polymer-type nanoparticles, retaining much of the same benefits while holding drugs in greater amounts, potentially, within their hollow shells.

2.6 A Word About Particle Shape and Size

The majority of nanoparticles are classic, spherical particles. The chemistry and processing conditions for their synthesis is straight forward. However, altering the shape of nanoparticles either by making chains of them (Karathanasis et al. 2016; Covarrubias et al. 2018), stretching them (Song et al. 2019), or synthesizing rods (Thompson et al. 2013; Quach and Kah 2017) can dramatically impact both their circulation time and the molecules and cells the particles interact with. The majority of research focuses on spheres, but that is just a starting point for the kinds of materials that could be used.

Even focusing on spheres, size matters. In the literature, nanoparticles describe systems that are as small as 1 nm to those close to 1000 nm. Three orders of magnitude is a wide range of particles, and the size and shape have impacts cell uptake, extravasation, and where particles move in blood vessels in a positive manner as it is reduced (Thompson et al. 2013; Namdee et al. 2014; Vashist et al. 2018; Kaur et al. 2019; Miller et al. 2019; Wu et al. 2019; Bharadwaj et al. 2020).

3. Targeting Molecules and Surfactants

For the vast majority of nanoparticles used for brain delivery, targeting systems have been deemed to be essential. The majority of targeting systems have been peptide based, but other, non-peptide and non-biologic surface modifications have, in many cases, proven to be as good or better than the traditional peptide targeting routes (Mann et al. 2016; Inyang et al. 2020).

3.1 Peptide Targeting Molecules: CAQK and beyond

The peptide, CAQK, was identified via phage display in mice with acute brain injury as a potential target peptide and has been shown to increase accumulation of nanoparticles in the injured region (Mann et al. 2016). The peptide is intriguing in that it has strong affinity to thrombin rich areas, a quality found immensely more in TBI damaged regions compared to uninjured areas (Wu et al. 2019). The conjugation of CAQK to nanoparticles results in distinct targeting towards impacted areas and has been shown to amplify the accumulation rates and effects of the drugs administered (Mann et al. 2016; Wu et al. 2019).

The Tat-NR2B9c peptide has been shown to be neuroprotective but delivery was a challenge. Wu et al. fabricated 30 nm Tat0NR2B9c loaded protein nanoparticles conjugated with CAQK (C-TN-APNP), as well a CAQK version specifically conjugated to the N-terminal cysteine (CC-

TN-APNP). Administration of the nanoparticles showed more penetration and accumulation results within the CC-TN-APNP particles than the C-TN-APNP particles in the thrombin rich areas. The CC-TN-APNPs also showed improvements in behavioral outcomes and reduction in lesion volume compared to unconjugated controls (Wu et al. 2019). The targeting peptide improves accumulation and outcomes, and the specific presentation of the peptide in the CC-TN-APNP case is important for the most robust response.

While we have all known for some time that targeting moieties do not alter the biodistribution of particles substantially (Wilhelm et al. 2016), the change at the site of injury can be enough to have an impact as seen here.

There are, of course, a large number of targeting peptides that have been considered. There are peptides for membrane targeting, blood vessel, clots, enzymes, and damage and the peptides range in size from 346 Da (RGD) to 1796 Da for an ER insertion sequence. A strong summary of peptide targeting molecules is available by Spicer et al. (Spicer et al. 2018).

For targeting peptides to be effective, it is essential that the nanoparticles have long circulation times and avoid clearance. Traditionally, as we have noted, this is done by PEGylation. PEGylation, the attachment of PEG molecules to a particle or molecule is relatively easy. PEG chemistry is fantastically flexible. However, PEG may not be the panacea we would hope. People make antibodies to PEG, and these have been implicated in clearance of molecules and nanoparticles (Gabizon and Szebeni 2020). To address this, researchers have delved into a range of other hydrated corona molecules including dextrans (Vogt et al. 2015; Coty et al. 2017; Shen et al. 2018) and zwitterionic systems (Barrán-Berdón et al. 2013; Maiolo et al. 2014; Safavi-Sohi et al. 2016; Debayle et al. 2019). The thought behind these systems is to reduce the protein absorption during systemic circulation to increase circulation time, impact targeting, and avoid infusion reactions (Moghimi 2018; Onwukwe et al. 2018; Fülöp et al. 2019; Moghimi et al. 2019; Szebeni and Bawa 2020).

3.2 Surfactants: P188 and Non-biologics

Poloxamer 188 (P188) is a non-ionic, surfactant copolymer with amphiphile characteristics that has shown in recent studies a similar conjugation ability to peptide-based polymer systems for introduction in TBI (Inyang et al. 2020). The polymer is a block copolymer of PEG-poly(propylene oxide)-PEG, and 188 refers to the molecular weight. Poloxamer 188 is well known for being a membrane sealant which has important implications for many cells including neurons (Moloughney and Weisleder 2012). Not surprisingly, systemically administered poloxamer 188 has been shown to reduce autophagy in a mouse model following TBI. (Bao et al. 2016).

Because of this membrane behavior, P188 has been encapsulated into polyester nanoparticles leading to some improvements following TBI (Inyang et al. 2020). However, the most common application of P188 with nanoparticles is as an additive to avoid nanoparticle aggregation during storage and lyophilization. The choice of surfactants for storage can have important knock on effects for the use of nanoparticles in vivo (Wei and Ge 2012; Jain et al. 2013; Selin et al. 2018). While a number of poloxamers do reseal membranes, not all do (Kwiatkowski et al. 2020). The molecular weight matters in the role that they play in vivo, being particularly optimal for balancing proper water solubility while maintaining a nontoxic composition (Moloughney and Weisleder 2012). Furthermore, surfactants can, independent of their interaction with

nanomaterials have significant immunological effects such as complement activation (Onwukwe et al. 2018).

While surfactants may play a role in targeting (Sun et al. 2004; Petri et al. 2007), that role is likely impacted by the nanomaterial, surface functionalities, and host. Things that work well in small animal models can lead to unexpected findings as one moves to large animal models and encounters the complexities of the immune systems in these species (Szeto and Lavik 2016).

4. Potential Future Directions in Nanoparticles Applications for TBI

4.1 Gold Nanoparticles

While polymer nanoparticles excel at delivering drugs and other important compounds to therapeutic targets in a distinct and effective manner, metallic nanoparticles have gained much attention for their ability to potentially combine visualization with delivery and, in some studies, travel effectively through tissues in which polymeric nanoparticles move poorly (Sanavio et al. 2018).

Gold nanoparticles can be conjugated easily to molecules to facilitate tracking and characterization of the molecular interactions. Microdialysis studies using gold-heparin nanoparticles contribute to the literature on inflammatory responses post TBI (Giorgi-Coll et al. 2017). The heparin acts as a capture molecule for inflammatory cytokines. Gold nanoparticles with heparin functionalization showed enhanced cytokine binding when assessed comparatively, proving to be a great alternative given the benefits of size, biocompatibility, and optical nature (Giorgi-Coll et al. 2017). Further noted for their modularity, gold nanoparticles open new directions in the brain post injury.

Gold nanoparticles have long been used as a key component of in vitro diagnostic tests and recently been used for a neuron-specific enolase test in blood plasma (Gao et al. 2017). Being able to use them in vivo potentially offers some neat opportunities. They can be modified to deliver drugs and nucleic acids (Labala et al. 2015; Yuan et al. 2018), and their ability to cross membranes is intriguing (Kim et al. 2009), although the mechanisms by which they cross is an active area of research.

4.2 Nanoparticles in the Later Stages of TBI

The majority of work thus far has focused on nanoparticle delivery systems for the acute phase of TBI, when the BBB is disrupted for easy diffusion of drug compounds. Research may focus on how to aid patients that recently receive injury, but many patients arrive long after the initial impact when the secondary effects impacted the surrounding tissue and the BBB is more intact.

As previously noted, anesthesia does cause the BBB to be briefly destabilized while in effect, potentially giving time for particle diffusion (Kannan et al. 2017). Likewise, focused ultrasound holds great promise for temporary disruption of the BBB and penetration of nanoparticles (Sanavio et al. 2018; Sultan et al. 2018; Wang et al. 2018; Ye et al. 2018).

Assuming nanoparticles can get to the region of interest, the big question remains as to what would be the most useful for chronic TBI from a nanoparticle delivery perspective. To date, there has been limited work in the area. However, we know that there is long term inflammation following TBI (Xiong et al. 2018; Needham et al. 2019; Yilmaz et al. 2019), and some of the acute approaches could, potentially, have impacts in the longer term.

On the delivery vehicle front, there are opportunities to understand diffusion of molecules and replicate the approach using, for example, polymersomes or peptide-based systems (Khalin et al. 2016; Mann et al. 2016; Wu et al. 2019).

5. Conclusion

The clinical landscape of treating TBI in the initial hours of impact remains a challenge, and it is arguably, easier to tackle than chronic TBI. The dearth of treatment options is incredibly frustrating, but there is hope in the research being done that suggests new opportunities to treat TBI.

While many strategies are currently being researched and tested under a variety of criteria, nanoparticle delivery remains a promising method to deliver drugs to therapeutic targets. Among those that have substantial research attributed to them, polymer nanoparticles have stood out as advantageous carriers on account of their permeability and accumulation rates, as well as their simplistic design process and biodegradability. As with most nanoparticle delivery methods however, much remains to be seen regarding the potential avenues polymers systems can be utilized in, and whether that role must remain solely drug delivery-based or if can be compounded with similar methods. To leverage this potential, we need to wade into the details of the chemistry and build interdisciplinary teams to unpack the relationship between the details of the particles, corona molecules, targeting strategies, and excipients to develop safe and effective strategies. The details matter.

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References

Abdal Dayem, A., M. K. Hossain, S. B. Lee, K. Kim, S. K. Saha, G. M. Yang, H. Y. Choi and S. G. Cho (2017). "The Role of Reactive Oxygen Species (ROS) in the Biological Activities of Metallic Nanoparticles." Int J Mol Sci **18**(1).

Aderibigbe, B. A. and T. Naki (2018). "Design and Efficacy of Nanogels Formulations for Intranasal Administration." Molecules **23**(6).

Alam Bony, B. and F. M. Kievit (2019). "A Role for Nanoparticles in Treating Traumatic Brain Injury." Pharmaceutics **11**(9).

Aluri, R., S. Saxena, D. C. Joshi and M. Jayakannan (2018). "Multistimuli-Responsive Amphiphilic Poly(ester-urethane) Nanoassemblies Based on l-Tyrosine for Intracellular Drug Delivery to Cancer Cells." Biomacromolecules **19**(6): 2166-2181.

Ashby, L. S., K. A. Smith and B. Stea (2016). "Gliadel wafer implantation combined with standard radiotherapy and concurrent followed by adjuvant temozolomide for treatment of newly diagnosed high-grade glioma: a systematic literature review." World J Surg Oncol **14**(1): 225.

Banda, N. K., G. Mehta, Y. Chao, G. Wang, S. Inturi, L. Fossati-Jimack, M. Botto, L. Wu, S. Moghimi and D. Simberg (2014). "Mechanisms of complement activation by dextran-coated superparamagnetic iron oxide (SPIO) nanoworms in mouse versus human serum." Part Fibre Toxicol **11**(1): 64.

Bao, H., X. Yang, Y. Zhuang, Y. Huang, T. Wang, M. Zhang, D. Dai, S. Wang, H. Xiao, G. Huang, J. Kuai and L. Tao (2016). "The effects of poloxamer 188 on the autophagy induced by traumatic brain injury." Neurosci Lett **634**: 7-12.

Barrán-Berdón, A. L., D. Pozzi, G. Caracciolo, A. L. Capriotti, G. Caruso, C. Cavaliere, A. Riccioli, S. Palchetti and A. Laganà (2013). "Time evolution of nanoparticle-protein corona in human plasma: relevance for targeted drug delivery." Langmuir **29**(21): 6485-94.

Bharadwaj, V. N., C. Copeland, E. Mathew, J. Newbern, T. R. Anderson, J. Lifshitz, V. D. Kodibagkar and S. E. Stabenfeldt (2020). "Sex-Dependent Macromolecule and Nanoparticle Delivery in Experimental Brain Injury." Tissue Eng Part A **26**(13-14): 688-701.

Bharadwaj, V. N., J. Lifshitz, P. D. Adelson, V. D. Kodibagkar and S. E. Stabenfeldt (2016). "Temporal assessment of nanoparticle accumulation after experimental brain injury: Effect of particle size." Sci Rep **6**: 29988.

Bharadwaj, V. N., R. K. Rowe, J. Harrison, C. Wu, T. R. Anderson, J. Lifshitz, P. D. Adelson, V. D. Kodibagkar and S. E. Stabenfeldt (2018). "Blood-brainbarrier disruption dictates nanoparticle accumulation following experimental brain injury." Nanomedicine **14**(7): 2155-2166.

Bouchemal, K., S. Briançon, E. Perrier, H. Fessi, I. Bonnet and N. Zydowicz (2004). "Synthesis and characterization of polyurethane and poly(ether urethane) nanocapsules using a new technique of interfacial polycondensation combined to spontaneous emulsification." Int J Pharm **269**(1): 89-100.

Boyd, B. J., A. Galle, M. Daglas, J. V. Rosenfeld and R. Medcalf (2015). "Traumatic brain injury opens blood-brain barrier to stealth liposomes via an enhanced permeability and retention (EPR)-like effect." J Drug Target **23**(9): 847-53.

Brem, H., M. G. Ewend, S. Piantadosi, J. Greenhoot, P. C. Burger and M. Sisti (1995). "The safety of interstitial chemotherapy with BCNU-loaded polymer followed by radiation therapy in the treatment of newly diagnosed malignant gliomas: phase I trial." J Neurooncol **26**(2): 111-23.

Bulbake, U., S. Doppalapudi, N. Kommineni and W. Khan (2017). "Liposomal Formulations in Clinical Use: An Updated Review." Pharmaceutics **9**(2).

Carroll, R. T., D. Bhatia, W. Geldenhuys, R. Bhatia, N. Miladore, A. Bishayee and V. Sutariya (2010). "Brain-targeted delivery of Tempol-loaded nanoparticles for neurological disorders." J Drug Target **18**(9): 665-74.

Cash, A. and M. H. Theus (2020). "Mechanisms of Blood-Brain Barrier Dysfunction in Traumatic Brain Injury." Int J Mol Sci **21**(9).

Chauhan, A. S. (2018). "Dendrimers for Drug Delivery." Molecules **23**(4).

Chung, C. Y., M. H. Lin, I. N. Lee, T. H. Lee, M. H. Lee and J. T. Yang (2017). "Brain-Derived Neurotrophic Factor Loaded PS80 PBCA Nanocarrier for In Vitro Neural Differentiation of Mouse Induced Pluripotent Stem Cells." Int J Mol Sci **18**(3).

Coty, J. B., E. Eleamen Oliveira and C. Vauthier (2017). "Tuning complement activation and pathway through controlled molecular architecture of dextran chains in nanoparticle corona." Int J Pharm **532**(2): 769-778.

Covarrubias, G., A. Cha, A. Rahmy, M. Lorkowski, V. Perera, B. O. Erokwu, C. Flask, P. M. Peiris, W. P. Schiemann and E. Karathanasis (2018). "Imaging breast cancer using a dual-ligand nanochain particle." PLoS One **13**(10): e0204296.

Cruz, L. J., M. A. Stammes, I. Que, E. R. van Beek, V. T. Knol-Blankevoort, T. J. A. Snoeks, A. Chan, E. L. Kaijzel and C. Lowik (2016). "Effect of PLGA NP size on efficiency to target traumatic brain injury." J Control Release **223**: 31-41.

Cuggino, J. C., E. R. O. Blanco, L. M. Gugliotta, C. I. Alvarez Igarzabal and M. Calderón (2019). "Crossing biological barriers with nanogels to improve drug delivery performance." J Control Release **307**: 221-246.

da Silva Santos, S., E. Igne Ferreira and J. Giarolla (2016). "Dendrimer Prodrugs." Molecules **21**(6).

Debayle, M., E. Balloul, F. Dembele, X. Xu, M. Hanafi, F. Ribot, C. Monzel, M. Coppey, A. Fragola, M. Dahan, T. Pons and N. Lequeux (2019). "Zwitterionic polymer ligands: an ideal surface coating to totally suppress protein-nanoparticle corona formation?" Biomaterials **219**: 119357.

Denora, N., A. Trapani, V. Laquintana, A. Lopedota and G. Trapani (2009). "Recent advances in medicinal chemistry and pharmaceutical technology--strategies for drug delivery to the brain." Curr Top Med Chem **9**(2): 182-96.

Doishita, S., T. Shimono, T. Yoneda, E. Yamada, T. Tsukamoto, D. Takemori, D. Kimura, H. Tatekawa, S. Sakamoto and Y. Miki (2018). "In vitro Study of Serial Changes to Carmustine Wafers (Gliadel) with MR Imaging and Computed Tomography." Magn Reson Med Sci **17**(1): 58-66.

Elgattar, A., K. S. Washington, S. Talebzadeh, A. Alwagdani, T. Khalil, O. Alghazwat, S. Alshammri, H. Pal, C. Bashur and Y. Liao (2019). "Poly(butyl cyanoacrylate) nanoparticle containing an organic photoCORM." Photochem Photobiol Sci **18**(11): 2666-2672.

Feng, X., G. Wang, K. Neumann, W. Yao, L. Ding, S. Li, Y. Sheng, Y. Jiang, M. Bradley and R. Zhang (2017). "Synthesis and characterization of biodegradable poly(ether-ester) urethane acrylates for controlled drug release." Materials Science and Engineering: C **74**: 270-278.

Fruchon, S., E. Bellard, N. Beton, C. Goursat, A. Oukhrib, A. M. Caminade, M. Blanzat, C. O. Turrin, M. Golzio and R. Poupot (2019). "Biodistribution and Biosafety of a Poly(Phosphorhydrazone) Dendrimer, an Anti-Inflammatory Drug-Candidate." Biomolecules **9**(9).

Fülöp, T., G. T. Kozma, I. Vashegyi, T. Mészáros, L. Rosivall, R. Urbanics, G. Storm, J. M. Metselaar and J. Szebeni (2019). "Liposome-induced hypersensitivity reactions: Risk reduction by design of safe infusion protocols in pigs." Journal of controlled release : official journal of the Controlled Release Society **309**: 333-338.

Gabizon, A. and J. Szebeni (2020). "Complement Activation: A Potential Threat on the Safety of Poly(ethylene glycol)-Coated Nanomedicines." ACS Nano **14**(7): 7682-7688.

Gao, C., Y. Wang, J. Sun, Y. Han, W. Gong, Y. Li, Y. Feng, H. Wang, M. Yang, Z. Li, Y. Yang and C. Gao (2020). "Neuronal mitochondria-targeted delivery of curcumin by biomimetic engineered nanosystems in Alzheimer's disease mice." Acta Biomater **108**: 285-299.

Gao, X., P. Zheng, S. Kasani, S. Wu, F. Yang, S. Lewis, S. Nayeem, E. B. Engler-Chiurazzi, J. G. Wigginton, J. W. Simpkins and N. Wu (2017). "Paper-Based Surface-Enhanced Raman Scattering Lateral Flow Strip for Detection of Neuron-Specific Enolase in Blood Plasma." Anal Chem **89**(18): 10104-10110.

Gilmore, J. L., X. Yi, L. Quan and A. V. Kabanov (2008). "Novel nanomaterials for clinical neuroscience." J Neuroimmune Pharmacol **3**(2): 83-94.

Giorgi-Coll, S., H. Blunt-Foley, P. J. Hutchinson and K. L. H. Carpenter (2017). "Heparin-gold nanoparticles for enhanced microdialysis sampling." Anal Bioanal Chem **409**(21): 5031-5042.

Gonzalez-Pizarro, R., M. Silva-Abreu, A. C. Calpena, M. A. Egea, M. Espina and M. L. Garcia (2018). "Development of fluorometholone-loaded PLGA nanoparticles for treatment of inflammatory disorders of anterior and posterior segments of the eye." Int J Pharm **547**(1-2): 338-346.

Goram, A. L. and P. L. Richmond (2001). "Pegylated liposomal doxorubicin: tolerability and toxicity." Pharmacotherapy **21**(6): 751-63.

Han, Y., X. Chu, L. Cui, S. Fu, C. Gao, Y. Li and B. Sun (2020). "Neuronal mitochondria-targeted therapy for Alzheimer's disease by systemic delivery of resveratrol using dual-modified novel biomimetic nanosystems." Drug Deliv **27**(1): 502-518.

Harilal, S., J. Jose, D. G. T. Parambi, R. Kumar, M. K. Unnikrishnan, M. S. Uddin, G. E. Mathew, R. Pratap, A. Marathakam and B. Mathew (2020). "Revisiting the blood-brain barrier: A hard nut to crack in the transportation of drug molecules." Brain Res Bull **160**: 121-140.

Hubbard, W. B., M. Lashof-Sullivan, S. Greenberg, C. Norris, J. Eck, E. Lavik and P. VandeVord (2018). "Hemostatic nanoparticles increase survival, mitigate neuropathology and alleviate anxiety in a rodent blast trauma model." Sci Rep **8**(1): 10622.

Hung, W. C., M. D. Shau, H. C. Kao, M. F. Shih and J. Y. Cherng (2009). "The synthesis of cationic polyurethanes to study the effect of amines and structures on their DNA transfection potential." Journal of Controlled Release **133**(1): 68-76.

Inyang, E., A. E. Kuriakose, B. Chen, K. T. Nguyen and M. Cho (2020). "Engineering Delivery of Nonbiologics Using Poly(lactic-co-glycolic acid) Nanoparticles for Repair of Disrupted Brain Endothelium." ACS Omega **5**(24): 14730-14740.

Jain, D., R. Athawale, A. Bajaj, S. Shrikhande, P. N. Goel and R. P. Gude (2013). "Studies on stabilization mechanism and stealth effect of poloxamer 188 onto PLGA nanoparticles." Colloids Surf B Biointerfaces **109**: 59-67.

Johnsen, H. and R. B. Schmid (2007). "Preparation of polyurethane nanocapsules by miniemulsion polyaddition." J Microencapsul **24**(8): 731-42.

Kaijzel, E. L., E. R. van Beek, M. A. Stammes, I. Que, A. B. Chan, C. Lowik and L. J. Cruz (2017). "Traumatic Brain Injury: Preclinical Imaging Diagnostic(s) and Therapeutic Approaches." Curr Pharm Des **23**(13): 1909-1915.

Kannan, G., S. P. Kambhampati and S. R. Kudchadkar (2017). "Effect of anesthetics on microglial activation and nanoparticle uptake: Implications for drug delivery in traumatic brain injury." J Control Release **263**: 192-199.

Karathanasis, E. and K. B. Ghaghada (2016). "Crossing the barrier: treatment of brain tumors using nanochain particles." Wiley Interdiscip Rev Nanomed Nanobiotechnol **8**(5): 678-95.

Katsuki, S., T. Matoba, J. I. Koga, K. Nakano and K. Egashira (2017). "Anti-inflammatory Nanomedicine for Cardiovascular Disease." Front Cardiovasc Med **4**: 87.

Kaur, H., B. Kumar, A. Chakrabarti, B. Medhi, M. Modi, B. D. Radotra, R. Aggarwal and V. R. Sinha (2019). "A New Therapeutic Approach for Brain Delivery of Epigallocatechin Gallate: Development and Characterization Studies." Curr Drug Deliv **16**(1): 59-65.

Khalin, I., R. Alyautdin, T. W. Wong, J. Gnanou, G. Kocherga and J. Kreuter (2016). "Brain-derived neurotrophic factor delivered to the brain using poly (lactide-co-glycolide) nanoparticles improves neurological and cognitive outcome in mice with traumatic brain injury." Drug Deliv **23**(9): 3520-3528.

Khan, A. R., X. Yang, M. Fu and G. Zhai (2018). "Recent progress of drug nanoformulations targeting to brain." J Control Release **291**: 37-64.

Kim, D. H., Y. K. Seo, T. Thambi, G. J. Moon, J. P. Son, G. Li, J. H. Park, J. H. Lee, H. H. Kim, D. S. Lee and O. Y. Bang (2015). "Enhancing neurogenesis and angiogenesis with target delivery of stromal cell derived factor-1α using a dual ionic pH-sensitive copolymer." Biomaterials **61**: 115-25.

Kim, E. S., D. Kim, S. Nyberg, A. Poma, D. Cecchin, S. A. Jain, K. A. Kim, Y. J. Shin, E. H. Kim, M. Kim, S. H. Baek, J. K. Kim, T. R. Doeppner, A. Ali, J. Redgrave, G. Battaglia, A. Majid and O. N. Bae (2020). "LRP-1 functionalized polymersomes enhance the efficacy of carnosine in experimental stroke." Sci Rep **10**(1): 699.

Kim, J. H., K. W. Kim, M. H. Kim and Y. S. Yu (2009). "Intravenously administered gold nanoparticles pass through the blood-retinal barrier depending on the particle size, and induce no retinal toxicity." Nanotechnology **20**(50): 505101.

Kolter, M., M. Ott, C. Hauer, I. Reimold and G. Fricker (2015). "Nanotoxicity of poly(n-butylcyano-acrylate) nanoparticles at the blood-brain barrier, in human whole blood and in vivo." J Control Release **197**: 165-79.

Kulkarni, P. V., C. A. Roney, P. P. Antich, F. J. Bonte, A. V. Raghu and T. M. Aminabhavi (2010). "Quinoline-n-butylcyanoacrylate-based nanoparticles for brain targeting for the diagnosis of Alzheimer's disease." Wiley Interdiscip Rev Nanomed Nanobiotechnol **2**(1): 35-47.

Kuramitsu, S., K. Motomura, A. Natsume and T. Wakabayashi (2015). "Double-edged Sword in the Placement of Carmustine (BCNU) Wafers along the Eloquent Area: A Case Report." NMC Case Rep J **2**(1): 40-45.

Kwiatkowski, T. A., A. L. Rose, R. Jung, A. Capati, D. Hallak, R. Yan and N. Weisleder (2020). "Multiple poloxamers increase plasma membrane repair capacity in muscle and nonmuscle cells." Am J Physiol Cell Physiol **318**(2): C253-c262.

Kwon, E. J., M. Skalak, R. Lo Bu and S. N. Bhatia (2016). "Neuron-Targeted Nanoparticle for siRNA Delivery to Traumatic Brain Injuries." ACS Nano **10**(8): 7926-33.

Labala, S., P. K. Mandapalli, A. Kurumaddali and V. V. Venuganti (2015). "Layer-by-layer polymer coated gold nanoparticles for topical delivery of imatinib mesylate to treat melanoma." Mol Pharm **12**(3): 878-88.

Ladak, A. A., S. A. Enam and M. T. Ibrahim (2019). "A Review of the Molecular Mechanisms of Traumatic Brain Injury." World Neurosurg **131**: 126-132.

Lamade, A. M., E. M. Kenny, T. S. Anthonymuthu, E. Soysal, R. S. B. Clark, V. E. Kagan and H. Bayir (2019). "Aiming for the target: Mitochondrial drug delivery in traumatic brain injury." Neuropharmacology **145**(Pt B): 209-219.

Leong, J., J. Y. Teo, V. K. Aakalu, Y. Y. Yang and H. Kong (2018). "Engineering Polymersomes for Diagnostics and Therapy." Adv Healthc Mater **7**(8): e1701276.

Liao, R., J. Pon, M. Chungyoun and E. Nance (2020). "Enzymatic protection and biocompatibility screening of enzyme-loaded polymeric nanoparticles for neurotherapeutic applications." Biomaterials **257**: 120238.

Lin, M. H., C. Y. Chung, K. T. Chen, J. C. Yeh, T. H. Lee, M. H. Lee, I. N. Lee, W. C. Huang and J. T. Yang (2019). "Comparison between Polybutylcyanoacrylate Nanoparticles with Either Surface-Adsorbed or Encapsulated Brain-Derived Neurotrophic Factor on the Neural Differentiation of iPSCs." Int J Mol Sci **20**(1).

Lutton, E. M., S. K. Farney, A. M. Andrews, V. V. Shuvaev, G. Y. Chuang, V. R. Muzykantov and S. H. Ramirez (2019). "Endothelial Targeted Strategies to Combat Oxidative Stress: Improving Outcomes in Traumatic Brain Injury." Front Neurol **10**: 582.

Maiolo, D., P. Bergese, E. Mahon, K. A. Dawson and M. P. Monopoli (2014). "Surfactant titration of nanoparticle-protein corona." Anal Chem **86**(24): 12055-63.

Maisha, N., T. Coombs and E. Lavik (2020). "Development of a Sensitive Assay to Screen Nanoparticles in Vitro for Complement Activation." ACS Biomaterials Science & Engineering **6**(9): 4903-4915.

Mann, A. P., P. Scodeller, S. Hussain, J. Joo, E. Kwon, G. B. Braun, T. Molder, Z. G. She, V. R. Kotamraju, B. Ranscht, S. Krajewski, T. Teesalu, S. Bhatia, M. J. Sailor and E. Ruoslahti (2016). "A peptide for targeted, systemic delivery of imaging and therapeutic compounds into acute brain injuries." Nat Commun **7**: 11980.

Mauri, E., P. Veglianese, S. Papa, A. Rossetti, M. De Paola, A. Mariani, Z. Posel, P. Posocco, A. Sacchetti and F. Rossi (2020). "Effects of primary amine-based coatings on microglia internalization of nanogels." Colloids Surf B Biointerfaces **185**: 110574.

Menikheim, S., J. Leckron, S. Bernstein and E. B. Lavik (2020). "On-Demand and Long-Term Drug Delivery from Degradable Nanocapsules." ACS Applied Bio Materials **3**(11): 7369-7375.

Miller, H. A., A. W. Magsam, A. W. Tarudji, S. Romanova, L. Weber, C. C. Gee, G. L. Madsen, T. K. Bronich and F. M. Kievit (2019). "Evaluating differential nanoparticle accumulation and retention kinetics in a mouse model of traumatic brain injury via K(trans) mapping with MRI." Sci Rep **9**(1): 16099.

Moghimi, S. M. (2018). "Nanomedicine safety in preclinical and clinical development: focus on idiosyncratic injection/infusion reactions." Drug Discov Today **23**(5): 1034-1042.

Moghimi, S. M., D. Simberg, T. Skotland, A. Yaghmur and A. C. Hunter (2019). "The Interplay Between Blood Proteins, Complement, and Macrophages on Nanomedicine Performance and Responses." J Pharmacol Exp Ther **370**(3): 581-592.

Moloughney, J. G. and N. Weisleder (2012). "Poloxamer 188 (p188) as a membrane resealing reagent in biomedical applications." Recent Pat Biotechnol **6**(3): 200-11.

Morton, J. G., E. S. Day, N. J. Halas and J. L. West (2010). "Nanoshells for photothermal cancer therapy." Methods Mol Biol **624**: 101-17.

Namdee, K., A. J. Thompson, A. Golinski, S. Mocherla, D. Bouis and O. Eniola-Adefeso (2014). "In vivo evaluation of vascular-targeted spheroidal microparticles for imaging and drug delivery application in atherosclerosis." Atherosclerosis **237**(1): 279-86.

Needham, E. J., A. Helmy, E. R. Zanier, J. L. Jones, A. J. Coles and D. K. Menon (2019). "The immunological response to traumatic brain injury." J Neuroimmunol **332**: 112-125.

Oberholzer, M. and R. M. Muri (2019). "Neurorehabilitation of Traumatic Brain Injury (TBI): A Clinical Review." Med Sci (Basel) **7**(3).

Onwukwe, C., N. Maisha, M. Holland, M. Varley, R. Groynom, D. Hickman, N. Uppal, A. Shoffstall, J. Ustin and E. Lavik (2018). "Engineering Intravenously Administered Nanoparticles to Reduce Infusion Reaction and Stop Bleeding in a Large Animal Model of Trauma." Bioconjug Chem **29**(7): 2436-2447.

Park, J., Y. Pei, H. Hyun, M. A. Castanares, D. S. Collins and Y. Yeo (2017). "Small molecule delivery to solid tumors with chitosan-coated PLGA particles: A lesson learned from comparative imaging." J Control Release **268**: 407-415.

Patel, M. M., B. R. Goyal, S. V. Bhadada, J. S. Bhatt and A. F. Amin (2009). "Getting into the brain: approaches to enhance brain drug delivery." CNS Drugs **23**(1): 35-58.

Patel, M. M. and B. M. Patel (2017). "Crossing the Blood-Brain Barrier: Recent Advances in Drug Delivery to the Brain." CNS Drugs **31**(2): 109-133.

Petri, B., A. Bootz, A. Khalansky, T. Hekmatara, R. Müller, R. Uhl, J. Kreuter and S. Gelperina (2007). "Chemotherapy of brain tumour using doxorubicin bound to surfactant-coated poly(butyl cyanoacrylate) nanoparticles: revisiting the role of surfactants." J Control Release **117**(1): 51-8.

Polak, R., R. M. Lim, M. M. Beppu, R. N. Pitombo, R. E. Cohen and M. F. Rubner (2015). "Liposome-Loaded Cell Backpacks." Adv Healthc Mater **4**(18): 2832-41.

Pramanik, S. K., S. Sreedharan, H. Singh, M. Khan, K. Tiwari, A. Shiras, C. Smythe, J. A. Thomas and A. Das (2018). "Mitochondria Targeting Non-Isocyanate-Based Polyurethane Nanocapsules for Enzyme-Triggered Drug Release." Bioconjug Chem **29**(11): 3532-3543.

Qu, Y., J. Yang, P. Zhan, S. Liu, K. Zhang, Q. Jiang, C. Li and B. Ding (2017). "Self-Assembled DNA Dendrimer Nanoparticle for Efficient Delivery of Immunostimulatory CpG Motifs." ACS Appl Mater Interfaces **9**(24): 20324-20329.

Quach, Q. H. and J. C. Kah (2017). "Non-specific adsorption of complement proteins affects complement activation pathways of gold nanomaterials." Nanotoxicology **11**(3): 382-394.

Rampton, D., J. Folkersen, S. Fishbane, M. Hedenus, S. Howaldt, F. Locatelli, S. Patni, J. Szebeni and G. Weiss (2014). "Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management." Haematologica **99**(11): 1671-6.

Rejinold, N. S., T. Baby, K. P. Chennazhi and R. Jayakumar (2014). "Dual drug encapsulated thermo-sensitive fibrinogen-graft-poly (N-isopropyl acrylamide) nanogels for breast cancer therapy." Colloids and Surfaces B: Biointerfaces **114**: 209-217.

Rueda, F. and L. J. Cruz (2017). "Targeting the Brain with Nanomedicine." Curr Pharm Des **23**(13): 1879-1896.

Safavi-Sohi, R., S. Maghari, M. Raoufi, S. A. Jalali, M. J. Hajipour, A. Ghassempour and M. Mahmoudi (2016). "Bypassing Protein Corona Issue on Active Targeting: Zwitterionic Coatings Dictate Specific Interactions of Targeting Moieties and Cell Receptors." ACS Appl Mater Interfaces **8**(35): 22808-18.

Sanavio, B., L. Librizzi, P. Pennacchio, G. V. Beznoussenko, F. Sousa, P. J. Silva, A. A. Mironov, C. Frassoni, F. Stellacci, M. de Curtis and S. Krol (2018). "Distribution of superparamagnetic Au/Fe nanoparticles in an isolated guinea pig brain with an intact blood brain barrier." Nanoscale **10**(47): 22420-22428.

Sandsmark, D. K., A. Bashir, C. L. Wellington and R. Diaz-Arrastia (2019). "Cerebral Microvascular Injury: A Potentially Treatable Endophenotype of Traumatic Brain Injury-Induced Neurodegeneration." Neuron **103**(3): 367-379.

Selin, M., S. Nummelin, J. Deleu, J. Ropponen, T. Viitala, M. Lahtinen, J. Koivisto, J. Hirvonen, L. Peltonen, M. A. Kostiainen and L. M. Bimbo (2018). "High-Generation Amphiphilic Janus-Dendrimers as Stabilizing Agents for Drug Suspensions." Biomacromolecules **19**(10): 3983-3993.

Sershen, S. R., S. L. Westcott, N. J. Halas and J. L. West (2000). "Temperature-sensitive polymer-nanoshell composites for photothermally modulated drug delivery." Journal of Biomedical Materials Research **51**(3): 293-298.

Sharma, A., K. Liaw, R. Sharma, Z. Zhang, S. Kannan and R. M. Kannan (2018). "Targeting Mitochondrial Dysfunction and Oxidative Stress in Activated Microglia using Dendrimer-Based Therapeutics." Theranostics **8**(20): 5529-5547.

Sharma, R., S. P. Kambhampati, Z. Zhang, A. Sharma, S. Chen, E. I. Duh, S. Kannan, M. O. M. Tso and R. M. Kannan (2020). "Dendrimer mediated targeted delivery of sinomenine for the treatment of acute neuroinflammation in traumatic brain injury." J Control Release **323**: 361-375.

Shen, L., S. Tenzer, W. Storck, D. Hobernik, V. K. Raker, K. Fischer, S. Decker, A. Dzionek, S. Krauthäuser, M. Diken, A. Nikolaev, J. Maxeiner, P. Schuster, C. Kappel, A. Verschoor, H. Schild, S. Grabbe and M. Bros (2018). "Protein corona-mediated targeting of nanocarriers to B cells allows redirection of allergic immune responses." J Allergy Clin Immunol **142**(5): 1558-1570.

Sironi, B., T. Snow, C. Redeker, A. Slastanova, O. Bikondoa, T. Arnold, J. Klein and W. H. Briscoe (2016). "Structure of lipid multilayers via drop casting of aqueous liposome dispersions." Soft Matter **12**(17): 3877-87.

Song, S., X. Jin, L. Zhang, C. Zhao, Y. Ding, Q. Ang, O. Khaidav and C. Shen (2019). "PEGylated and CD47-conjugated nanoellipsoidal artificial antigen-presenting cells minimize phagocytosis and augment anti-tumor T-cell responses." International journal of nanomedicine **14**: 2465-2483.

Spicer, C. D., C. Jumeaux, B. Gupta and M. M. Stevens (2018). "Peptide and protein nanoparticle conjugates: versatile platforms for biomedical applications." Chem Soc Rev **47**(10): 3574-3620.

Suk, J. S., Xu, Q., Kim, N., Hanes, J., & Ensign, L. M. (2016). PEGylation as a strategy for improving nanoparticle-based drug and gene delivery. *Adv Drug Deliv Rev, 99*(Pt A), 28-51. doi:10.1016/j.addr.2015.09.012

Sultan, D., D. Ye, G. S. Heo, X. Zhang, H. Luehmann, Y. Yue, L. Detering, S. Komarov, S. Taylor, Y. C. Tai, J. B. Rubin, H. Chen and Y. Liu (2018). "Focused Ultrasound Enabled Trans-Blood Brain Barrier Delivery of Gold Nanoclusters: Effect of Surface Charges and Quantification Using Positron Emission Tomography." Small **14**(30): e1703115.

Sun, W., C. Xie, H. Wang and Y. Hu (2004). "Specific role of polysorbate 80 coating on the targeting of nanoparticles to the brain." Biomaterials **25**(15): 3065-71.

Szebeni, J. (2012). "Hemocompatibility testing for nanomedicines and biologicals: predictive assays for complement mediated infusion reactions." European Journal of Nanomedicine **4**(1): 33-53.

Szebeni, J. and R. Bawa (2020). "Human Clinical Relevance of the Porcine Model of Pseudoallergic Infusion Reactions." Biomedicines **8**(4).

Szeto, G. L. and E. B. Lavik (2016). "Materials design at the interface of nanoparticles and innate immunity." J Mater Chem B **4**(9): 1610-1618.

Tahara, K., Y. Miyazaki, Y. Kawashima, J. Kreuter and H. Yamamoto (2010). "Brain targeting with surface-modified poly(D,L-lactic-co-glycolic acid) nanoparticles delivered via carotid artery administration." Eur J Pharm Biopharm **77**(1): 84-8.

Taylor, C. A., J. M. Bell, M. J. Breiding and L. Xu (2017). "Traumatic Brain Injury-Related Emergency Department Visits, Hospitalizations, and Deaths - United States, 2007 and 2013." MMWR Surveill Summ **66**(9): 1-16.

Thompson, A. J., E. M. Mastria and O. Eniola-Adefeso (2013). "The margination propensity of ellipsoidal micro/nanoparticles to the endothelium in human blood flow." Biomaterials **34**(23): 5863-71.

Tian, X., S. Nyberg, S. S. P, J. Madsen, N. Daneshpour, S. P. Armes, J. Berwick, M. Azzouz, P. Shaw, N. J. Abbott and G. Battaglia (2015). "LRP-1-mediated intracellular antibody delivery to the Central Nervous System." Sci Rep **5**: 11990.

Tian, X. H., X. N. Lin, F. Wei, W. Feng, Z. C. Huang, P. Wang, L. Ren and Y. Diao (2011). "Enhanced brain targeting of temozolomide in polysorbate-80 coated polybutylcyanoacrylate nanoparticles." Int J Nanomedicine **6**: 445-52.

Vashist, A., A. Kaushik, A. Vashist, J. Bala, R. Nikkhah-Moshaie, V. Sagar and M. Nair (2018). "Nanogels as potential drug nanocarriers for CNS drug delivery." Drug Discov Today **23**(7): 1436-1443.

Veenith, T. V., E. L. Carter, T. Geeraerts, J. Grossac, V. F. Newcombe, J. Outtrim, G. S. Gee, V. Lupson, R. Smith, F. I. Aigbirhio, T. D. Fryer, Y. T. Hong, D. K. Menon and J. P. Coles (2016). "Pathophysiologic Mechanisms of Cerebral Ischemia and Diffusion Hypoxia in Traumatic Brain Injury." JAMA Neurol **73**(5): 542-50.

Vinogradov, S. V. (2007). "Polymeric nanogel formulations of nucleoside analogs." Expert Opin Drug Deliv **4**(1): 5-17.

Vogt, C., M. Pernemalm, P. Kohonen, S. Laurent, K. Hultenby, M. Vahter, J. Lehtiö, M. S. Toprak and B. Fadeel (2015). "Proteomics Analysis Reveals Distinct Corona Composition on Magnetic Nanoparticles with Different Surface Coatings: Implications for Interactions with Primary Human Macrophages." PLoS One **10**(10): e0129008.

Wang, J. B., M. Aryal, Q. Zhong, D. B. Vyas and R. D. Airan (2018). "Noninvasive Ultrasonic Drug Uncaging Maps Whole-Brain Functional Networks." Neuron **100**(3): 728-738.e7.

Wang, K., D. Cui and L. Gao (2016). "Traumatic brain injury: a review of characteristics, molecular basis and management." Front Biosci (Landmark Ed) **21**: 890-9.

Wang, W. X., P. Prajapati, H. J. Vekaria, M. Spry, A. L. Cloud, P. G. Sullivan and J. E. Springer (2021). "Temporal changes in inflammatory mitochondria-enriched microRNAs following traumatic brain injury and effects of miR-146a nanoparticle delivery." Neural Regen Res **16**(3): 514-522.

Wei, C. C. and Z. Q. Ge (2012). "Influence of electrolyte and poloxamer 188 on the aggregation kinetics of solid lipid nanoparticles (SLNs)." Drug Dev Ind Pharm **38**(9): 1084-9.

Weiss, C. K., M. V. Kohnle, K. Landfester, T. Hauk, D. Fischer, J. Schmitz-Wienke and V. Mailänder (2008). "The first step into the brain: uptake of NIO-PBCA nanoparticles by endothelial cells in vitro and in vivo, and direct evidence for their blood-brain barrier permeation." ChemMedChem **3**(9): 1395-403.

Weissig, V. (2017). "Liposomes Came First: The Early History of Liposomology." Methods Mol Biol **1522**: 1-15.

Wilhelm, S., A. J. Tavares, Q. Dai, S. Ohta, J. Audet, H. F. Dvorak and W. C. Chan (2016). "Analysis of nanoparticle delivery to tumours." Nature reviews materials **1**(5): 1-12.

Wu, P., H. Zhao, X. Gou, X. Wu, S. Zhang, G. Deng and Q. Chen (2019). "Targeted delivery of polypeptide nanoparticle for treatment of traumatic brain injury." Int J Nanomedicine **14**: 4059-4069.

Xiong, Y., A. Mahmood and M. Chopp (2018). "Current understanding of neuroinflammation after traumatic brain injury and cell-based therapeutic opportunities." Chin J Traumatol **21**(3): 137-151.

Ye, D., X. Zhang, Y. Yue, R. Raliya, P. Biswas, S. Taylor, Y.-C. Tai, J. B. Rubin, Y. Liu and H. Chen (2018). "Focused ultrasound combined with microbubble-mediated intranasal delivery of gold nanoclusters to the brain." Journal of controlled release : official journal of the Controlled Release Society **286**: 145-153.

Yilmaz, C., K. Karali, G. Fodelianaki, A. Gravanis, T. Chavakis, I. Charalampopoulos and V. I. Alexaki (2019). "Neurosteroids as regulators of neuroinflammation." Front Neuroendocrinol **55**: 100788.

Yuan, X., Y. He, G. Zhou, X. Li, A. Feng and W. Zheng (2018). "Target challenging-cancer drug delivery to gastric cancer tissues with a fucose graft epigallocatechin-3-gallate-gold particles nanocomposite approach." J Photochem Photobiol B **183**: 147-153.

Zhang, Y., M. Chopp, Z. G. Zhang, M. Katakowski, H. Xin, C. Qu, M. Ali, A. Mahmood and Y. Xiong (2017). "Systemic administration of cell-free exosomes generated by human bone marrow derived mesenchymal stem cells cultured under 2D and 3D conditions improves functional recovery in rats after traumatic brain injury." Neurochem Int **111**: 69-81.

Zhang, Z., S. Tongchusak, Y. Mizukami, Y. J. Kang, T. Ioji, M. Touma, B. Reinhold, D. B. Keskin, E. L. Reinherz and T. Sasada (2011). "Induction of anti-tumor cytotoxic T cell responses through PLGA-nanoparticle mediated antigen delivery." Biomaterials **32**(14): 3666-78.

Zhou, H., Z. Fan, P. Y. Li, J. Deng, D. C. Arhontoulis, C. Y. Li, W. B. Bowne and H. Cheng (2018). "Dense and Dynamic Polyethylene Glycol Shells Cloak Nanoparticles from Uptake by Liver Endothelial Cells for Long Blood Circulation." ACS Nano **12**(10): 10130-10141.

Zhu, Y., C. Liu and Z. Pang (2019). "Dendrimer-Based Drug Delivery Systems for Brain Targeting." Biomolecules **9**(12).