Drug delivery across length scales

Derfogail Delcassian,[a,b,c] Asha K. Patel,[a,d] Abel B. Cortinas,[a,e] Robert Langer[a,e,f,g] *

[a]*David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA, USA;*

[b]*Department of Anaesthesiology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA;*

[c]*Division of Regenerative Medicine and Cellular Therapies, School of Pharmacy, University of Nottingham, Nottingham, UK;*

[d] *Division of Cancer and Stem Cells, School of Medicine, and Division of Advanced Materials and Healthcare Technologies, School of Pharmacy, University of Nottingham, UK.*

[e] *Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA*

[f] *Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA, USA*

[g] *Media Lab, Massachusetts Institute of Technology, Cambridge, MA, USA;*

*corresponding author; Robert Langer; rlanger@mit.edu

Drug delivery across length scales

Over the last century there has been a dramatic change in the nature of therapeutic, biologically active molecules available to treat disease. Therapies have evolved from extracted natural products towards rationally designed biomolecules, including small molecules, engineered proteins, and nucleic acids. The use of potent drugs which target specific organs, cells, or biochemical pathways, necessitates new tools which can enable controlled delivery and dosing of these therapeutics to their biological targets. Here, we review the miniaturisation of drug delivery systems from the macro- to nano- scale, focusing on controlled dosing and controlled targeting as two key parameters in drug delivery device design. We describe how the miniaturisation of these devices enables the move from repeated, systemic dosing, to on demand, targeted delivery of therapeutic drugs, and highlight areas of focus for the future.

Keywords: drug delivery; length scale; targeting; macro; micro; nano

INTRODUCTION

Over the last century there has been a dramatic change in the nature of therapeutic, biologically active molecules available to treat disease. This is represented by the move from extracted natural products and synthesised natural product mimics[1], towards rationally designed biomolecules including small molecules, engineered proteins, and nucleic acids[2-4]. The evolution of potent drugs which target specific organs, cells, or biochemical pathways, necessitates new tools which can enable controlled delivery and dosing of these therapeutics to their biological targets. Therapies which can be administered as a single procedure, either through the delivery of a single dose of a potent curative therapeutic, or through the implantation of a device that can maintain a precise, long term drug dosing regime, are highly desired.

Macro-scale drug delivery devices have been widely adopted since the 1970s, when long-acting intra-uterine contraceptive implants were offered as an alternative to daily repeated oral administration of systemically released hormones[5]. These implants could be inserted during a single procedure, and remained effective for several years through localised and controlled release of contraceptive hormones. Since then, a wide range of systems for therapeutic drug delivery have been developed, broadly focused on systems which can help to regulate drug dosing[6], and those which aid targeted delivery for site-specific therapeutic action[7-10]. Drug delivery devices are in widespread clinical use, however, many of these systems are limited in their ability to deliver therapeutics to smaller biological structures with control over both drug dosing and therapeutic targeting.

For certain drugs, failure to adhere to a specific dosing schedule can dramatically impact therapeutic efficacy. In vaccination, the timing of drug dosing (e.g.

the dosing regimen as well as the time of day) is an important parameter in the development of robust immunity[11]. Drug dosing is therefore a crucial consideration in drug delivery device design, and many strategies have been explored to regulate dosing; including continuous, controlled release systems[7, 12-15], enhanced therapeutic circulation time[16, 17] and stimuli responsive drug administration[7, 18-22]. Separately, as therapeutic targets become increasingly specific, and therapies become increasingly potent, delivering site specific therapeutic action becomes a more critical design feature. Control over both of these aspects can improve patient safety, quality of life and compliance by lessening the stringent requirements of strict medication schedules and reducing off-target effects.

Here, we review drug delivery systems across the macro- to nano- scale, highlighting systems which enable controlled dosing, and those which aid drug targeting. We explore the role of length scale in the function of these systems, considering macro-, micro- and nano- systems which are capable of delivery to organs, cells and cellular substructures of interest (Figure 1). We describe how the miniaturisation of these devices enables the move from repeated, systemic dosing, to on demand, targeted delivery of therapeutic drugs, and consider areas of future interest.

MACRO SCALE DELIVERY SYSTEMS

Macro scale delivery systems, measuring from 1 mm upwards in size, are particularly suited for long-term drug delivery. Their scale allows a single device to contain a considerable therapeutic reservoir, and enables precise engineering of accompanying parts required for more complex controlled drug administration, such as pumps, batteries, catheters and sensors[23, 24]. For effective systemic drug delivery, drugs must first traverse the body's natural physical barriers and reach the systemic circulation,

which can prove challenging for macro scale devices[25]. A number of approaches have been used to address this challenge, with examples including ingestible devices[26-28], topical delivery through transdermal systems[29-32], controlled release implants inserted close to vasculature[6], and infusion pump systems which are connected to the systemic circulatory system via cannula or catheter[23]. Here, we review a range of macro scale drug delivery devices, and discuss how their scale impacts their ability to deliver therapeutics.

Systemic delivery systems

Ingestible devices

Ingestion is one of the most convenient administration routes for devices small enough to pass through the oesophagus[25]. Although a widely used drug delivery route, ingestion based delivery mechanisms have typically had limited usefulness in long term and controlled delivery systems, due to frequent gastric emptying times of between 2-3 hours[33]. To combat this, several approaches have been developed to improve gastric retention times for macro devices small enough to swallow. These approaches focus on retaining devices within the stomach to provide continuous, systemic drug release, through adhesion to the stomach wall or changes in device geometry. In one example, macro devices composed of drug eluting polymers can be folded into a capsule small enough to swallow, which then expands in the stomach. These low density, floating devices are buoyant, and cannot pass through the pyloric sphincter and into the intestines intact[28, 33-35]. Inclusion of a biodegradable moiety allows the devices to slowly degrade *in vivo,* and subsequently passage through the gastro intestinal tract post drug delivery. Advances in device design will enable systems to be retained beyond the current limit of a few months, potentially allowing longer term macro scale delivery systems which can

be administered without surgical intervention. Although ingestible devices offer a robust controlled delivery system that can passage through the gastro intestinal (GI) system, orally delivered drugs must first be absorbed through the gut to become bioavailable. The GI tract consists of the stomach, small intestine (duodenum, jejunum and ileum), the large intestine (colon), and the rectum; drug absorption can occur across the entire GI tract. The majority of drug absorption is occurs via the highly adapted microvilli in the small intestine, however class III/IV drugs have been shown to preferentially absorb across the colon[36]. Several drug delivery systems utilise the distinct chemical environments present in specific regions of the gastrointestinal tract to facilitate a more targeted drug delivery approach, discussed in detail in the targeted delivery section below. Regardless of absorption site, orally administered drugs are subject to first-pass metabolism and hepatic clearance, and so systemic bioavailability of a therapeutic drug concentration may be lower when compared to intravenous administration.

Transdermal delivery

In contrast to ingestible devices, transdermal drug delivery methods offer many benefits over the more traditionally administered oral route[37]. Firstly, compared to orally delivered pharmacologics of the same dose, they can provide increased levels of circulating, bioavailable drugs. This leads to a reduction in the drug dose needed to elicit a specific pharmacological effect[38-40], and can therefore reduce side effects. Transdermal patches provide a controlled release system which is well suited to the delivery of small molecules, though dermal penetration and delivery efficacy is affected by both the molecular size and hydrophilicity of the therapeutic being administered. Transdermal patches have been widely used to deliver small molecules such as nicotine in smoking cessation therapies[41], and contraceptive/postmenopausal hormones such as estradiol and estrone[38]. Drug delivery patches are well suited for the continuous,

systemic delivery of low dose therapeutics. Drug delivery profiles range from a few days to a few weeks due to limitations in drug loading capacity, and patches must remain attached to the skin for the duration of delivery.

Polymer implants

Implantable polymer devices have been in use since the 1970's for longer term systemic drug delivery. Early examples included the Norplant® and Jadelle® non-degradable subcutaneous contraceptive implants, which provided controlled release of contraceptive hormones over 5 years. Early devices were composed of an implanted polymer-drug composite coated with a porous ethyl vinyl acetate membrane[42-44]. This membrane facilitated controlled kinetic release of the hormones, and similar devices have been used to systemically deliver a range of pharmaceuticals including anti-inflammatory drugs and antibiotics[45-48]. As with the early Norplant® devices, many of these systems are based on non-degradable polymers with a fixed-rate delivery profile, controlled by drug diffusion from within the device. Devices are usually implanted, and removed, via a minor surgical procedure at the end of their delivery lifetimes. To minimise surgical intervention required in the removal of these devices, longer-acting, degradable subcutaneous rod implants are currently in development[49].

In a similar approach, polymer hydrogel systems can be used for kinetically controlled systemic drug release[7, 13, 50]. Hydrogels have the potential to deliver virtually any therapeutic[13, 51]; controlled release parameters are widely tuneable, with the nature of the hydrogel crosslinking determining the kinetics of controlled release and the biodegradability of the system. Both chemical (covalent) and physical (electrostatic assembly, stereo-complexation, supramolecular host-guest inclusion) crosslinking can be used to form hydrogel structures, however care must be taken to ensure the crosslinking agent does not impact drug potency. The wide range of cross-linking

chemistries and polymer compositions provides tuneable delivery profiles that can last from several days up to several years, making polymer implants a versatile class of materials for drug delivery.

Pump systems

A number of implantable infusion pump systems have been developed for long-term delivery of therapeutics with metered dosing[23]. These devices can measure up to 10 cm in diameter, and are often surgically implanted into patients. They generally consist of a reservoir-pump system which offers dosing schedules based on continuous fixed rate delivery, timed dose delivery, or on-demand delivery in response to specific stimuli. Dosing is usually controlled by an integrated pump system, which can be driven through mechanical, peristaltic means[52-55], propellant systems[56-59], or is driven by osmosis/diffusion[60]. Due to the invasive surgical nature of implantation, these devices are primarily used for continuous therapeutic release in chronic medical conditions[54, 56, 57]. Examples include intrathecal delivery of opioid based analgesic therapies, or delivery of muscle relaxants such as baclofen in patients with severe contractions. This continuous, metered dosing is particularly useful for analgesics in long term and palliative care, where the risk of misadministration and accidental overdose, a current concern with prescribed opioid tablets, can be reduced.

For metered and on-demand dosing, stimuli responsive pumps can be used. These have proven particularly useful in diabetes, where sensors implanted under the skin can monitor and respond to glucose levels (MiniMed, Paradigm® Revel™)[61]. In these systems, reservoirs containing insulin, or twin reservoirs containing insulin and glucagon, are connected to sensors and facilitate metered drug delivery in response to hypo- or hyper-glycaemic events. Recently, wireless, smartphone connected sensors

have been developed which allow patients and healthcare professionals to manage glucose levels in real time[62, 63]. These devices enable a truly patient specific, on-demand therapy, and are now clinically used in systemic applications[60, 62, 64]. However, the reservoir-based systems described limits the drug formulations to liquid systems, and device lifetimes are limited by the reservoir loading capacity. Additionally, the use of a power source to run the pumps in peristaltic devices limits the usefulness of these devices due to short battery lifetimes (usually limited to 4-7 years)[65]. Finally, due to their scale these more complex systems currently remain unsuitable for targeted or localised delivery approaches, which require smaller scale devices.

Localised delivery systems

Proximal polymer implants

Many smaller macro scale devices can be surgically implanted within target organs to allow for proximal drug release, enabling therapeutic efficacy using lower doses than required in systemic delivery systems. A widespread example are contraceptive devices introduced into the body via the vaginal tract. Contraceptive devices, briefly discussed earlier, are widely adopted clinically, and intra uterine devices (IUDs)[5] have been in widespread use since the 1970s. IUDs and contraceptive vaginal rings can both be applied via a minor surgical procedure, and systems such as the NuvaRing® and Nestorone® offer controlled release on the order of 1 month to 3 years[66, 67] before removal. For increased efficacy and reduced side effects, new progestin-infused rings or combination drug devices that include both progesterone and estrogenic steroids are in development[66]. Future developments are focused on combining localised contraceptive drug release with systemic drug release, providing a multiplexed system to reduce the risk of sexually transmitted infections[67, 68] in a vaginal ring device.

To reach less accessible target organs, surgical intervention is often required to position macro devices correctly. A number of polymer-based macro devices are indicated for controlled drug delivery to target organs, exemplified by stent-based[69] drug delivery. Stents are used for drug delivery in coronary interventions, and additionally in non-vascular target organs including the oesophagus, biliary duct, trachea, bronchi, sinus cavities, ureters, and urethra[70, 71]. First-generation vascular stents were approved by the FDA in 1994, and were manufactured from bare metal alloys or ceramic composites. However, these stents caused complications including hyperplastic growth and restenosis. Next generation stents therefore included novel metallic and polymeric stent materials with more open mesh-like frameworks, and simultaneously eluted anti-inflammatory drugs[71, 72] to reduce restenosis. Stents often provide a physical support coupled with drug eluting capabilities. The continued optimisation of stent structures to reduce plaque prolapse (through increased radial strength) and increase biocompatibility (using fluoropolymer materials) renders these devices as versatile tools for the delivery of a diverse class of drugs. Many systems have been developed for the controlled delivery of anti-inflammatory, antimicrobial, and analgesic drugs[70, 71] using diffusion based release profiles.

In contrast, less rigid polymer systems, have been used for non-structural drug delivery. Both biodegradable polymer stents, and implantable hydrogel systems can be used for localised therapeutic delivery. Biodegradable polymer systems are particularly useful for non-structural drug delivery systems[70], as they can be packed into surgical sites and release drugs during healing before being resorbed into the body. These polymer systems have been used in applications ranging from advanced wound healing to the delivery of chemotherapeutics[73, 74]. In contrast, macro scale polymer-based hydrogel systems are useful for both surgical and non-surgical drug administration. A

widespread example is hydrogel contact lenses used for ocular drug delivery. These devices can increase the bioavailability of drugs otherwise limited by burdensome ocular administration dosing regimens[48, 75]. They have proven particularly useful for delivery of medications for eye diseases including glaucoma, and delivery of antibacterial agents to the eye[76-78]. In general, hydrogel thickness can be used to control drug loading, and delivery profiles can be tuned to offer zero-order release kinetics. Many hydrogel systems are unsuitable for localised ocular delivery applications due to their limited transparency, stability, and the use of non-biocompatible crosslinking agents during formation. Drug delivery contact lenses must be designed to possess luminous transmittance, oxygen permeability, mechanical stability, and biocompatibility[76-79] in addition to their drug loading capacity. These stringent material requirements highlight the complexities in designing drug delivery systems which match localised tissue requirements. Next, we discuss advances in macro scale drug delivery systems which enable a more targeted delivery approach.

Targeted delivery systems

Targeted delivery systems, where a device enables the delivery of a therapeutic to a target organ or cell based in a different location to the administration site, are relatively limited in macro scale devices. Due to their scale, macro devices are often too large to engage with many biological structures and target cells. A notable exception to this is the use of stimuli responsive macro scale devices for delivery to chemically distinct regions of the gastrointestinal tract[34, 80-82]. The chemical environment of the stomach often poses a challenge to pH sensitive and enzymatically degraded protein and peptide therapeutics. Drug delivery devices frequently utilise local variations in target tissue pH to control drug release, with hydrogels sensitive to alkali pH and enteric tablet coatings facilitating delivery to the intestines.

For many other target tissues, macro scale devices are too large to travel through the vasculature or lymphatic system and move towards target organs. In an alternative approach, macro devices which can recruit a target cell towards the device to selectively deliver a therapeutic drug to a target cell type have been developed. These devices have been trialled in vaccination systems, where chemokines (CXCL12) have been incorporated into a polymer material to encourage the recruitment of immune cells. Once the immune cells reach the macro device, they "collect" the drug. In this way, the macro device can overcome the transport limitation imposed due to its size, and provides a targeted delivery system to specific cells by recruiting the cell of interest[83-85] to the device location. This relatively new concept offers promise for the design of a range of macro devices which can act in a targeted manner

Summary

Macro scale devices and their component parts can be precisely engineered to allow fine control over drug dosing schedules, and in some cases, can be coupled with sensor technology to enable patient specific systemic drug release. The dimensions of most macro scale devices and their capacity to hold large therapeutic reservoirs renders them suitable to long term drug delivery. However, these dimensions also limit their usefulness in targeting smaller biological structures. Although some smaller macro devices can be surgically inserted into larger target organs (i.e. uterus, large arteries) to facilitate proximal or localised drug release, devices cannot migrate through the body, limiting their ability to deliver drugs in a targeted fashion. The advent of new polymer implants which can directly recruit target cells offers the potential to combine the intrinsic advantages of macro devices (drug loading capacity, precision engineering, patient specific stimuli responsive systems) with the targeting advantages usually found

in smaller scale systems, and is an exciting future direction for macroscale device development.

MICRO SCALE DELIVERY SYSTEMS

Devices at the micron scale range from 1-1000µm, allowing them to be introduced within the body without the need for a major surgical procedure through ingestion (orally administered osmotic pumps)[24, 86, 87], inhalation, and inoculation (microparticles, microneedles)[88-92]. Many key biological structures are organised on the micron length scale, with cells themselves measuring from 5-20 microns in diameter and possessing cellular substructures on the order of nano- to micro-meters. Several biological transport networks are also organised on the micro-scale; lymphatic capillaries[93, 94] have a diameter of ~10-60 µm, whilst circulatory vasculature[95] measures on the order of 10 mm in arteries and veins to around 1 µm in capillaries. Micro-scale drug delivery devices therefore offer the unique advantage of being able to interface with organoid, cellular, and subcellular structures on a comparable length scale to their biological targets. In addition, they may be able to navigate through the body's transport networks, rendering them particularly suitable for localised and targeted delivery systems. Here, we review a range of micro scale delivery systems with increasing target specificity.

Systemic delivery systems

Microfabricated electromechanical systems (MEMS)

Microfabrication techniques and advances in pump technology have allowed injection and infusion devices (described earlier in the macro section) to be created on smaller and smaller length scales. Micro fabricated electromechanical systems (MEMS) offer a micron sized infusion device that can provide localised fixed rate or variable dose

delivery, and recently further miniaturisation of fabrication technologies has encouraged development of nanoelectromechanical systems[96] (NEMS). MEMS systems can deliver both liquid and solid-phase drug formulations[97-104] in a manner analogous to macro scale infusion pumps. The delivery dose is controlled by an infusion system, which is either fixed rate (i.e. diffusion-based) or active (i.e. pumped) [9, 97]. In pumped systems, devices can be either non-mechanical (i.e. electrophoresis, electro osmosis) or mechanical in nature (piezoelectric, electromagnetic, shape memory alloy), with the choice of pump system impacting both the delivery dosage schedule and device life time[101-103, 105, 106]. For example, non-mechanical pumps usually have a limited flow rate compared to variable piezoelectric pumps[101, 104, 105, 107-110] yet piezoelectric pump systems often require higher voltage systems and increased operating power, reducing battery and device lifetime. Although these devices are small enough to be implanted within the body, they have a reduced reservoir capacity compared to their macro scale counterparts. To combat the low loading capacity, refillable devices[99] are being developed which enable reservoir replenishment and dose manipulation post-implantation. Due to the placement of these devices within the body, refilling these systems will likely require an additional surgical procedure, rendering these devices unsuitable for non-surgical applications.

Microneedles

Microneedle patches have been developed which facilitate drug delivery without surgical intervention. These consist of an array of high aspect ratio needles[90, 91] on the order of 500-1000 μm in length, which can penetrate the epidermis and reach the underlying dermal layer. Once they are in contact with this layer, they can be used to deliver small molecules, proteins, or nucleic acids via hollow, solid, or biodegradable needles[30]. The needles are usually made of metal, silica, or polymer composites, and are

fabricated through microlithography[29, 88-91, 111] using etching, casting, or printing methods. The simplest of these systems use solid and porous non-degradable needles coated with a drug, or biodegradable drug-polymer composite that can dissolve into the tissue once the microneedles contact the dermal layer. Alternatively, the microneedles can be uncoated, and removed once they have penetrated the epidermal barrier, allowing topical application of therapeutics to the area. An alternative system uses hollow needles coupled to a liquid reservoir, using capillary action to inject liquid into the dermal layer in an analogous manner to traditional macro needles. In contrast, biodegradable needle systems can be applied directly to the skin and used to deliver drugs with a more continuous release profile. By carefully tuning polymer compositions, these systems can controllably deliver drugs in a single administration lasting a few seconds, or with a longer kinetic release profile of a few weeks[30, 90].

Polymer implants

A range of injectable administration methods have been developed to implant polymer based micro scaled drug delivery systems. The simplest of these involve micro scaled polymer masses which are administered using a clinical gauge needle to directly penetrate the skin barrier, and deposited subcutaneously. A wide range of injectable polymer compositions have been explored, from early studies using polylactic acid and biodegradable polylactide-co-glycolide acid polymer systems, to newer stimuli responsive copolymer systems, and novel hydrogel systems[112].

Micro scale injectable hydrogels with controlled release properties[83, 113-115] have emerged as promising polymer delivery systems for clinical applications. For example, shear-thinning hydrogels are particularly well suited to subcutaneous systemic delivery devices[115-117], as they remain liquid during application and solidify on placement post-

injection. This renders shear thinning hydrogel systems suitable for delivery to a wide range of target locations, however for longer term release profiles (over 6 months) multiple hydrogel injections would likely be required in a clinical setting. To prevent overloading the subcutaneous space with polymer materials, hydrogels with tuneable degradation rates (matched to the rate of drug release) can ensure polymer residue does not remain in the body after the therapeutic has been delivered. As an alternative, refillable drug delivery depots have recently been developed, which aim to overcome the drug loading limitations inherent in microscopic drug delivery depots. These systems use "tagged" drugs which can be administered intravenously and migrate towards the polymer depot[118, 119], providing a refillable controlled release depot.

Microparticles

Microparticles typically consist of a degradable, drug loaded microparticle that acts as a drug delivery depot. These particles can be suspended in saline, and injected intravenously where, if appropriately sized, they circulate systemically. Microparticles are typically formed by emulsion or solvent evaporation techniques[15, 32, 120-125], potentially resulting in a loss of potency for sensitive therapeutics after exposure to organic solvents during the fabrication method. In an alternative approach, ultra-sonication and freezing can be used to generate microparticles with control over polydispersity[11], reducing the need for organic solvents and maintaining drug potency. A variety of polymers have been used to fabricate microparticles, and the choice of polymer directly impacts both the microparticle targeting ability and the specific release kinetics. For example, PLGA microparticles are FDA approved for clinical use in a range of applications, including chemotherapeutic drug delivery and hormone release. Their release profiles can be tuned to continuously deliver therapeutic load over the course of two days, or for up to eight weeks, depending on the lactide to

glycolide ratio[126-128] within the polymer. Recently, more advanced microparticles have been developed which offer a more complex kinetic release profile. These materials combine several different polymer architectures to offer a single particle that can release therapeutic load in 2-3 distinct bursts. These systems are likely to prove extremely useful in vaccine development, where an entire multi-dose vaccination schedule could be administered systemically in one injection[11, 129].

Localised delivery systems

Implantable microchips

As infusion pump and microchip devices have been miniaturised, they have become increasingly suitable for localised drug delivery applications. Recently, new MEMS devices have been developed which offer an implantable "pharmacy-on-a-chip" design, allowing the delivery of multiple therapeutics, each at a specified time. These devices can provide precise dosing control through as many as 100 unique reservoirs opened on the order of microseconds. The first "pharmacy-on-a-chip" devices successfully completed phase one human clinical trials in 2012, and were used to deliver human parathyroid hormone fragment[86, 130] to eight osteoporotic patients. Taking this technology further, micron-sized reservoir-based devices holding up to 100 drugs and drug combinations in a small microchip have been implanted into tumour sites. Due to their high aspect ratio and small scale, implants can be extracted using a conventional biopsy needle, and the tissue can be examined to determine tumour regression in response to each of the therapeutic drugs and drug combinations tested. In this way, surgeons and oncologists can develop a personalised drug treatment plan for cancer patients based on positive responses to specific drug combination therapies[131, 132], tested using the microchip.

Controlled polymer architecture

Polymers can be modified to display controlled topographical and physical features, enabling delivery of therapeutics to a specific biological target organ. For example, the Nektar aerosolised inhaler based systems deliver microparticles containing a range of therapeutics, and uses microparticles with a reduced density to aid pulmonary particle delivery[133]. Microparticle geometry has also been shown to directly impact cellular uptake, with both particle size and shape[134-138] playing an important role in the response of specific tissues and cells. Given the importance of the three dimensional structure to cellular interactions, shape memory polymers are being developed that can be injected into a target organ using a syringe, and then resume a specific 2D or 3D shape on reaching 37°C in the body. One example of these systems involves bio-adhesive shape memory hydrogel sheets, which provide an easily applied, injectable patch drug delivery device for local drug administration[72, 139-142].

Targeted delivery systems

Ligand targeting

The identification of organ and cell specific ligands has facilitated targeted delivery of micro scale systems. This is often accomplished using conjugation strategies which link targeting ligands onto polymers. Ligand conjugated polymers can be used to form drug delivery microparticles, which can be formulated to encapsulate a range of therapeutic cargo including proteins, small molecules, and cytokines within a ligand decorated polymer shell[17, 143]. Conjugation of specific ligands can also alter the systemic circulation time; for example the inclusion of a polyethylene glycol (PEG) moiety is thought to prevent binding and uptake of microparticles by non-targeted cell types. The inclusion of specific ligands facilitates microparticle binding to specific cells and tissues

presenting the receptor for the attached ligand. These systems have proven particularly useful for targeting the liver though the ASGPR1 receptor[144, 145], or targeting systemically circulating dendritic cells[146, 147]. As ligands of other target organs are identified, this method will enable more specific targeting.

Microbubbles

In an alternative approach, smaller, drug loaded microbubbles have been injected systemically. The application of ultrasound (which bursts these bubbles) can be used to target drug release to a specific therapeutic area. This emerging technology makes use of clinically available imaging facilities located in hospitals and clinics to induce controlled release in target biological structures. The technique has proven popular in delivering drugs to larger target organs, such as the kidney[148-150]. The development of ultrasound mediated drug deliver follows previous discoveries that traditional delivery through topical administration to the skin, gastrointestinal tract and mucus membranes is enhanced with simultaneous application of an ultrasound probe[151, 152].

Summary

Micro scale systems offer a robust tool to facilitate drug delivery in systemic, localised, and targeted fashions. Whilst macro scale devices can offer controlled release for durations of months to years, micro systems have limited reservoir and loading capacity, usually limiting drug delivery to weeks and months. There are also limited examples of systems with programmed release profiles, as the majority of the drug delivery systems rely on diffusion and biodegradation to provide a continuous and fixed rate delivery. Recently, pulsatile hydrogel release systems, pulsatile microparticles, and stimuli responsive drug delivery approaches have been developed which offer the promise of greater control over complex dosing schedules. Although micro systems are

limited by therapeutic reservoir and release profiles, they excel in providing localised and targeted drug delivery. Their small scale enables implantation into key organs, and microparticles and microbubbles can travel through the vasculature to enable both systemic and more targeted delivery. Poorly vascularised tissues, and those isolated by complex physiological barriers such as the blood-brain barrier, remain difficult to target. As new approaches to crossing physiological barriers are identified, micro scale systems will play an increasingly important role in targeted delivery.

NANO SCALE DELIVERY SYSTEMS

Nanoscale systems are generally defined as being of the order of between 1 to 100 nm (ISO/TS 80004-1:2015), however in practice can range from 1 to 1000 nm[153]. Nanotechnology can be used to improve the pharmacokinetic properties of traditional pharmaceuticals, increase circulation time, solubility, and enhance delivery into difficult-to-access tissues. In addition, nanostructures below 200 nm can undergo uptake in various cell types and avoid clearance by phagocytosis[154], making nanoscale systems particularly promising for targeted intra-cellular delivery of a variety of therapeutic cargo. This section will provide an overview of recent advances in nanotechnology for drug delivery, and identify remaining challenges.

Systemic delivery systems

Nanoparticles

Nanoparticle systems enable the systemic delivery of sensitive or unstable therapeutics by protecting them against degradation, extending circulation time, and facilitating delivery across biological barriers that would normally be prevented due to hydrophilicity, size or charge [9, 10]. Re-formulating existing drugs into nanoparticle

delivery systems can reduce toxicity, and nanoparticles can be formulated using a variety of materials including lipids, polymers and peptides. Nanoparticle formulations can also be used to deliver sensitive cargo at risk of degradation from ubiquitous nucleases *in vivo*, such as nucleic acids. Systemic nanoparticle mediated delivery has been demonstrated for mRNA[155], and localized delivery of DNA has been demonstrated following topical application of DNA nanoparticles to the skin[156] in patients with epidermolysis bullosa.

To improve solubility, drugs are often encapsulated inside micelle carriers, or conjugated to water soluble polymers. Liposome-based carriers were first described in the 1960s and are amongst the most well established nano-carriers for systemic delivery [157]. They have been widely used to improve aqueous solubility of hydrophobic drugs, illustrated by the antifungal amphotericin B, which is insoluble at physiological pH and also highly toxic. The liposomal formulation of this drug, AmBisome®, can be administered systemically with dramatically reduced toxicity[158-160].

Synthetic conjugates have also been used to formulate drug delivery nanoparticles, and inclusion of water soluble polymers, such as polyethylene glycol, can aid systemic solubility without the inclusion of dose-limiting solvents. Paclitaxel is an example of a poorly water-soluble drug that has been formulated within degradable polylactide-polyethylene glycol block co-polymers, allowing better delivery through nanoscale drug delivery micelles (Genexol-PM). These micellar nanoparticle formulations can also enhance transdermal drug delivery[161-163], and have been used to deliver hormones such as estradiol via topical application.The incorporation of polyethylene glycol (PEG) into these nanoparticle systems can increase particle stability[164-166], reduce protein adsorption (opsonization), and prevent subsequent phagocytic clearance. For example, PEGylated liposomal doxorubicin formulations have been shown to extend circulation

times[164, 167] when compared to uncoated liposomes, or free doxorubicin. However, studies have indicated that repeated administration of PEGylated formulations can lead to an increased clearance rate of subsequent doses of PEGylated liposomes. This is likely due to IgM antibodies raised after first exposure [164] or pre-existing IgG antibodies to PEG. [168]

Nanowires, nanoneedles and nanotubes

High-aspect-ratio nanoscale systems[169-171] such as nanowires, nanoneedles and nanotubes have been used to deliver a wide variety of biomolecules, and can be combined with macro and micro systems to enhance drug delivery technologies. For example, micron scaled drug delivery particles have been coated with nanowires which enhance retention in the mucosal tract. This strategy enables prolonged retention to mucosal epithelial tissue[172], facilitating enhanced drug delivery and limiting clearance. In addition, nano scale needles (nanoneedles), wires, and tubes can be loaded directly with drugs for intracellular drug delivery. Biodegradable silicon nanoneedles grafted onto micron sized patches have been used for the intra-cellular delivery of VEGF DNA to localised regions of skin and exposed muscle[169], where they are able to enhance neovascularization compared to delivery of naked DNA. Recently, more sophisticated systems have been developed which can release cargo in response to specific stimuli[29, 92], including changes in pH and temperature, and the presence of specific enzymes. High-aspect delivery systems are typically silicon-based, however alternative materials (such as carbon nanotube based drug reservoirs[173-176]) are currently being developed. These material systems will need to meet stringent nano scale safety and toxicity requirements before widespread clinical use.

Nanogels

Nanoscale hydrogels (nanogels) broadly consist of crosslinked polymeric particles which can be synthesized using a range of synthetic and naturally derived materials including polyacrylamides, polydimethylsiloxane, and chitosan[166, 177-180]. Nanogels offer a large surface area for bioconjugation, and as for the microgel systems described earlier, cross-linking can be used to fine tune drug delivery release kinetics for the delivery of hydrophobic, hydrophilic and charged solutes. Nanogels have been used for both targeted intracellular delivery and systemic delivery. These systems have recently been applied to intra-nasal vaccine delivery, where they can be retained in nasal mucosa to generate systemic immunity as well as local mucosal immunity[181, 182].

Localised delivery systems

Stimuli responsive nanosystems

In an effort to move towards systems with spatio-temporal control of drug delivery, a number of nanosystems have been developed which can be triggered to release cargo by exposure to external stimuli such as heat, light and ultrasound. Ultrasound has been utilized to increase transdermal delivery of a variety of nanoparticles through the skin[29, 149, 150], whilst heat and light sensitive nanosystems have enabled delivery to deeper tissues. For example, thermosensitive lipids that have transition temperatures between 40-45°C can be used to formulate liposomes that become unstable and release cargo once exposed to this temperature. ThermoDox® is a temperature-sensitive doxorubicin-PEGylated liposome that is systemically delivered but releases cargo in regions where local temperatures are elevated to 40 °C by application of radiofrequency. The thermo-responsive formulation was shown to increase local concentration of the drug several folds higher in the radiofrequency treatment area compared to intravenously

administered doxorubicin, and compared to non-thermosensitive liposomal formulations of doxorubicin[183].

Alternatively, light has been used as an external stimulus for photodynamic therapies. Visudyne® is a liposomal formulation of verteporfin[184, 185] used to treat ocular conditions. It is systemically administered but only exerts its toxic effects when exposed to light. When light is applied to the eye, this formulation can be used to treat ocular neovascularization due to diseases such as age-related macular degeneration. For these treatments to be successful, stimuli must be able to penetrate to the target tissue to facilitate drug release. This renders tissues closer to the surface more amenable to these therapies; for deeper structures alternative targeted delivery systems are required.

Targeted delivery systems

Site-specific accumulation

Systemically delivered nanoparticle systems may accumulate in organs such as the liver, lung and in tumors. This site-specific accumulation after systemic administration has been observed using nanocarriers where there is no specific targeting moiety. Nanoparticles that tend to accumulate at tumor sites are thought to be subject to the enhanced permeability and retention[186] (EPR) effect. Nanoparticles are small enough to traverse through the leaky blood-tumor barrier resulting in accumulation and therefore enhanced drug delivery to the tumor site. Lung accumulation is thought to be due to the cationic nature of nanoparticles leading blood component aggregation and accumulation in pulmonary vasculature.[187, 188]

Selective biodistribution has also been attributed to *in vivo* post-modification of nanoparticles, where particular apolipoproteins are preferentially adsorbed onto the nanoparticle, and can facilitate trafficking to, and enhance retention in, the

corresponding organ. In one example, polysorbate 80 modified polybutylcyanoacrylate nanoparticles were used to deliver doxorubicin to the brain. Doxorubicin does not cross the blood brain barrier alone, but when delivered as a nanoparticle formulation, delivery to the brain was achieved[189] and found to be due to adsorption of apolipoprotein onto the polymer nanoparticles. Similarly, lipid nanoparticles carrying nucleic acids were shown to accumulate in the liver after adsorption of apolipoprotein E[190, 191]. These examples demonstrate that nanoparticle design must consider factors such as particle size, charge and shape[170, 192], which can influence tissue accumulation and therefore targeting efficacy.

Receptor-mediated targeting

In a similar manner to microparticle based delivery, nanoparticles can be formulated with protein and ligand tags to enable selective delivery. Identifying specific receptor ligand pairs which enable cell selective delivery is a topic of great interest. To reduce phagocytosis and enhance therapeutic efficacy, nanosystems can be conjugated with "self" peptides such as CD47[193] which act as a "don't eat me" marker. For tumor targeting, nanoparticles can be decorated with ligands that target receptors that are overexpressed in cancer cells, such as the transferrin receptor[194]. Protein and antibody tagging can also facilitate organ and cellular targeting; HER2 antibodies have been conjugated to liposomal doxorubicin[165] to mediate targeted binding in breast cancer. Antibody presentation on nanoparticles can also increase cellular particle uptake; when trastuzumab and rituximab were bound to PLA particles, particle uptake was increased six-fold compared with PLA particles lacking targeting molecules[195]. In an alternative strategy, Abraxane, an albumin bound nanoparticle formulation of paclitaxel, is thought to undergo an albumin-receptor (gp60) mediated endothelial transcytosis[196-198], enabling the drug to pass through endothelial cell walls in tumor micro vessels to achieve

enhanced intra-tumoral concentrations and anti-tumor activity.

In addition to targeting specific cells, nanocarriers that contain cargo must also efficiently enter cells to deliver the therapeutic component. Particle shape, size, and composition can all affect penetration efficacy, and coating the nanoparticle with cell penetrating peptides is proving a promising strategy. By screening a library of cell penetrating peptides (CPP) using a high throughput strategy, three human peptides were identified which improved *in vivo* delivery when conjugated to lipid-like nanoparticles[199]. As the mechanism for cellular entry and endosomal escape become better understood, new ligands will be identified to enhance these processes and enhance intracellular targeting with increased specificity and efficiency.

Summary

Nano based systems are an enabling technology for the delivery of traditional drugs and novel therapies such as nucleic acid based drugs. Nanoparticles can be used to optimize the pharmacokinetics of conventional therapeutics, and offer a promising platform for targeting specific cells and organelles by manipulating biological pathways such as endocytosis and ligand targeting to gain cellular entry. Due to their small scale, drug loading and precision engineering is challenging, rendering current nanoscale systems less suited for the continued or controlled release of therapeutic loads. Additionally, the development of safe and effective nanoscale materials presents a significant hurdle for clinical translation.

CONCLUSIONS

Modern drug therapies include small molecules, proteins, and genetic engineering based strategies. These therapies often have precise biological therapeutic targets, and are most effective when delivered with specific dosing regimens. The need

to combine targeted delivery and dosing in smaller and smaller scale systems has driven the miniaturisation of drug delivery devices from the macro to micro to the nano scale. We have reviewed a range of devices and described their ability to controllably deliver biomolecules, summarised in Table 1 and Figure 4. In general, macro devices offer precisely engineered systems which can provide systemic and localised drug delivery over a period of several years. Devices have a defined lifetime, usually limited by battery power and reservoir capacity, before they need to be surgically replaced. In some cases, precision engineering and the incorporation of wireless sensors for on-demand sensing has enabled patient specific drug delivery, most commonly applied to insulin therapies. As the length scale of these devices is reduced to smaller macro devices, they can be surgically implanted into additional target organs to enable localised therapeutic delivery, however their scale limits their ability to target smaller biological structures. In a smart workaround, cell specific delivery can be achieved using macro scale polymer implants that recruit desired cells for targeted delivery, and when coupled with refillable drug depots this will provide an exciting future direction for cell specific delivery.

In contrast, micro and nano systems can often be coupled with targeting ligands and can travel through the vasculature and lymphatic systems to reach specific cell targets. Several of these systems can undergo burst release in response to external stimuli such as light, heat, or ultrasound. However, there are limited examples of these systems being able to intrinsically facilitate controlled dosing schedules. Notable exceptions are burst release polymer particles which offer a single administration of an entire dosing schedule, and stimuli responsive nanoneedle delivery systems which use cleavable linkers to deliver therapeutics in response to target enzyme expression. These systems straddle the boundary between sensing and drug delivery and offer an exciting direction

for responsive drug delivery therapies. A major limitation to micro and nano scale systems is the limited therapeutic load these systems can carry, limiting the duration of controlled release to between hours and, at most, a few months. This suggests micro- and nano- scale systems are best suited to short term delivery of up to 3 months, or the targeted delivery of curative and preventative therapeutics that can be administered with a single application.

Moving forwards, next generation devices will focus on increasing the efficacy of therapeutic delivery at smaller and smaller length scales. As mechanisms of nanoparticle cellular entry and endosomal escape are elucidated, nanoscale systems with greater delivery efficacy and therapeutic effect will be developed. Additionally, the development of stimuli responsive polymer systems will enable on-demand and patient-specific delivery systems to be developed in response to specific cues. Future devices will combine the advantages of macro scale delivery systems with the precise targeting capabilities of devices on the nano scale.

FIGURES AND TABLES:

FIGURE 1: Length scales in drug delivery An overview of the biological length scales important in drug delivery, including target organs, biological barriers and sub-cellular structure of interest.

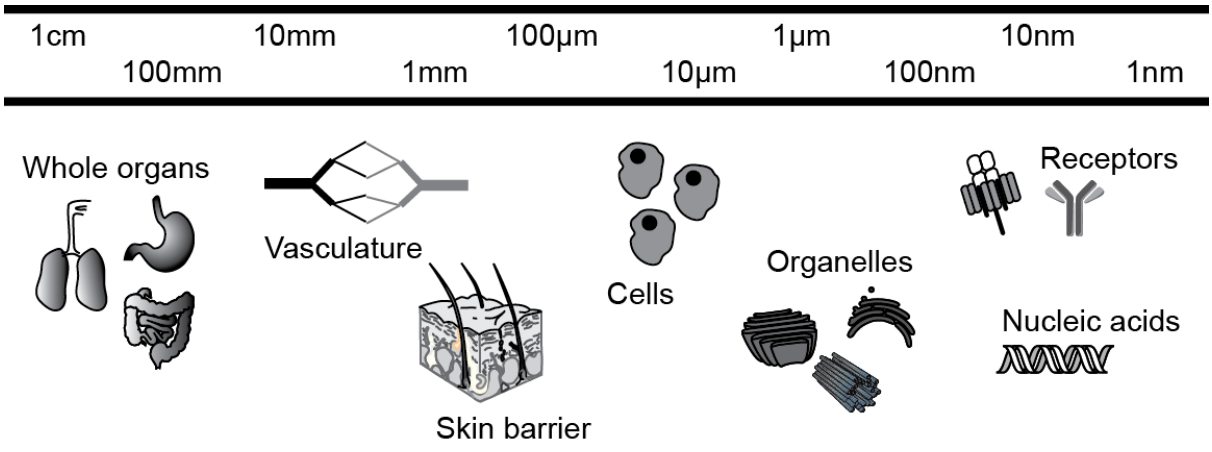

FIGURE 2: Miniaturisation of controlled dosing pump systems Infusion based devices have progressed rapidly from macroscale implantable pump systems able to deliver single therapeutics (A) to micro scaled pumps capable of delivering over 100 individual doses (B). Figures were adapted from the following references with permission: A- Adapted with permission from Nature Biotechnology [200] © 2003; B- Reprinted with permission from Science Translational Medicine [130] © 2012.

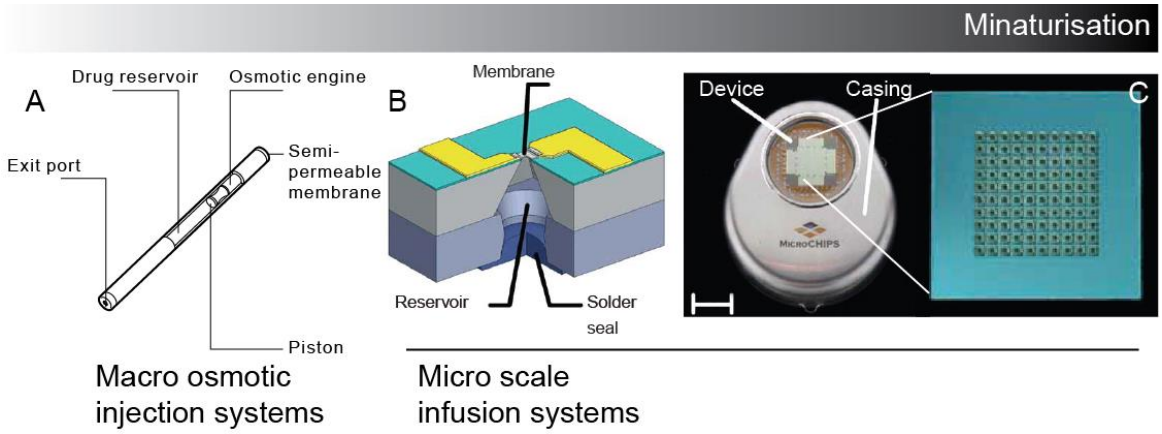

FIGURE 3: Polymer based drug delivery systems across length scales Polymer based drug delivery systems offer extremely versatile morphologies for drug delivery applications across several orders of magnitude. On the macro scale, flexible polymers have been folded into capsules small enough to swallow. (A) Precision engineering has enabled macro scale stents which possess micron scale features. These features are often made of, or coated in, biodegradable polymer substrates (B) providing both rigidity and drug eluting capabilities. (C) Polymer nanoneedles can be fabricated with a variety of aspect ratios to penetrate cells for nucleic acid drug delivery. Figures were adapted from the following references with permission: A- Reprinted with permission from Science Translational Medicine [201] © 2016. B- Reprinted with permission from the Journal of Interventional Cardiology [202] © 2004. C- Reprinted by permission from Macmillan Publishers Ltd [165] © 2015.

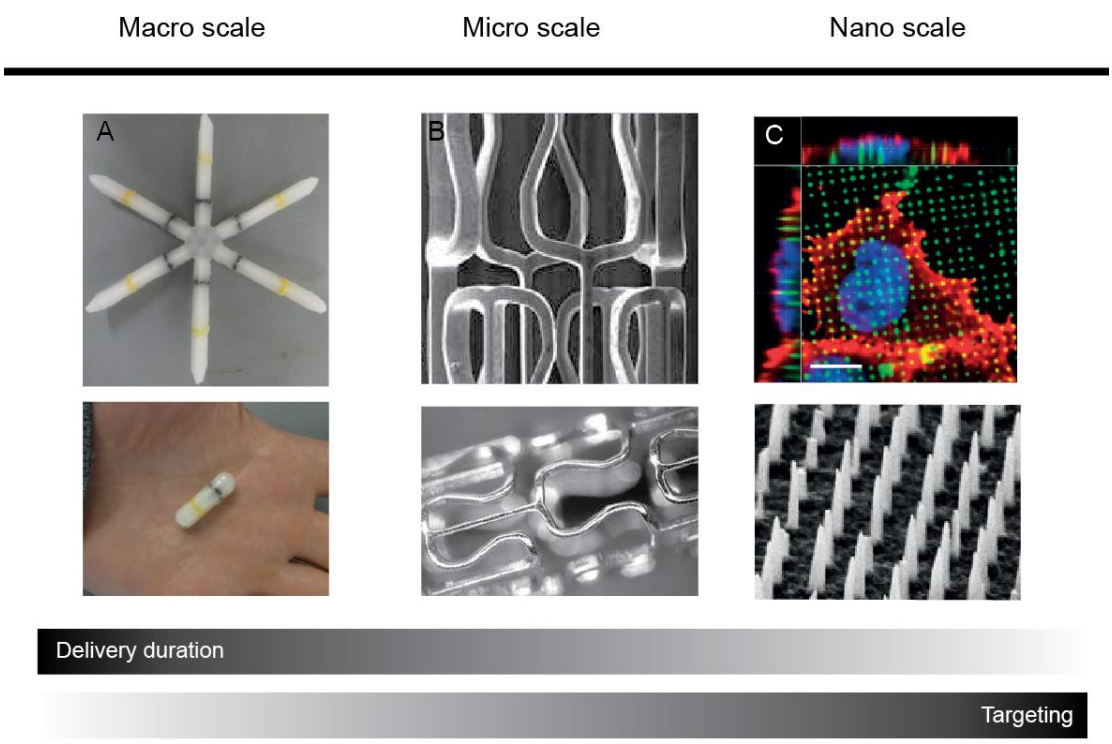

FIGURE 4: Overview of drug delivery systems by length scale A comparison between drug delivery strategies across length scales, illustrated by material delivery class, scale and the targeting ability to each therapy. Due to their scale, there are few examples of targeted macro scale drug delivery systems.

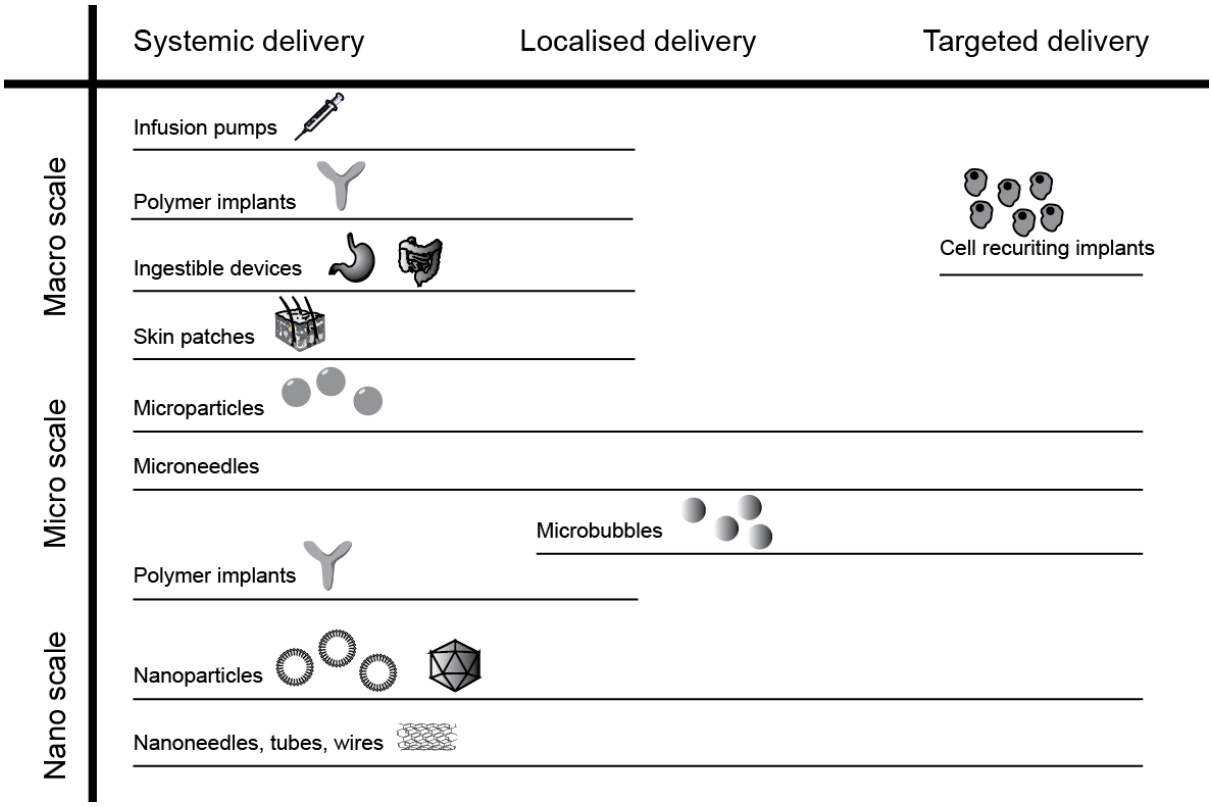

TABLE 1: Considerations in drug delivery device design The table provides an extension to Figure 4, and overview of the main considerations in drug delivery device design according to device scale. Types of device, typical therapeutics, targeting ability and typical delivery profiles are indicated for highlighted delivery systems.

Scale	Device (administration route)	Types of therapeutic typically delivered	Targeting			Delivery Duration					
			Systemic	Localised	Targeted	Hours	Days	Weeks	Months	6 months+	Years +
Macro	Ingestible devices (ingestion)	Peptides, Proteins, Small molecules	■	■		■	■	■	■	■	
	Skin patches	Peptides, Proteins, small molecules	■			■	■	■	■		
	Polymer implants	Peptides, Proteins, Small Molecules	■	■	■	■	■	■	■	■	■
	Pumps	Proteins, Small Molecules	■				■	■	■	■	■
Micro	Microneedles	Peptides, Proteins, Small Molecules, nucleic acids	■	■		■	■	■			
	Microparticles	Proteins, Small Molecules	■	■	■	■	■	■	■		
	Polymer implants	Proteins, Small Molecules	■	■		■	■	■	■		
	Microbubbles	Proteins		■	■	■					
Nano	Nanoneedles, tubes and wires	Peptides, Proteins, nucleic acids, small molecules	■	■	■	■	■	■			
	Nanogels	Peptides, proteins, small molecules	■	■	■	■	■	■	■		
	Nanoparticles	Peptides, Proteins, nucleic acids, small molecules, nucleic acids	■	■	■	■	■				

ACKNOWLEDGEMENTS

A.K.P and D.D gratefully acknowledge the Engineering and Physical Sciences Research Council (EPSRC) for the Engineering, Tissue Engineering and Regenerative Medicine (E-TERM) award (EP/I017801/1).

DECLARATIONS OF INTEREST

R.L. is co-inventor on multiple patents and patent applications describing drug delivery systems, and has a financial interest in Lyndra Inc., a biotechnology company focused on the development of oral drug delivery for long drug release. The rest of the authors declare no competing financial interests.

REFERENCES

1. Newman, D. J.; Cragg, G. M. *Journal of Natural Products* **2007,** 70, (3), 461.
2. Muralidhara, B. K.; Baid, R.; Bishop, S. M.; Huang, M.; Wang, W.; Nema, S. *Drug Discovery Today* **2016,** 21, (3), 430.
3. Sharma, C.; Awasthi, S. K. *Chemical Biology & Drug Design* **2017,** 89, (1), 16.
4. Kimchi-Sarfaty, C.; Schiller, T.; Hamasaki-Katagiri, N.; Khan, M. A.; Yanover, C.; Sauna, Z. E. *Trends in Pharmacological Sciences* **2013,** 34, (10), 534.
5. Eckstein, P. *British Medical Bulletin* **1970,** 26, (1), 52.
6. Sutradhar, K. B.; Sumi, C. D. *Drug Deliv.* **2016,** 23, (1), 1.
7. Fox, C. B.; Kim, J.; Le, L. V.; Nemeth, C. L.; Chirra, H. D.; Desai, T. A. *Journal of Controlled Release* **2015,** 219, 431.
8. Goffredo, R.; Accoto, D.; Guglielmelli, E. *Expert Review of Medical Devices* **2015,** 12, (5), 585.
9. Grayson, A. C. R.; Choi, I. S.; Tyler, B. M.; Wang, P. P.; Brem, H.; Cima, M. J.; Langer, R. *Nature materials* **2003,** 2, (11), 767.
10. Kearney, C. J.; Mooney, D. J. *Nature materials* **2013,** 12, (11), 1004.
11. McHugh, K. J.; Guarecuco, R.; Langer, R.; Jaklenec, A. *Journal of Controlled Release* **2015,** 219, 596.
12. Franzesi, G. T.; Ni, B.; Ling, Y. B.; Khademhosseini, A. *J. Am. Chem. Soc.* **2006,** 128, (47), 15064.
13. Ganji, F.; Vasheghani-Farahani, E. *Iranian Polymer Journal* **2009,** 18, (1), 63.
14. Reeves, A. R. D.; Spiller, K. L.; Freytes, D. O.; Vunjak-Novakovic, G.; Kaplan, D. L. *Biomaterials* **2015,** 73, 272.
15. Rodriguez Villanueva, J.; Bravo-Osuna, I.; Herrero-Vanrell, R.; Molina Martinez, I. T.; Guzman Navarro, M. *European Journal of Pharmaceutical Sciences* **2016,** 92, 287.
16. Guo, X.; Cui, F.; Xing, Y.; Mei, Q.; Zhang, Z. *Pharmazie* **2011,** 66, (12), 948.
17. Simon-Yarza, T.; Formiga, F. R.; Tamayo, E.; Pelacho, B.; Prosper, F.; Blanco-Prieto, M. J. *International Journal of Pharmaceutics* **2013,** 440, (1), 13.
18. Deng, Y. H.; Wang, C. C.; Shen, X. Z.; Yang, W. L.; An, L.; Gao, H.; Fu, S. K. *Chem.-Eur. J.* **2005,** 11, (20), 6006.

19. Li, H.; Go, G.; Ko, S. Y.; Park, J. O.; Park, S. *Smart Mater. Struct.* **2016,** 25, (2), 9.
20. Wanakule, P.; Liu, G. W.; Fleury, A. T.; Roy, K. *Journal of Controlled Release* **2012,** 162, (2), 429.
21. White, E. M.; Yatvin, J.; Grubbs, J. B.; Bilbrey, J. A.; Locklin, J. *Journal of Polymer Science Part B-Polymer Physics* **2013,** 51, (14), 1084.
22. Zorzetto, L.; Brambilla, P.; Marcello, E.; Bloise, N.; De Gregori, M.; Cobianchi, L.; Peloso, A.; Allegri, M.; Visai, L.; Petrini, P. *International Journal of Nanomedicine* **2016,** 11, 2695.
23. Blackshear, P. J.; Rohde, T. D.; Prosl, F.; Buchwald, H. *Medical Progress through Technology* **1979,** 6, (4), 149.
24. Theeuwes, F.; Yum, S. I. *Annals of Biomedical Engineering* **1976,** 4, (4), 343.
25. Schneider, M.; Windbergs, M.; Daum, N.; Loretz, B.; Collnot, E. M.; Hansen, S.; Schaefer, U. F.; Lehr, C. M. *European Journal of Pharmaceutics and Biopharmaceutics* **2013,** 84, (2), 239.
26. Avery, M.; Liu, D. *Food and Drug Law Journal* **2011,** 66, (3), 329.
27. van der Schaar, P. J.; Dijksman, F.; Shimizu, J.; Wanke, C.; Siersema, P. D. *Gastroenterology* **2011,** 140, (5), S766.
28. van der Schaar, P. J.; Dijksman, J. F.; Broekhuizen-de Gast, H.; Shimizu, J.; van Lelyveld, N.; Zou, H.; Iordanov, V.; Wanke, C.; Siersema, P. D. *Gastrointestinal Endoscopy* **2013,** 78, (3), 520.
29. Barry, B. W. *European Journal of Pharmaceutical Sciences* **2001,** 14, (2), 101.
30. Caffarel-Salvador, E.; Donnelly, R. F. *Current Pharmaceutical Design* **2016,** 22, (9), 1105.
31. Garg, N. K.; Singh, B.; Tyagi, R. K.; Sharma, G.; Katare, O. P. *Colloid Surf. B-Biointerfaces* **2016,** 147, 17.
32. Park, C. H.; Tijing, L. D.; Kim, C. S.; Lee, K.-M. *Colloid Surf. B-Biointerfaces* **2014,** 123, 710.
33. Singh, B. N.; Kim, K. H. *Journal of Controlled Release* **2000,** 63, (3), 235.
34. Rujivipat, S.; Bodmeier, R. *European Journal of Pharmaceutics and Biopharmaceutics* **2010,** 76, (3), 486.
35. Zhang, S. Y.; Bellinger, A. M.; Glettig, D. L.; Barman, R.; Lee, Y. A. L.; Zhu, J. H.; Cleveland, C.; Montgomery, V. A.; Gu, L.; Nash, L. D.; Maitland, D. J.; Langer, R.; Traverso, G. *Nature materials* **2015,** 14, (10), 1065.
36. Dahlgren, D.; Roos, C.; Lundqvist, A.; Abrahamsson, B.; Tannergren, C.; Hellstrom, P. M.; Sjogren, E.; Lennernas, H. *Molecular Pharmaceutics* **2016,** 13, (9), 3013.
37. Prausnitz, M. R.; Langer, R. *Nat Biotechnol* **2008,** 26, (11), 1261.
38. Chetkowski, R. J.; Meldrum, D. R.; Steingold, K. A.; Randle, D.; Lu, J. K.; Eggena, P.; Hershman, J. M.; Alkjaersig, N. K.; Fletcher, A. P.; Judd, H. L. *New England Journal of Medicine* **1986,** 314, (25), 1615.
39. Davis, S. R.; Dinatale, I.; Rivera-Woll, L.; Davison, S. *Journal of Endocrinology* **2005,** 185, (2), 207.
40. Prausnitz, M. R.; Mitragotri, S.; Langer, R. *Nature Reviews Drug Discovery* **2004,** 3, (2), 115.
41. Wadgave, U.; Nagesh, L. *International Journal of Health Sciences-Ijhs* **2016,** 10, (3), 425.
42. Polaneczky, M.; Slap, G.; Forke, C.; Rappaport, A.; Sondheimer, S. *New England Journal of Medicine* **1994,** 331, (18), 1201.
43. Shoupe, D.; Mishell, D. R. *American Journal of Obstetrics and Gynecology* **1989,** 160, (5), 1286.
44. Sivin, I. *Studies in Family Planning* **1988,** 19, (2), 81.
45. Brem, H.; Mahaley, S.; Vick, N. A.; Black, K. L.; Schold, S. C.; Burger, P. C.; Friedman, A. H.; Ciric, I. S.; Eller, T. W.; Cozzens, J. W.; Kenealy, J. N. *Journal of Neurosurgery* **1991,** 74, (3), 441.
46. Chew, S. A.; Danti, S. *Advanced Healthcare Materials* **2017,** 6, (2), 22.

47. Gollwitzer, H.; Ibrahim, K.; Meyer, H.; Mittelmeier, W.; Busch, R.; Stemberger, A. *Journal of Antimicrobial Chemotherapy* **2003,** 51, (3), 585.
48. Lee, S. S.; Hughes, P.; Ross, A. D.; Robinson, M. R. *Pharmaceutical Research* **2010,** 27, (10), 2043.
49. Ochoa, M.; Mousoulis, C.; Ziaie, B. *Advanced Drug Delivery Reviews* **2012,** 64, (14), 1603.
50. Abolmaali, S. S.; Tamaddon, A. M.; Dinarvand, R. *Journal of Nanoparticle Research* **2013,** 15, (12).
51. Calo, E.; Khutoryanskiy, V. V. *European Polymer Journal* **2015,** 65, 252.
52. Bory, C.; Lege, P.; Chalencon, E.; Milano, S. *Journal of Pharmacological and Toxicological Methods* **2014,** 70, (3), 349.
53. Tan, T.; Watts, S. W.; Davis, R. P. *Frontiers in Pharmacology* **2011,** 2.
54. Albright, A. L.; Awaad, Y.; Muhonen, M.; Boydston, W. R.; Gilmartin, R.; Krach, L. E.; Turner, M.; Zidek, K. A.; Wright, E.; Swift, D.; Bloom, K. *Journal of Neurosurgery* **2004,** 101, (1), 64.
55. Gilmartin, R.; Bruce, D.; Storrs, B. B.; Abbott, R.; Krach, L.; Ward, J.; Bloom, K.; Brooks, W. H.; Johnson, D. L.; Madsen, J. R.; McLaughlin, J. F.; Nadell, J. *Journal of Child Neurology* **2000,** 15, (2), 71.
56. Baert, L.; Schueller, L.; Tardy, Y.; Macbride, D.; van't Klooster, G.; Borghys, H.; Clessens, E.; Van den Mooter, G.; Van Gyseghem, E.; Van Remoortere, P.; Wigerinck, P.; Rosier, J. *International Journal of Pharmaceutics* **2008,** 355, (1-2), 38.
57. Ethans, K. D.; Schryvers, O. I.; Nance, P. W.; Casey, A. R. *Spinal Cord* **2005,** 43, (4), 214.
58. Kemeny, N.; Seiter, K.; Niedzwiecki, D.; Chapman, D.; Sigurdson, E.; Cohen, A.; Botet, J.; Oderman, P.; Murray, P. *Cancer* **1992,** 69, (2), 327.
59. Selam, J. L.; Micossi, P.; Dunn, F. L.; Nathan, D. M.; Fogel, H.; Gaz, R.; Haggen, C.; McKitrick, C.; Larkin, M.; Dunn, F.; Lavintomplins, J.; Thompson, M.; Byrd, P.; Sakiewicz, L.; Grant, J.; Selam, J. L.; Charles, M. A.; Waxman, K.; Raccah, D.; Jeandidier, N.; Lozano, J.; Micossi, P.; Cristallo, M.; Galimberti, G.; Petrella, G.; Librenti, M. C.; Scavini, M.; Pozza, G.; Bucci, V.; Wingrove, T.; Cafferty, M.; Day, J.; Sarmiento, M.; Blackshear, P. *Diabetes Care* **1992,** 15, (7), 877.
60. Anderson, S. M.; Raghinaru, D.; Pinsker, J. E.; Boscari, F.; Renard, E.; Buckingham, B. A.; Nimri, R.; Doyle, F. J.; Brown, S. A.; Keith-Hynes, P.; Breton, M. D.; Chernavvsky, D.; Bevier, W. C.; Bradley, P. K.; Bruttomesso, D.; Del Favero, S.; Calore, R.; Cobelli, C.; Avogaro, A.; Farret, A.; Place, J.; Ly, T. T.; Shanmugham, S.; Phillip, M.; Dassau, E.; Dasanayake, I. S.; Kollman, C.; Lum, J. W.; Beck, R. W.; Kovatchev, B.; Control Range Study, G. *Diabetes Care* **2016,** 39, (7), 1143.
61. Pickup, J.; Mattock, M.; Kerry, S. *British Medical Journal* **2002,** 324, (7339), 705.
62. Blauw, H.; van Bon, A. C.; Koops, R.; DeVries, J. H.; Consortium, P. *Diabetes Obesity & Metabolism* **2016,** 18, (7), 671.
63. Ramotowska, A.; Szypowska, A. *Diabetes-Metabolism Research and Reviews* **2014,** 30, (2), 146.
64. Kovatchev, B.; Cheng, P. Y.; Anderson, S. M.; Pinsker, J. E.; Boscari, F.; Buckingham, B. A.; Doyle, F. J.; Hood, K. K.; Brown, S. A.; Breton, M. D.; Chernavvsky, D.; Bevier, W. C.; Bradley, P. K.; Bruttomesso, D.; Del Favero, S.; Calore, R.; Cobelli, C.; Avogaro, A.; Ly, T. T.; Shanmugham, S.; Dassau, E.; Kollman, C.; Lum, J. W.; Beck, R. W.; Control Range Study, G. *Diabetes Technology & Therapeutics* **2017,** 19, (1), 18.
65. Bottros, M. M.; Christo, P. J. *Journal of Pain Research* **2014,** 7, 615.
66. Brache, V.; Payan, L. J.; Faundes, A. *Contraception* **2013,** 87, (3), 264.
67. Huang, Y. M.; Merkatz, R. B.; Hillier, S. L.; Roberts, K.; Blithe, D. L.; Sitruk-Ware, R.; Creinin, M. D. *Plos One* **2015,** 10, (8).
68. Hubacher, D.; Lara-Ricalde, R.; Taylor, D. J.; Guerra-Infante, F.; Guzman-Rodriguez, R. *New England Journal of Medicine* **2001,** 345, (8), 561.

69. Nakazawa, G.; Otsuka, F.; Nakano, M.; Vorpahl, M.; Yazdani, S. K.; Ladich, E.; Kolodgie, F. D.; Finn, A. V.; Virmani, R. *Journal of the American College of Cardiology* **2011,** 57, (11), 1314.
70. Jaworska, J.; Jelonek, K.; Sobota, M.; Kasperczyk, J.; Dobrzynski, P.; Musial-Kulik, M.; Smola-Dmochowska, A.; Janeczek, H.; Jarzabek, B. *J. Appl. Polym. Sci.* **2015,** 132, (17).
71. Katz, G.; Harchandani, B.; Shah, B. *Current Atherosclerosis Reports* **2015,** 17, (3).
72. Wache, H. M.; Tartakowska, D. J.; Hentrich, A.; Wagner, M. H. *Journal of Materials Science-Materials in Medicine* **2003,** 14, (2), 109.
73. Westphal, M.; Hilt, D. C.; Bortey, E.; Delavault, P.; Olivares, R.; Warnke, P. C.; Whittle, I. R.; Jaaskelainen, J.; Ram, Z. *Neuro-Oncology* **2003,** 5, (2), 79.
74. Westphal, M.; Ram, Z.; Riddle, V.; Hilt, D.; Bortey, E.; Executive Comm Gliadel Study, G. *Acta Neurochirurgica* **2006,** 148, (3), 269.
75. Saher, O.; Ghorab, D. M.; Mursi, N. M. *Journal of Drug Delivery Science and Technology* **2016,** 31, 22.
76. Gulsen, D.; Chauhan, A. *Investigative Ophthalmology & Visual Science* **2004,** 45, (7), 2342.
77. Jain, M. R. *British Journal of Ophthalmology* **1988,** 72, (2), 150.
78. Kim, J.; Conway, A.; Chauhan, A. *Biomaterials* **2008,** 29, (14), 2259.
79. Kim, J.; Chauhan, A. *Abstracts of Papers of the American Chemical Society* **2008,** 235.
80. Dong, L. C.; Hoffman, A. S. *Journal of Controlled Release* **1991,** 15, (2), 141.
81. Goyanes, A.; Fina, F.; Martorana, A.; Sedough, D.; Gaisford, S.; Basit, A. W. *International Journal of Pharmaceutics* **2017,** 527, (1-2), 21.
82. Park, H. J.; Jung, H. J.; Ho, M. J.; Lee, D. R.; Cho, H. R.; Choi, Y. S.; Jun, J.; Son, M.; Kang, M. J. *European Journal of Pharmaceutical Sciences* **2017,** 102, 172.
83. Kim, J.; Li, W. A.; Choi, Y.; Lewin, S. A.; Verbeke, C. S.; Dranoff, G.; Mooney, D. J. *Nat Biotechnol* **2015,** 33, (1), 64.
84. Kim, J.; Mooney, D. J. *Nano Today* **2011,** 6, (5), 466.
85. Li, W. A.; Mooney, D. J. *Current Opinion in Immunology* **2013,** 25, (2), 238.
86. Dobnig, H.; Turner, R. T. *Endocrinology* **1997,** 138, (11), 4607.
87. Waterman, K. C.; Goeken, G. S.; Konagurthu, S.; Likar, M. D.; MacDonald, B. C.; Mahajan, N.; Swaminathan, V. *Journal of Controlled Release* **2011,** 152, (2), 264.
88. Arya, J.; Prausnitz, M. R. *Journal of Controlled Release* **2016,** 240, 135.
89. Baek, S. H.; Shin, J. H.; Kim, Y. C. *Biomedical Microdevices* **2017,** 19, (1), 11.
90. Chandrasekhar, S.; Iyer, L. K.; Panchal, J. P.; Topp, E. M.; Cannon, J. B.; Ranade, V. V. *Expert Opinion on Drug Delivery* **2013,** 10, (8), 1155.
91. Ma, G. J.; Wu, C. W. *Journal of Controlled Release* **2017,** 251, 11.
92. Yu, J. C.; Zhang, Y. Q.; Ye, Y. Q.; DiSanto, R.; Sun, W. J.; Ranson, D.; Ligler, F. S.; Buse, J. B.; Gu, Z. *Proceedings of the National Academy of Sciences of the United States of America* **2015,** 112, (27), 8260.
93. Ferris, R. L.; Lotze, M. T.; Leong, S. P. L.; Hoon, D. S. B.; Morton, D. L. *Clinical & Experimental Metastasis* **2012,** 29, (7), 729.
94. Margaris, K. N.; Black, R. A. *Journal of the Royal Society Interface* **2012,** 9, (69), 601.
95. Potter, R. F.; Groom, A. C. *Microvascular Research* **1983,** 25, (1), 68.
96. Santini, J. T.; Cima, M. J.; Langer, R. *Nature* **1999,** 397, (6717), 335.
97. Elman, N. M.; Duc, H. L. H.; Cima, M. J. *Biomedical Microdevices* **2009,** 11, (3), 625.
98. Goffredo, R.; Pecora, A.; Maiolo, L.; Ferrone, A.; Guglielmelli, E.; Accoto, D. *J. Microelectromech. Syst.* **2016,** 25, (2), 362.
99. Lo, R.; Li, P. Y.; Saati, S.; Agrawal, R. N.; Humayun, M. S.; Meng, E. *Biomedical Microdevices* **2009,** 11, (5), 959.
100. Meng, E.; Hoang, T. *Advanced Drug Delivery Reviews* **2012,** 64, (14), 1628.
101. Nguyen, C. T. C. *Ieee Transactions on Ultrasonics Ferroelectrics and Frequency Control* **2007,** 54, (2), 251.
102. Nguyen, C. T. C. *Ieee Transactions on Microwave Theory and Techniques* **1999,** 47, (8), 1486.

103. Ruhhammer, J.; Zens, M.; Goldschmidtboeing, F.; Seifert, A.; Woias, P. *Science and Technology of Advanced Materials* **2015,** 16, (1).
104. Tsai, N. C.; Sue, C. Y. *Sensors and Actuators a-Physical* **2007,** 134, (2), 555.
105. Zordan, E.; Amirouche, F. *Proceedings of the Institution of Mechanical Engineers Part H-Journal of Engineering in Medicine* **2007,** 221, (H2), 143.
106. Huesgen, T.; Lenk, G.; Albrecht, B.; Vulto, P.; Lemke, T.; Woias, P. *Sensors and Actuators a-Physical* **2010,** 162, (1), 137.
107. Johnson, D. G.; Borkholder, D. A. *Micromachines* **2016,** 7, (6), 16.
108. Nguyen, N. T.; Huang, X. Y.; Chuan, T. K. *Journal of Fluids Engineering-Transactions of the Asme* **2002,** 124, (2), 384.
109. Pirmoradi, F. N.; Jackson, J. K.; Burt, H. M.; Chiao, M. *Lab on a Chip* **2011,** 11, (16), 2744.
110. Zainal, M. A.; Ahmad, A.; Ali, M. S. M. *Biomedical Microdevices* **2017,** 19, (1), 10.
111. Gill, H. S.; Prausnitz, M. R. *J Diabetes Sci Technol* **2007,** 1, (5), 725.
112. Jalil, R. U. *Drug Development and Industrial Pharmacy* **1990,** 16, (16), 2353.
113. Gong, C.; Qi, T.; Wei, X.; Qu, Y.; Wu, Q.; Luo, F.; Qian, Z. *Current Medicinal Chemistry* **2013,** 20, (1), 79.
114. Kurisawa, M.; Chung, J. E.; Yang, Y. Y.; Gao, S. J.; Uyama, H. *Chem Commun* **2005**, (34), 4312.
115. Sun, J. E. P.; Stewart, B.; Litan, A.; Lee, S. J.; Schneider, J. P.; Langhans, S. A.; Pochan, D. J. *Biomaterials Science* **2016,** 4, (5), 839.
116. Yan, C. Q.; Altunbas, A.; Yucel, T.; Nagarkar, R. P.; Schneider, J. P.; Pochan, D. J. *Soft Matter* **2010,** 6, (20), 5143.
117. Ye, H. Y.; Owh, C.; Jiang, S.; Ng, C. Z. Q.; Wirawan, D.; Loh, X. J. *Polymers* **2016,** 8, (4).
118. Brudno, Y.; Mooney, D. J. *Journal of Controlled Release* **2015,** 219, 8.
119. Brudno, Y.; Silva, E. A.; Kearney, C. J.; Lewin, S. A.; Miller, A.; Martinick, K. D.; Aizenberg, M.; Mooney, D. J. *Proceedings of the National Academy of Sciences of the United States of America* **2014,** 111, (35), 12722.
120. Acharya, A. P.; Lewis, J. S.; Keselowsky, B. G. *Biomaterials* **2013,** 34, (13), 3422.
121. Rafati, A.; Boussahel, A.; Shakesheff, K. M.; Shard, A. G.; Roberts, C. J.; Chen, X.; Scurr, D. J.; Rigby-Singleton, S.; Whiteside, P.; Alexander, M. R.; Davies, M. C. *Journal of Controlled Release* **2012,** 162, (2), 321.
122. Rahimian, S.; Fransen, M. F.; Kleinovink, J. W.; Amidi, M.; Ossendorp, F.; Hennink, W. E. *Current Pharmaceutical Design* **2015,** 21, (29), 4201.
123. Wang, N. X.; Bazdar, D. A.; Sieg, S. F.; von Recum, H. A. *Biotechnol. Bioeng.* **2012,** 109, (7), 1835.
124. White, L. J.; Kirby, G. T. S.; Cox, H. C.; Qodratnama, R.; Qutachi, O.; Rose, F.; Shakesheff, K. M. *Materials Science & Engineering C-Materials for Biological Applications* **2013,** 33, (5), 2578.
125. Xia, Y. J.; Pack, D. W. *Chemical Engineering Science* **2015,** 125, 129.
126. Goldray, D.; Weisman, Y.; Jaccard, N.; Merdler, C.; Chen, J.; Matzkin, H. *Journal of Clinical Endocrinology & Metabolism* **1993,** 76, (2), 288.
127. Parmar, H.; Rustin, G.; Lightman, S. L.; Phillips, R. H.; Hanham, I. W.; Schally, A. V. *British Medical Journal* **1988,** 296, (6631), 1229.
128. De Leede, L. G. J.; Humphries, J. E.; Bechet, A. C.; Van Hoogdalem, E. J.; Verrijk, R.; Spencer, D. G. *J. Interferon Cytokine Res.* **2008,** 28, (2), 113.
129. Tzeng, S. Y.; Guarecuco, R.; McHugh, K. J.; Rose, S.; Rosenberg, E. M.; Zeng, Y. Y.; Langer, R.; Jaklenec, A. *Journal of Controlled Release* **2016,** 233, 101.
130. Farra, R.; Sheppard, N. F.; McCabe, L.; Neer, R. M.; Anderson, J. M.; Santini, J. T.; Cima, M. J.; Langer, R. *Science translational medicine* **2012,** 4, (122).
131. Jonas, O.; Calligaris, D.; Methuku, K. R.; Poe, M. M.; Francois, J. P.; Tranghese, F.; Changelian, A.; Sieghart, W.; Ernst, M.; Krummel, D. A. P.; Cook, J. M.; Pomeroy, S. L.; Cima, M.; Agar, N. Y. R.; Langer, R.; Sengupta, S. *Journal of Biomedical Nanotechnology* **2016,** 12, (6), 1297.

132. Jonas, O.; Landry, H. M.; Fuller, J. E.; Santini, J. T.; Baselga, J.; Tepper, R. I.; Cima, M. J.; Langer, R. *Science translational medicine* **2015,** 7, (284).
133. *Nature Reviews Drug Discovery* **2008,** 7, (12), 964.
134. Champion, J. A.; Katare, Y. K.; Mitragotri, S. *Journal of Controlled Release* **2007,** 121, (1-2), 3.
135. Mandal, S.; Hammink, R.; Tel, J.; Eksteen-Akeroyd, Z. H.; Rowan, A. E.; Blank, K.; Figdor, C. G. *ACS Chem. Bio.* **2015,** 10, (2), 485.
136. Meyer, R. A.; Sunshine, J. C.; Green, J. J. *Trends Biotechnol.* **2015,** 33, (9), 514.
137. Perica, K.; Kosmides, A. K.; Schneck, J. P. *Biochim. Phys. Acta.* **2015,** 1853, (4), 781.
138. Veiseh, O.; Doloff, J. C.; Ma, M.; Vegas, A. J.; Tam, H. H.; Bader, A. R.; Li, J.; Langan, E.; Wyckoff, J.; Loo, W. S.; Jhunjhunwala, S.; Chiu, A.; Siebert, S.; Tang, K.; Hollister-Lock, J.; Aresta-Dasilva, S.; Bochenek, M.; Mendoza-Elias, J.; Wang, Y.; Qi, M.; Lavin, D. M.; Chen, M.; Dholakia, N.; Thakrar, R.; Lacik, I.; Weir, G. C.; Oberholzer, J.; Greiner, D. L.; Langer, R.; Anderson, D. G. *Nat. Mater.* **2015,** 14, (6), 643.
139. Bencherif, S. A.; Sands, R. W.; Bhatta, D.; Arany, P.; Verbeke, C. S.; Edwards, D. A.; Mooney, D. J. *Proceedings of the National Academy of Sciences of the United States of America* **2012,** 109, (48), 19590.
140. Sun, L.; Huang, W. M.; Ding, Z.; Zhao, Y.; Wang, C. C.; Purnawali, H.; Tang, C. *Materials & Design* **2012,** 33, 577.
141. Wang, L.; Shansky, J.; Borselli, C.; Mooney, D.; Vandenburgh, H. *Tissue Eng. Part A* **2012,** 18, (19-20), 2000.
142. Chirra, H. D.; Desai, T. A. *Small* **2012,** 8, (24), 3839.
143. Wischke, C.; Zimmermann, J.; Wessinger, B.; Schendler, A.; Borchert, H. H.; Peters, J. H.; Nesselhut, T.; Lorenzen, D. R. *International Journal of Pharmaceutics* **2009,** 365, (1-2), 61.
144. Rudd, P. M.; Wormald, M. R.; Stanfield, R. L.; Huang, M. D.; Mattsson, N.; Speir, J. A.; DiGennaro, J. A.; Fetrow, J. S.; Dwek, R. A.; Wilson, I. A. *J. Mol. Biol.* **1999,** 293, (2), 351.
145. Liang, H. F.; Chen, C. T.; Chen, S. C.; Kulkarni, A. R.; Chiu, Y. L.; Chen, M. C.; Sung, H. W. *Biomaterials* **2006,** 27, (9), 2051.
146. Lewis, J. S.; Dolgova, N. V.; Zhang, Y.; Xia, C. Q.; Wasserfall, C. H.; Atkinson, M. A.; Clare-Salzler, M. J.; Keselowsky, B. G. *Clinical Immunology* **2015,** 160, (1), 90.
147. Yoon, Y. M.; Lewis, J. S.; Carstens, M. R.; Campbell-Thompson, M.; Wasserfall, C. H.; Atkinson, M. A.; Keselowsky, B. G. *Scientific Reports* **2015,** 5.
148. Bull, J. L. *Expert Opinion on Drug Delivery* **2007,** 4, (5), 475.
149. Ren, S. T.; Liao, Y. R.; Kang, X. N.; Li, Y. P.; Zhang, H.; Ai, H.; Sun, Q.; Jing, J.; Zhao, X. H.; Tan, L. F.; Shen, X. L.; Wang, B. *Pharmaceutical Research* **2013,** 30, (6), 1574.
150. Wu, S. Z.; Li, L.; Wang, G.; Shen, W. W.; Xu, Y. L.; Liu, Z.; Zhuo, Z. X.; Xia, H. M.; Gao, Y. H.; Tan, K. B. *International Journal of Nanomedicine* **2014,** 9, 5639.
151. Kost, J.; Leong, K.; Langer, R. *Proceedings of the National Academy of Sciences of the United States of America* **1989,** 86, (20), 7663.
152. Mitragotri, S.; Blankschtein, D.; Langer, R. *Science* **1995,** 269, (5225), 850.
153. *Nature Nanotechnology* **2009,** 4, (3), 135.
154. Sheikh, Z.; Brooks, P. J.; Barzilay, O.; Fine, N.; Glogauer, M. *Materials* **2015,** 8, (9), 5671.
155. Kaczmarek, J. C.; Patel, A. K.; Kauffman, K. J.; Fenton, O. S.; Webber, M. J.; Heartlein, M. W.; DeRosa, F.; Anderson, D. G. *Angewandte Chemie-International Edition* **2016,** 55, (44), 13808.
156. Zhou, D. Z.; Gao, Y. S.; Ahern, J. O.; Sigen, A.; Xu, Q.; Huang, X. B.; Greiser, U.; Wang, W. X. *Acs Applied Materials & Interfaces* **2016,** 8, (50), 34218.
157. Felnerova, D.; Viret, J. F.; Gluck, R.; Moser, C. *Current Opinion in Biotechnology* **2004,** 15, (6), 518.
158. Boswell, G. W.; Bekersky, I.; Buell, D.; Hiles, R.; Walsh, T. J. *Antimicrobial Agents and Chemotherapy* **1998,** 42, (2), 263.
159. Boswell, G. W.; Buell, D.; Bekersky, I. *Journal of Clinical Pharmacology* **1998,** 38, (7), 583.

160. Walsh, T. J.; Yeldandi, V.; McEvoy, M.; Gonzalez, C.; Chanock, S.; Freifeld, A.; Seibel, N. I.; Whitcomb, P. O.; Jarosinski, P.; Boswell, G.; Bekersky, I.; Alak, A.; Buell, D.; Barret, J.; Wilson, W. *Antimicrobial Agents and Chemotherapy* **1998,** 42, (9), 2391.
161. Sheu, M. T.; Chen, S. Y.; Chen, L. C.; Ho, H. O. *Journal of Controlled Release* **2003,** 88, (3), 355.
162. Soo, P. L.; Lovric, J.; Davidson, P.; Maysinger, D.; Eisenberg, A. *Molecular Pharmaceutics* **2005,** 2, (6), 519.
163. Chiechi, L. M. *Idrugs* **2004,** 7, (9), 860.
164. Ishida, T.; Atobe, K.; Wang, X. Y.; Kiwada, H. *Journal of Controlled Release* **2006,** 115, (3), 251.
165. Nellis, D. F.; Giardina, S. L.; Janini, G. M.; Shenoy, S. R.; Marks, J. D.; Tsai, R.; Drummond, D. C.; Hong, K.; Park, J. W.; Ouellette, T. F.; Perkins, S. C.; Kirpotin, D. B. *Biotechnology Progress* **2005,** 21, (1), 221.
166. Sekine, Y.; Moritani, Y.; Ikeda-Fukazawa, T.; Sasaki, Y.; Akiyoshi, K. *Advanced Healthcare Materials* **2012,** 1, (6), 722.
167. Zhang, C. Y.; Yang, Y. Q.; Huang, T. X.; Zhao, B.; Guo, X. D.; Wang, J. F.; Zhang, L. J. *Biomaterials* **2012,** 33, (26), 6273.
168. Ganson, N. J.; Povsic, T. J.; Sullenger, B. A.; Alexander, J. H.; Zelenkofske, S. L.; Sailstad, J. M.; Rusconi, C. P.; Hershfield, M. S. *Journal of Allergy and Clinical Immunology* **2016,** 137, (5), 1610.
169. Chiappini, C.; De Rosa, E.; Martinez, J. O.; Liu, X.; Steele, J.; Stevens, M. M.; Tasciotti, E. *Nature materials* **2015,** 14, (5), 532.
170. Serda, R. E.; Godin, B.; Blanco, E.; Chiappini, C.; Ferrari, M. *Biochimica Et Biophysica Acta-General Subjects* **2011,** 1810, (3), 317.
171. Shalek, A. K.; Robinson, J. T.; Karp, E. S.; Lee, J. S.; Ahn, D. R.; Yoon, M. H.; Sutton, A.; Jorgolli, M.; Gertner, R. S.; Gujral, T. S.; MacBeath, G.; Yang, E. G.; Park, H. *Proceedings of the National Academy of Sciences of the United States of America* **2010,** 107, (5), 1870.
172. Fischer, K. E.; Aleman, B. J.; Tao, S. L.; Daniels, R. H.; Li, E. M.; Bunger, M. D.; Nagaraj, G.; Singh, P.; Zettl, A.; Desai, T. A. *Nano Letters* **2009,** 9, (2), 716.
173. Brammer, K. S.; Choi, C.; Oh, S.; Cobb, C. J.; Connelly, L. S.; Loya, M.; Kong, S. D.; Jin, S. *Nano Letters* **2009,** 9, (10), 3570.
174. Uskokovic, V.; Lee, P. P.; Walsh, L. A.; Fischer, K. E.; Desai, T. A. *Biomaterials* **2012,** 33, (5), 1663.
175. Bianco, A.; Kostarelos, K.; Prato, M. *Current Opinion in Chemical Biology* **2005,** 9, (6), 674.
176. Fadel, T. R.; Sharp, F. A.; Vudattu, N.; Ragheb, R.; Garyu, J.; Kim, D.; Hong, E.; Li, N.; Haller, G. L.; Pfefferle, L. D.; Justesen, S.; Herold, K. C.; Fahmy, T. M. *Nat. Nanotechnol.* **2014,** 9, (8), 639.
177. Li, D. D.; Kordalivand, N.; Fransen, M. F.; Ossendorp, F.; Raemdonck, K.; Vermonden, T.; Hennink, W. E.; van Nostrum, C. F. *Adv. Funct. Mater.* **2015,** 25, (20), 2993.
178. Naeye, B.; Raemdonck, K.; Remaut, K.; Sproat, B.; Demeester, J.; De Smedt, S. C. *European Journal of Pharmaceutical Sciences* **2010,** 40, (4), 342.
179. Raemdonck, K.; Demeester, J.; De Smedt, S. *Soft Matter* **2009,** 5, (4), 707.
180. Van Thienen, T. G.; Demeester, J.; De Smedt, S. C. *International Journal of Pharmaceutics* **2008,** 351, (1-2), 174.
181. Kong, I. G.; Sato, A.; Yuki, Y.; Nochi, T.; Takahashi, H.; Sawada, S.; Mejima, M.; Kurokawa, S.; Okada, K.; Sato, S.; Briles, D. E.; Kunisawa, J.; Inoue, Y.; Yamamoto, M.; Akiyoshi, K.; Kiyono, H. *Infection and Immunity* **2013,** 81, (5), 1625.
182. Nochi, T.; Yuki, Y.; Takahashi, H.; Sawada, S.; Mejima, M.; Kohda, T.; Harada, N.; Kong, I. G.; Sato, A.; Kataoka, N.; Tokuhara, D.; Kurokawa, S.; Takahashi, Y.; Tsukada, H.; Kozaki, S.; Akiyoshi, K.; Kiyono, H. *Nature materials* **2010,** 9, (7), 572.
183. Yarmolenko, P. S.; Zhao, Y. L.; Landon, C.; Spasojevic, I.; Yuan, F.; Needham, D.; Viglianti, B. L.; Dewhirst, M. W. *International Journal of Hyperthermia* **2010,** 26, (5), 485.
184. Blinder, K. J.; Blumenkranz, M. S.; Bressler, N. M.; Bressler, S. B.; Donati, G.; Lewis, H.; Lim, J. I.; Menchini, U.; Miller, J. W.; Mones, J. M.; Potter, M. J.; Pournaras, C.; Reaves,

A.; Rosenfeld, P.; Schachat, A. P.; Schmidt-Erfurth, U.; Sickenberg, M.; Singerman, L. J.; Slakter, J.; Strong, H. A.; Virgili, G.; Williams, G. A.; Grp, V. I. P. S. *Ophthalmology* **2003,** 110, (4), 667.
185. Spaide, R. F.; Sorenson, J.; Maranan, L. *Ophthalmology* **2003,** 110, (8), 1517.
186. Matsumura, Y.; Maeda, H. *Cancer Research* **1986,** 46, (12), 6387.
187. Ogris, E.; Mudrak, I.; Mak, E.; Gibson, D.; Pallas, D. C. *Journal of Virology* **1999,** 73, (9), 7390.
188. Ogris, M.; Brunner, S.; Schuller, S.; Kircheis, R.; Wagner, E. *Gene Therapy* **1999,** 6, (4), 595.
189. Kreuter, J.; Shamenkov, D.; Petrov, V.; Ramge, P.; Cychutek, K.; Koch-Brandt, C.; Alyautdin, R. *Journal of Drug Targeting* **2002,** 10, (4), 317.
190. Akinc, A.; Querbes, W.; De, S. M.; Qin, J.; Frank-Kamenetsky, M.; Jayaprakash, K. N.; Jayaraman, M.; Rajeev, K. G.; Cantley, W. L.; Dorkin, J. R.; Butler, J. S.; Qin, L. L.; Racie, T.; Sprague, A.; Fava, E.; Zeigerer, A.; Hope, M. J.; Zerial, M.; Sah, D. W. Y.; Fitzgerald, K.; Tracy, M. A.; Manoharan, M.; Koteliansky, V.; de Fougerolles, A.; Maier, M. A. *Molecular Therapy* **2010,** 18, (7), 1357.
191. Semple, S. C.; Akinc, A.; Chen, J. X.; Sandhu, A. P.; Mui, B. L.; Cho, C. K.; Sah, D. W. Y.; Stebbing, D.; Crosley, E. J.; Yaworski, E.; Hafez, I. M.; Dorkin, J. R.; Qin, J.; Lam, K.; Rajeev, K. G.; Wong, K. F.; Jeffs, L. B.; Nechev, L.; Eisenhardt, M. L.; Jayaraman, M.; Kazem, M.; Maier, M. A.; Srinivasulu, M.; Weinstein, M. J.; Chen, Q. M.; Alvarez, R.; Barros, S. A.; De, S.; Klimuk, S. K.; Borland, T.; Kosovrasti, V.; Cantley, W. L.; Tam, Y. K.; Manoharan, M.; Ciufolini, M. A.; Tracy, M. A.; de Fougerolles, A.; MacLachlan, I.; Cullis, P. R.; Madden, T. D.; Hope, M. J. *Nat Biotechnol* **2010,** 28, (2), 172.
192. Blanco, E.; Shen, H.; Ferrari, M. *Nat Biotechnol* **2015,** 33, (9), 941.
193. Rodriguez, P. L.; Harada, T.; Christian, D. A.; Pantano, D. A.; Tsai, R. K.; Discher, D. E. *Science* **2013,** 339, (6122), 971.
194. Daniels-Wells, T. R.; Penichet, M. L. *Immunotherapy* **2016,** 8, (9), 991.
195. Nobs, L.; Buchegger, F.; Gurny, R.; Allemann, E. *Bioconjugate Chemistry* **2006,** 17, (1), 139.
196. Desai, N.; Trieu, V.; Yao, Z. *Clinical Cancer Research* **2006,** 12, (12), 3869.
197. Desai, N. P.; Trieu, V.; Hwang, L. Y.; Wu, R. J.; Soon-Shiong, P.; Gradishar, W. J. *Anti-Cancer Drugs* **2008,** 19, (9), 899.
198. Ng, S. S. W.; Sparreboom, A.; Shaked, Y.; Lee, C.; Man, S.; Desai, N.; Soon-Shiong, P.; Figg, W. D.; Kerbel, R. S. *Clinical Cancer Research* **2006,** 12, (14), 4331.
199. Karagiannis, E. D.; Urbanska, A. M.; Sahay, G.; Pelet, J. M.; Jhunjhunwala, S.; Langer, R.; Anderson, D. G. *Acs Nano* **2013,** 7, (10), 8616.
200. LaVan, D. A.; McGuire, T.; Langer, R. *Nat Biotechnol* **2003,** 21, (10), 1184.
201. Bellinger, A. M.; Jafari, M.; Grant, T. M.; Zhang, S. Y.; Slater, H. C.; Wenger, E. A.; Mo, S.; Lee, Y. A. L.; Mazdiyasni, H.; Kogan, L.; Barman, R.; Cleveland, C.; Booth, L.; Bensel, T.; Minahan, D.; Hurowitz, H. M.; Tai, T.; Daily, J.; Nikolic, B.; Wood, L.; Eckhoff, P. A.; Langer, R.; Traverso, G. *Science translational medicine* **2016,** 8, (365).
202. C. Di Mario, H. G., O. Goktekin, N. Peeters, J. Verbist, M. Bosiers, K. Deloose, B. Heublein, R. Rohde, V. Kasese, C. Ilsley, R. Erbel. *Journal of Interventional Cardiology* **2004,** 17, (6), 391.