Microneedle array-based platforms for future theranostic applications

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Abstract

Theranostics involves *finding* the biomarkers of a disease, *fighting* them through site specific drug delivery and *following* them for prognosis of the disease. Microneedle array technology has been used for drug delivery and extended for continuous monitoring of analytes present in the skin compartment. We envisage the use of microneedle arrays for future theranostic applications. The potential of using combined microneedle array-based drug delivery and diagnostics as part of closed-loop control system for the management of diseases and delivery of precision drugs in individual patients, is reported in this paper.

Abbreviations:

MNA: Microneedle arrays; ISF: Interstitial fluid; CGM: continuous glucose monitoring; TDM: Therapeutic drug monitoring; PK: pharmacokinetics; PD: pharmacodynamics;

Keywords

Theranostics, Microneedle arrays, Artificial pancreas, Transdermal

1.0 Introduction:

The concept of **"***theranostics*" refers to the *find, fight* and *follow* strategy, which is used for personalised patient treatment involving diagnosis and therapy (Figure 1). (Riehemann, 2009) Although the term "theranostics" was coined by Funkhouser (Funkhouser, 2002) to indicate the amalgamation of diagnostics and therapeutic potential into a single agent, this concept dates back to more than 70 years with nuclear medicine practices employing radionuclides for management of cancer. (Levine, 2017) Seidlin et al published the first study on radioiodine therapy for diagnostic imaging and target-expression confirmation in metastatic thyroid cancer. (Seidlin,1946) Peptide receptor scintigraphy (PRS) for imaging cancer and ^{90}Y and ^{177}Lu radionuclides for peptide receptor radionuclide therapy (PRRT) for treatment of neuroendocrine tumours is one of the most successful examples of the theranostic concept. (Krenning, 1989)

Insert Figure 1 here

Current theranostic approaches combining imaging and therapy are based on the developments in the area of nanomedicine. (Kelkar, 2011) Appropriate probes such as contrast agents, fluorescent markers and nuclear image agents are used to *find* the heterogeneity of the tumour using Magnetic resonance imaging (MRI), Near Infra-Red (NIR) fluorescence and Positron Emission Tomography/ Single Photon Emission Computed Tomography (PET/SPECT/CT) techniques, respectively. The delivery of therapeutic drugs to *fight* the tumour includes strategies such as nucleic acid delivery, chemotherapy, hyperthermia in photothermal ablation, photodynamic and radiation therapy. (Ho, 2010) & (Riehemann, 2009) The effects of the therapy can then be *followed* by imaging the probes.

The nanoparticles and nanomaterials used as carriers include various inorganic nanoparticles (noble metal, metal oxide, and mesoporous silica nanoparticles, semiconductor quantum dots, and magnetic nanoparticles), organic systems (such as liposomes, peptide assemblies and exosomes) and synthetic polymer systems (such as vesicles and micelles). These inorganic nanoparticles often have unique physicochemical properties that allow applications in imaging and even therapy for example, photothermal ablation and magnetic fluid hyperthermia. Liposomes, peptides and polymer nanoparticles have the capacity to carry various molecules, such as DNA, RNA, proteins, enzymes, and lipophilic organic drugs. They can also be further tagged with imaging labels. Oncologists rely on integration of information derived from a

diagnostic test for drug selection which allows patient stratification ultimately leading to personalised medicine.

The global theranostic market size was estimated at USD 5.62 billion in 2016 and is expected to reach USD 18.3 billion by 2025, according to a new report by Grand View Research, Inc. (web reference1) Diagnostics is coming to grips with the wave of pharmacogenomic tests that are followed by new biological therapy introductions. These tests enable cost-effective treatment that add value to the process of patient-stratification. Advantages associated with the usage of these tests such as; disease risk prediction, patient stratification, and therapeutic response monitoring over the traditional methods is anticipated to be a significant source of progress in this market. (web reference2)

In an ideal scenario, effective drugs would allow selective and rapid accumulation in diseased tissue, report on biochemical and morphological characteristics of the tissue of interest, deliver effective therapy, be safe and biodegradable with non-toxic by products, and lack immunogenicity. However, due to the complexity of nanoparticles in terms of toxicity and non-biodegradability, the clinical translation is not simple and straightforward. In addition, there are a number of biological barriers in the living subject that challenge the efficacy of nanoparticle delivery. These include walls of blood vessels, physical entrapment of particles in tissue and capillaries, opsonisation and removal of particles by phagocytic cells.

Robust processes that facilitate scale-up and manufacturing are a pre-requisite. Studies of biological responses to nanoparticles need to consider many factors, including exposure levels, systemic accumulation, excretion profiles, tissue and organ distributions, and the characteristics (age, gender, etc.) of test subjects. It is essential to investigate and understand potential toxic responses, particularly long-term toxic effects, before they may be tested in humans to image and treat diseases.

Validation of novel methods for theranostic applications is required. This will include looking at alternate means of drug delivery and monitoring therapeutic benefits over disease progression. One potential approach for future theranostic applications is the development of closed-loop systems based on Microneedle Array (MNA) devices accessing the skin compartment matrix. Typically ranging from 400 – 1000 μM in height, MNAs can penetrate the *stratum corneum* and sit in the dermal interstitial fluid (ISF). This offers a minimally invasive means for real time monitoring of analytes present in the ISF. Similarly, MNAs can

be used for precision drug delivery and the transdermal route is known to increase the "bioavailability" of the drug. We report the current state of the art within the field of Microneedle arrays that offers a novel approach for the development of MNA based closed loop systems.

2.0 Concept of microneedle arrays platform for future theranostic applications

The key concepts of a MNA based theranostic system for personalised medicine have been outlined in Figure 2. Ideally, monitoring of the therapeutics should be done continuously or frequently in a minimally invasive format. MNAs as electrochemical biosensors for continuous glucose monitoring has already been tested in Type 1 diabetics, demonstrating their safety, tolerability and performance. (Sharma, 2018)

Insert Figure 2 here

Given that the concentration of several analytes of clinical significance (Tran, 2018), (Paliwal, 2013) in the ISF are generally in equilibrium with the blood concentration, MNAs can be used to monitor ISF concentrations and estimate blood concentration of the analytes in near real-time without requiring blood sampling. However, it may also offer a novel option for chronic skin diseases where the relevant analyte concentrations would be higher than that in blood. For diseases, where the biomarker concentration is very low or does not correlate with the blood concentration, MNA arrays can be used for diagnostic purposes and therapeutic drug monitoring (TDM) in the ISF. TDM linked with Bayesian forecasting provides a powerful opportunity for delivering individualised care for patients. (Roberts, 2014), (Felton, 2014)

Data generated by the MNA sensors can then be linked with machine-driven, closed loop control algorithms such as Proportional- Integral-Derivative (PID) and Iterative learning controllers (ILC) to allow for the optimization of therapeutic agent delivered by the MNAs. The drug delivery MNAs comprise of either solid microneedles coated with responsive hydrogels or hollow microneedles through which the drugs can be delivered using an infusion pump.

Although theranostic approaches have been primarily used for cancer, the MNAs reported here are anticipated to address other clinical challenges such as skin, metabolic and infectious diseases. The current state of art of each of the component of the closed-loop theranostic MNA are further described in the next sections.

3.0 Microneedle arrays for monitoring in dermal ISF

Microneedle arrays (MNAs) were introduced mainly for transdermal delivery of drugs and vaccines. (Henry, 1998) Their diagnostic prowess has been exploited in the last decade to monitor metabolites such as glucose and lactate in the skin compartment. (Trzebinski, 2012) They offer a minimally invasive route for monitoring of metabolites and drugs. The commercially available continuous glucose monitoring sensors are expensive to fabricate and thus usually implanted into the subcutaneous tissue for a duration of 10-14 days, leading to biofouling of the sensor surface and thus explains the false alarms and poor acceptability (<10%). To address these issues associated with costs and biofouling, minimally invasive polycarbonate MNAs have been fabricated using high throughput technologies at very low costs. (Sharma, 2017) Microneedle arrays for continuous glucose monitoring applications have been extensively reviewed elsewhere. (El-Laboudi, 2013)

Insert Figure 3 here

Using injection moulding, more than 1000 polycarbonate MNAs can be produced in a day with the cost of polycarbonate being a few pence. These MNAs also were tested on force stations and shown to withstand axial forces of up to 400 N. Optical coherence tomography of the MNAs indicate that these can penetrate human skin under moderate thumb pressure (<10N). (Sharma, 2017) In a human pilot study conducted in healthy volunteers and participants with Type 1 diabetes, it has been established that the occurrence of infection, bleeding and pain have not been reported, and these MNA have been reportedly tolerated very well in both healthy volunteers and participants with Type 1 diabetes studies. (Sharma, 2018)

So far, MNAs have been modified to fabricate electrochemical sensors and used for monitoring metabolites (glucose and lactate), drugs such as theophylline (Sharma, 2017) and penicillin (Rawson 2017). This is done either entrapping the molecular recognition element (in the case of glucose sensors it is the enzyme glucose oxidase) either in a polymer such as electropolymerised polyphenol (Sharma, 2016) or in hydrogels on platinum or graphene (Lee, 2016) coated MNAs.

Eltayib et al have reported minimally invasive monitoring MNAs for monitoring lithium. (Eltayib, 2016) Similar experiment in Morris's lab, show the potential of MNAs to access intracellular CDK4 thanks to specific peptide substrates (Prével, 2016), in both cultured cells and frozen skin samples onto which they were applied. Western blot analyses reveal that CDK4

can be found on the microneedle arrays following insertion into A375 melanoma cells grown on plastic dishes.

4.0 Microneedle arrays for transdermal drug delivery:

Limitations of oral (Sastry, 2000) and parenteral (Simoneson, 1999) drug delivery have led to alternate approaches such as transdermal drug delivery. Transdermal drug delivery offers many benefits such as; avoidance of first-pass metabolism, prevention of gastrointestinal degradation, ability to maintain relatively constant plasma concentrations and increased patient compliance. (Molinuevo, 2012) However, the *stratum corneum* layer acts as an excellent barrier, consequently, transdermal delivery has been limited by the lack of molecules possessing the required physicochemical properties to passively cross it. Various chemical and physical methods have been investigated to reduce the barrier effects of the *stratum corneum* and reap the benefits of transdermal delivery. Microneedle array (MNA) technology for enhanced transdermal drug delivery has received particular attention and is rapidly progressing towards commercialisation.

MNAs for drug delivery were introduced in the 1970s and since then, they have been fabricated by a variety of methods, from a range of materials, in varying geometries. These minimally invasive devices, puncture the *stratum corneum*, forming aqueous conduits through which drugs diffuse to dermal microcirculation. This technology marries the patient-friendly benefits of a transdermal patch with the advantage of delivering drugs through the *stratum corneum*. The MNAs penetrate the *stratum corneum* and sit sufficiently in the dermal space to enable access to the skin's rich microcirculation, yet with a length varying from 50 - 900 μm, they are short enough to avoid stimulation of dermal nerves. (Donnelly, 2011)

MNs have been employed in five different formats for drug delivery. These include, solid (Ling-Teo, 2005; Douroumis , 2018), coated (Zhu, 2012), dissolving (Migalska, 2011), hollow (Gardeniers, 2003) and swelling (Donnelly, 2014). They can be developed using different materials such as metal (Martanto, 2006), glass (Martanto, 2004), silicon (Ji, 2006), carbohydrates (Martin, 2012) and polymers (both solid and dissolving) (Donnelly, 2013). These MNAs increase the number of compounds amenable to transdermal delivery by penetrating the *stratum corneum* and creating a pathway for drug permeation to the dermal tissue below. MNAs for drug delivery applications have reviewed elsewhere. (Larrañeta, 2016) Regulatory guidance is needed alongside scale-up of the technology to progress towards a

commercially available MNA product. There are a number of patient factors relating to safety, usability and long-term use of MNAs which will need to be addressed moving forward.

5.0 Closed-loop control for drug delivery

Closed-loop controllers (CLCs) have a been employed particularly in the field of diabetes and have been instrumental in the developments of the artificial pancreas system. (Absalom, 2002), (Madhavan, 2011) Furthermore, they have been demonstrated as effective during surgical procedures, in controlling delivery of both intravenous and inhaled anaesthetic agents during surgery. (Madhavan, 2011) CLCs have also been demonstrated in pre-clinical and *in silico* studies for the optimisation of antimicrobial dosing. (Gorchkov , 1996), (Ulldemolins, 2014) Two of the most widely used controllers for continuous and intermittent bolus infusions are the PID and ILC controllers, respectively. (Frimodt-Møller , 2002) These controllers are algorithms that optimize the delivery of an agent against a pre-determined set point.

5.1 Proportional-Integral-Derivative (PID) control

PID controllers depend on frequent or constant monitoring and can be used to control continuous infusions maintaining drug concentrations at a set target (for example either target concentration or pharmacokinetic-pharmacodynamics (PK-PD) index). PID has three coefficients; the proportional, integral, and derivative. It alters these three coefficients to optimize the response against its target for therapy. The simplicity and robustness of PID algorithms make them extremely suitable for a plethora of healthcare applications. One such example is acute treatment or critical care units for continuous infusions of beta-lactam antimicrobials and vancomycin, which are nephrotoxic, to optimize the PK exposure and PD properties. (Johnson, 2005), (Cataldo, 2012) Moreover, it enables a real time response in accordance to individual patient PK especially when there are differences in the patient PK from that measured through therapeutic drug monitoring in blood samples. (Chagnac, 2000)

5.2 Iterative Learning Control in closed-loop control

Iterative Learning Control (ILC) relies on information obtained from continuous or real time monitoring of a biomarker and thus facilitates optimization of bolus or drug therapy. (Madady, 2008) The information from continuous monitoring is used to optimize the amount, timing, and rate at which a drug is delivered. Similar to PID, ILC algorithms have wide applications but work on the assumption that during repetitive tasks there will be some level of error in target attainment (for example an overshoot or an undershoot). Therefore, the input, such as the bolus dose, is adjusted to reduce the transient error encountered during routine drug delivery, in order to optimize the accuracy in closed loop systems. This will be more applicable to theranostic applications of microneedle arrays especially in a simpler setting, for example using theranostic MNA patches for drug dosing. It can also be extended to specialist populations, such as pediatrics and pregnancy, where rich data collection will allow for tailored therapy to be determined and adjusted, based on real time data and potentially utilizing previous experience housed within machine learning algorithms. A classic example of this is the Case-Based-Reasoning in diabetes management. (Herrero, 2015) Both PID and ILC systems can automatically control the delivery of an agent in optimised precision drug delivery.

6.0 Discussion and Conclusions

The biggest challenge in translating microneedle array based electrochemical sensors and microneedle arrays drug delivery into a closed-loop control system is the accuracy of the MNA sensors especially during the initial phase of monitoring, when the sensors baseline has not reached a steady state. Sensor warm up time for electrochemical sensors has been reported in the literature (Sharma 2018). Addressing this issue will impact the further development of MNA theranostic closed loop systems.

As demonstrated in this paper, MNA technology has been successfully implemented for discrete diagnostic and drug delivery applications. Interfacing the two theranostic components

using closed loop systems will offer MNAs based devices for future theranostic applications. Future MNA based theranostic devices will either measure analytes of clinical significance in the skin compartment or measure the drug/ metabolite concentrations in response to a drug therapy. Both these approaches will allow personalization of the drug therapy through precision delivery of drugs.

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Competing interests

The authors have no conflicts of interest to declare.

Captions:

Figure 1: Showing concept of theranostics.

Figure 2: Showing the schematic for a closed-loop control microneedle arrays theranostic device. Left (top): MNA sensors (bottom): SEM of Hollow drug delivery MNAs. Right: The red dotted circle showing the microneedle arrays patches stuck on the forearm of a healthy volunteer; the white dotted circle showing a PCB based device with a controller for the potentiostat and the infusion pump.

Figure 3: Showing SEM images of MNAs made in different ways using different materials. (a) MNAs fabricated by photolithography of SU8 100; (b)MNAs made by casting PDMS moulds with SU8 50 followed by UV cross linking and (c)MNAs fabricated using injection moulding of polycarbonate.

Figure 4: Western blot showing amount of CDK4 proteins extracted by insertion of microneedle arrays array structures. Here C1 and C2 represent conditions in which the microneedle arrays were gently tapped into the skin 3-4 times and then rinsed with 50ul PBS and microneedle arrays left in the skin sample for 5 minutes under moderate thumb pressure followed by rinsing with PBS, respectively. As evident from the Western blot, there is plenty of CDK4 in condition C2.

Figures

Figure 1:

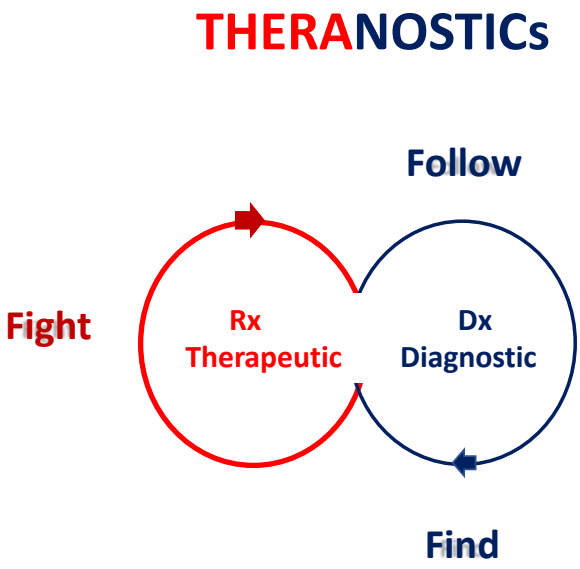


Figure 2:

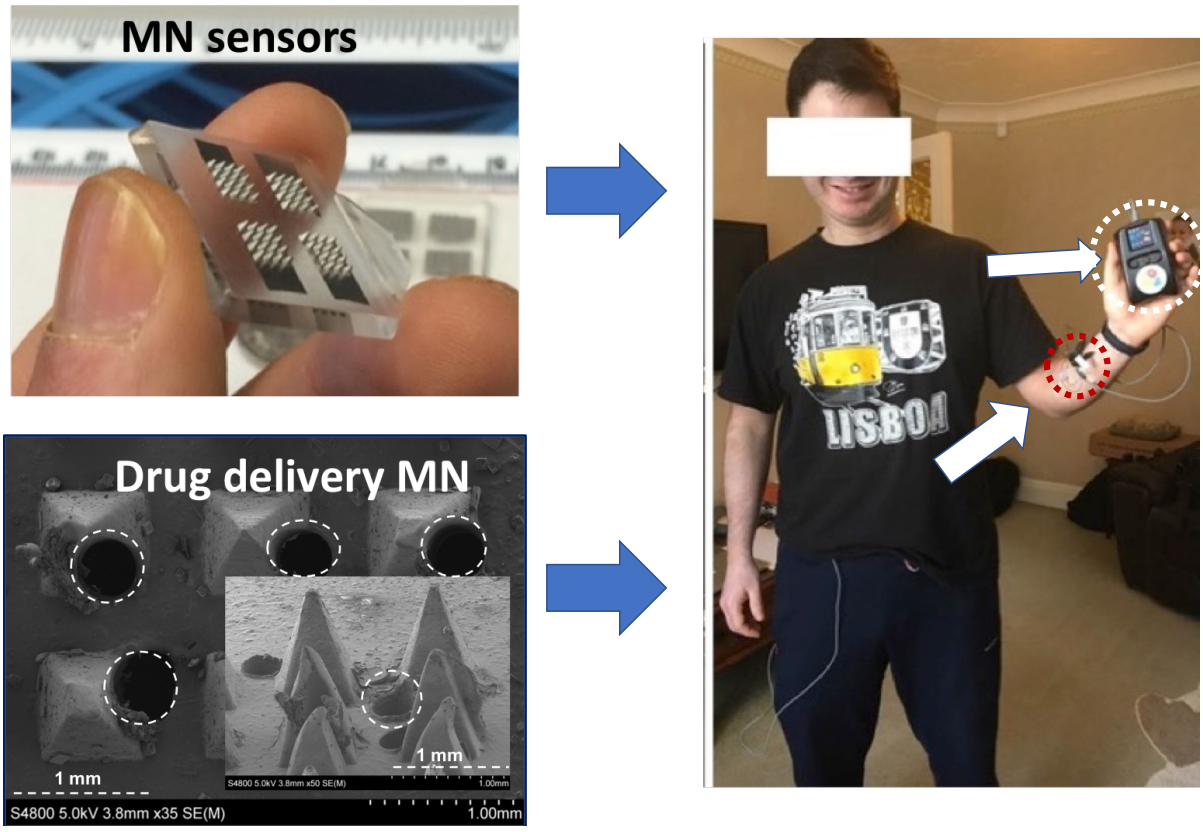


Figure 3:

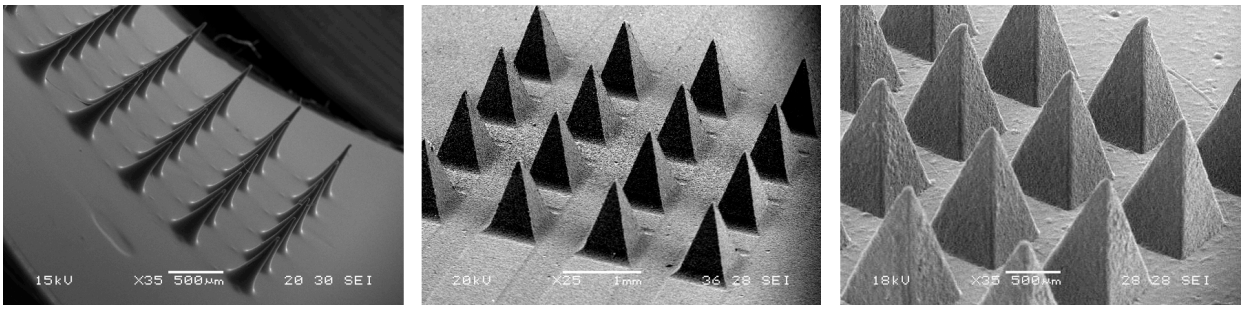
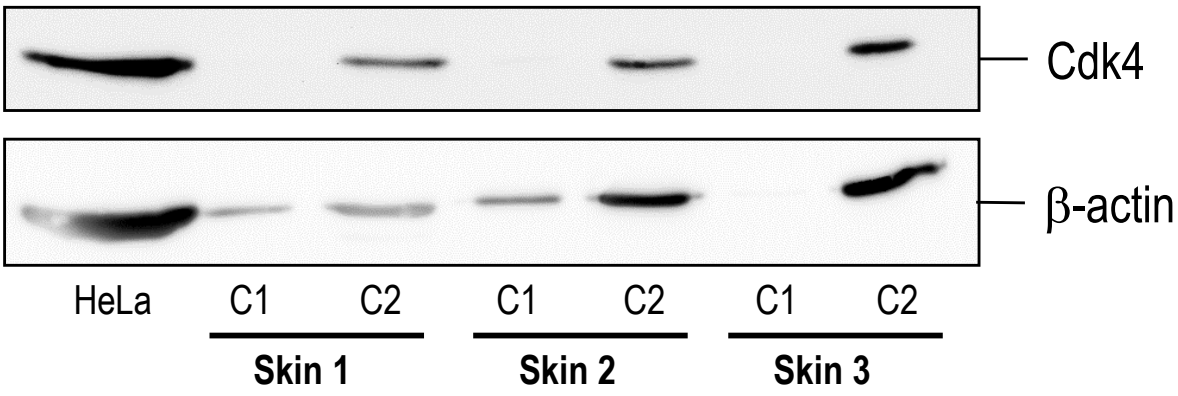


Figure 4:



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