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Research review paper

Augmented reality for personalized nanomedicines

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ABSTRACT

As our understanding of onset and progress of diseases at the genetic and molecular level rapidly progresses, the potential of advanced technologies, such as 3D-printing, Socially-Assistive Robots (SARs) or augmented reality (AR), that are applied to personalized nanomedicines (PNMs) to alleviate pathological conditions, has become more prominent. Among advanced technologies, AR in particular has the greatest potential to address those challenges and facilitate the translation of PNMs into formidable clinical application of personalized therapy.

As AR is about to adapt additional new methods, such as speech, voice recognition, eye tracing and motion tracking, to enable interaction with host response or biological systems in 3-D space, a combination of multiple approaches to accommodate varying environmental conditions, such as public noise and atmosphere brightness, will be explored to improve its therapeutic outcomes in clinical applications. For instance, AR glasses still being developed by Facebook or Microsoft will serve as new platform that can provide people with the health information they are interested in or various measures through which they can interact with medical services.

This review has addressed the current progress and impact of AR on PNMs and its application to the biomedical field. Special emphasis is placed on the application of AR based PNMs to the treatment strategies against senior care, drug addiction and medication adherence.

1. Introduction

Nanomedicines (NMs) have been widely used to ameliorate conclusive pathological conditions, such as cardiovascular diseases, sexually transmitted diseases and various cancers. **NMs** ranging from the medical applications of nanomaterials and biological devices to nanoelectronic biosensors have become a new field of interest in recent years due to their ability to accommodate biomedical and nano-technologies for individual patients' specificity, and generate efficient therapeutic outcomes. As prerequisite, NMs should possess improved stability, enhanced biocompatibility, favorable bio-distribution profiles, and negligible side effects.

As technological advancements including human genome research based on single nucleotide polymorphism (SNP) allow us to identify unique genetic variability for each patient, personalized nanomedicine has rapidly spread through our lives. For instance, it was reported from the human genome mapping investigation that a tiny inter-individual genetic variability as low as 0.9% is responsible for the immense difference among patients (Novelli, 2010). Subsequently, the conventional medical therapy that has a theranostic treatment scheme to a heterogeneous population can be replaced with the personalized treatment regimen or specifically designed personalized nanomedicines (PNMs) that can improve therapeutic outcomes (Fig. 1).

The recent developments of 3-D printing, versatile nanomaterial including graphene, and advanced biotechnology, such as microarray and biochips, have further facilitated PNM based treatment to be customized for individual patients through incorporation of genetic algorithms, targeted delivery and synchronized theranostics. Especially, the recent revolution of augmented reality (AR) (i.e., represented by Pokemon Go) makes it feasible to trace and monitor patients' behavior in-time and impose appropriate PNMs on patients according to the environmental conditions. PNMs equipped with AR technology can be applicable to cure for various pathological symptoms including Alzheimer and age-related dementia, and pharmaceutical medications including medication adhesion and drug addiction.

This review will address the effects of AR on PNMs and its application to the biomedical field. This review has specially focused on the application of AR based PNMs to treatment strategies against elderly care, drug addiction and medication adherence.

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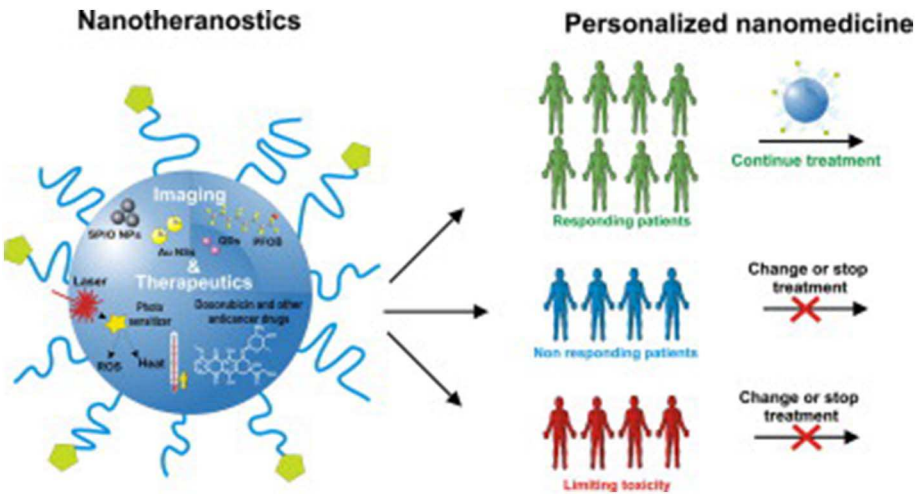

Fig. 1. Nanotheranostics integrate imaging and therapeutic functions in a single platform for personalized nanomedicine (cited from Mura and Couvreur, 2012).

2. History of personalized nanomedicines (PNMs)

2.1. Requirement and benefits of personalized nanomedicines (PNMs)

Personalized nanomedicines (PNMs) is a growing trend in health society for efficient treatment against various diseases based on specific genetic disposition or characteristics of each patient. PMNs has been considered as a comprehensive therapeutic strategy (i.e., a combination of conventional and targeted nanomedicine) to diagnose using precise detection methods like real-time image-guided analysis, treat and monitor disease progress and status in ways that achieve specific and the most beneficial health-care outcomes (Rizzo et al., 2013).

There is a complex relationship between advanced systems' physicochemical properties (e.g., size, surface charge, functional activity) and their interaction with inherent conditions of individual patient as well as the components in the biological system (Harper et al., 2008). The host response expressed with genomics and metabolomics (Steemers et al., 2000; Suhre et al., 2011), and the biological interactions, such as protein binding, ligand mediated interaction, and interactions during intracellular processing (Zhang et al., 2012), will determine the loading capacity, stability, biocompatibility, therapeutic outcomes and toxicities of PNMs. Therefore, the ideal design and efficient optimization of personalized PNMs is integral to achieve successful outcomes of individual therapy.

The major properties of PMN that influence the development of a patient's disease are predisposition, monitoring, diagnosis and prognosis, and pharmacogenomics (Ginsburg and McCarthy, 2001; Acharya et al., 2017). PNM can i) accurately diagnose the pathological status based on specific genetic characteristics of patients, ii) predict the probability of onset of a specific disease based on patient's genome and suggest protective mechanism, and iii) discover biological markers of each pathological condition, thus securing for advanced treatment strategies and lower mortality.

2.2. Personalized treatment based on genome-mapping and microarray biochip

The genetic progress including SNP and genome-mapping has led to various personalized nanomedicines especially in the area of chemotherapeutics, Alzheimer diseases or cardiovascular diseases. In addition, the microarray biochip has revolutionized the field of personalized medicine by expanding the capability of analyzing and storing a patient's entire genome (Schena et al., 1995; Michael et al., 1998; Steemers et al., 2000). In a digital microfluidic biochip, a group of cells in the microfluidic array can be arranged to work as a storage, functional operation as well as for dynamical transporting fluid droplets (Fair, 2007). Biochip technology allows for efficiently conducting SNP genotyping, and subsequently enables scientists and clinicians to achieve the rapid progress in diagnostic and therapeutic outcomes based on fundamental protein analysis.

For instance, an identification of 'synthetic lethal pairs (SLPs)' based on genome-mapping and microarray biochip in cancer cells was attempted to find a specific strategy of killing cancer cells, while leaving healthy cells intact (Baugh, 2005). Synthetic lethality causes a cell to die when the expression of two or more genes are inactivated (Hartwell, 2014), whereas a deficiency in only one of these genes does not cause genetic perturbations. The deficiencies are mainly due to mutations, epigenetic alterations or inhibitors of one of the genes (Nijman, 2011).

The genetic screen process based on computational data mining can validate its approach by analyzing large sets of cancer genomic information and applying them to already known SLPs of certain tumor suppressors and oncogenes. It generally starts with identification of a mutation process that does not kill the cell, and then systematically test other mutations at additional loci to determine which confers a synthetic lethal (Hartman et al., 2001; Ferrari et al., 2010). The algorithm can capture the known pairs of genes (Jerby-Arnon et al., 2014). Therefore, SLPs could offer a personalized option to kill cancer cells by inhibiting the SLP partners of activated oncogenes in tumors, laying the basis for quantitative identification of synthetic dosage lethality in species and cell types (Megchelenbrink et al., 2015).

2.3. Personalized treatment based on metabolomics

Modern metabolomics is aimed to measure the byproducts of metabolism on a broad scale and able to assess small molecules in the sample at a low cost (Krauss et al., 2013). Metabolomics based on molecular biology and biochemistry have enabled scientists and clinicians to elucidate the underlying mechanisms of individual differences in patients responses to certain drugs (Yerges-Armstrong et al., 2013; Suhre et al., 2011), such as the microbiome composition (i.e., statin) (Krauss et al., 2013), the degree of perturbations in purine metabolism (i.e., aspirin) (Ellero-Simatos et al., 2014), and endogenous metabolism associated with specific neurotransmitter pathways (i.e., anti-depressants) (Zhu et al., 2013).

For instance, statins reduce the risk of cardiovascular disease by lowering plasma LDL concentrations and improving endothelial function. The plasma concentrations of several microbial metabolites, such as lithocholic acid, bile acids, glyco-lithocholic acid and tauro-lithocholic acid, were considerably different in patients who are susceptible to statin as compared with those less-susceptible to statin (Krauss et al., 2013). This finding indicates that certain components of gut microorganisms or overall composition may predispose patients to statin

(Suhre et al., 2011; Yerges-Armstrong et al., 2013), contributing to the outcomes of inter-individual variation to statin treatment.

Metabolomics has been used to differentiate susceptible patients from less-susceptible patients for a variety of drugs by examining the serum levels or composition of a principal metabolites (Wishart, 2016). Subsequently, an integration of metabolomics and genetics in a biological system can identify novel genetic markers behind cancer and cardiovascular disease (Shah and Newgard, 2015), and can be explored to personalize an individual's dosing level of selected pharmaceuticals (Wikoff et al., 2013; Shin et al., 2014).

2.4. Personalized treatment based on image-guided analysis

An introduction of image-guided analysis is based on the concept that individual patient's pathology and progress can be visualized to design an efficient treatment strategy through optimized targeting and pharmacokinetic profiles of loaded drugs that are free of toxicity. Image-guided tracking of kinetic ADME process is highly useful for pre-screening of patients, discovering which pathological oncogenes are amenable to nanomedicine treatment, and thereby predicting which patients are susceptible to a given nanomedicine. Subsequently, as shown in Fig. 2, image-guided individualized treatments seem to be ideal for target-specific nanomedicine treatments (Lammers et al., 2012) and have offered great potential for being transformed into personalized medication (Theek et al., 2014).

The successful application of image-guided analysis to various diseases requires that drugs or a carrier as a whole can be imaged locally or activated at the targeted site, which can be achieved by using functional nanomaterials (Atwal et al., 2011; Oh et al., 2015; Giri and Lee, 2016). It has been reported that amphiphilic nanoparticles like thiolated-Graphene Quantum Dots (SH-GQDs) conjugated with macrophage scavenger receptor (MSR) antibodies having a size around 160 nm are capable of conducting universal ligand–receptor recognition and targeted drug delivery, and display superb biocompatibility at the cellular level as supported by the studies on their bio-distribution and cell apoptosis analysis (as shown in Fig. 3) (Oh and Lee, 2015; Oh and Lee, 2016).

The imaging modalities used in the clinical application include ultrasound (US), magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), and single-photon emission computed tomography (SPECT). These techniques are significantly different from each other in investigating molecular mechanisms and physical principles, and therefore have distinct characteristics in terms of resolution, contrast and sensitivity (Massoud and Gambhir, 2003). Fluorescence resonance energy transfer (FRET) and flow cytometry have been widely used as a sensitive and reliable biological analysis tool for definitive pathological diseases. The efficiency and biocompatibility donor–acceptor pairs are integral to improve the efficiency of fluorescence resonance energy transfer and the resulting analytical performance (Jares-Erijman and Jovin, 2003). However, fluorescent probes including organic dyes and inorganic semiconductor quantum dots (QDs) have their own drawbacks, such as poor photostability, liable to photo-bleaching, small stokes shifts and short half-life (Kelly et al., 2004). SH-GQD greatly alleviated those drawbacks and can serve as an efficient tool for the monitoring and treatment of diseases including atherosclerosis, and subsequently pave the way to find an effective personalized treatment strategy (Oh and Lee, 2016).

3. Recent advanced techniques for PNMs

3.1. 3D Printing for PNMs

The personalized medicine and biomedical devices have recently advanced with the development of 3D printing whose value has become more potentiated, as modern healthcare environment is leaning toward individual configuration (Shafiee and Atala, 2016). 3D printing has been used to generate a variety of cell types or fabricate customized implants, such as spinal implants, craniofacial implants and cardiovascular stents. 3D bioprinting is defined as the creating process of cell patterns in a restrained space, in which cell function and viability are preserved within the printed construct (Doyle, 2014; Chua and Yeong, 2015). A research team of scientists have introduced a novel technique for printing a grid-like 3D structure laden with stem cells (Tasoglu and Demirci, 2013), as stem cell can facilitate the discovery of advanced PMNs (Wang et al., 2015).

3.1.1. 3D printing custom-skin grafts

3D printing has been explored for skin grafting that is known as a surgical procedure involved with the removal of the skin from one area of the body and transplanting it to another area of the body (Murphy and Atala, 2014). A large size of skin graft was created by scientists at the University of Toronto via printing thin layers of skin-cell preloaded

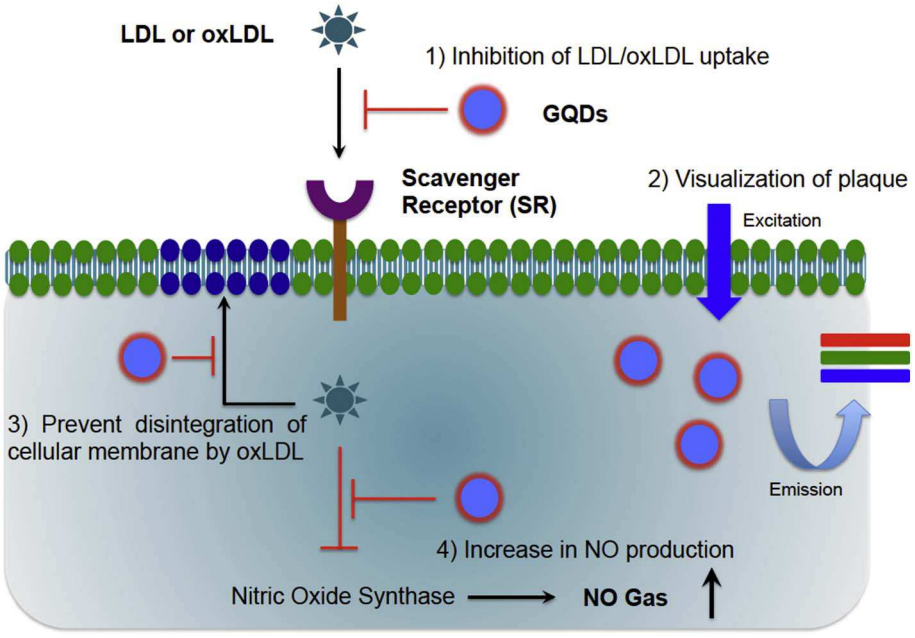

Fig. 2. Personalized delivery of nanomedicine targeted at the scavenger receptors in atherosclerosis.

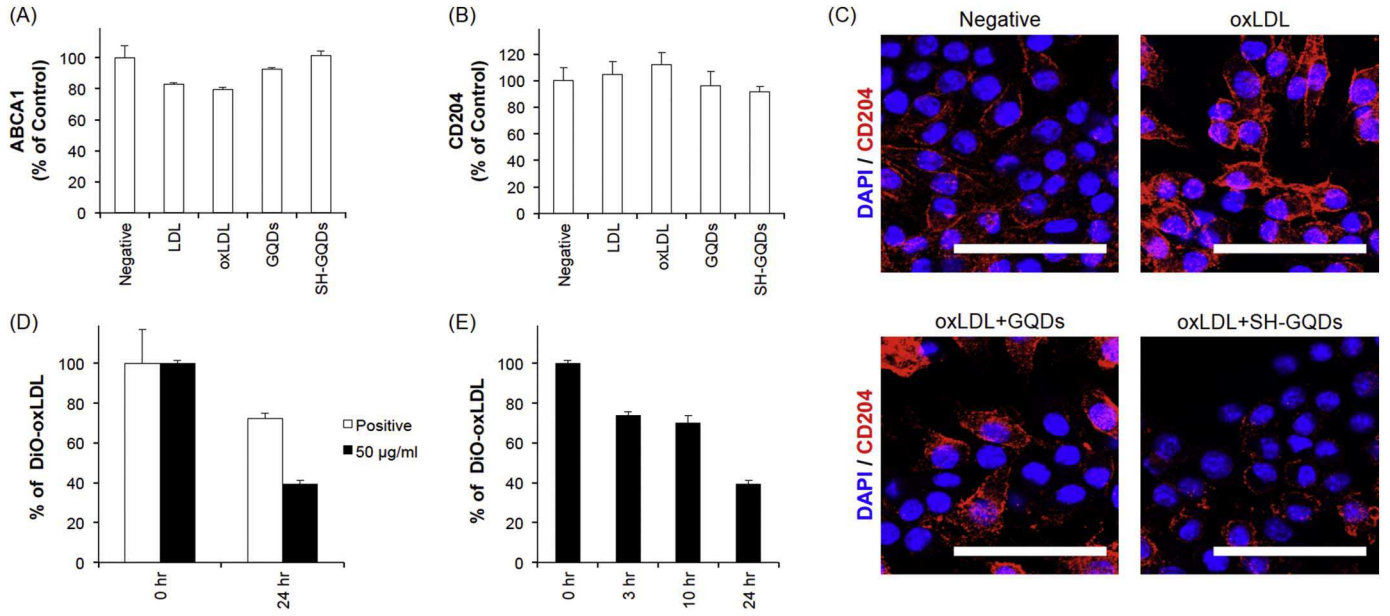

Fig. 3. Development and evaluation of personalized nanomedicine targeted at the scavenger receptors (A) and (B) Percent of expression of ABCA1 and CD204. (C) Immunocytofluorescence analysis of CD204. Scale bars indicate 50 μm. (D) Efflux of oxLDL after SH-GQDs treatment. (E) Time-dependent efflux of oxLDL after SH-GQDs treatment.

polymer solutions (PSFK, 2014). These skin grafts could eliminate the removal process of large areas of transplant skin from otherwise healthy parts of the body. Moreover, this approach could recover vascularization that has been the biggest challenge in the treatment of burn wound patients. Thus, skin grafts based on 3D printing are considered as the most effective means of creating artificial grafts.

The development and application of skin grafts to the treatment of chronic wounds based on 3D printing has continuously evolved. The inkjet printing platform developed by MicroFab (Winston-Salem, NC) includes a set of devices that allow for printing a wide variety of necessary materials including polymers, sensitive protein solutions, tissue extracts and live cells. In addition, the devices can be heat sterilized or gamma irradiated without being damaged during the fabrication process. They obtained promising results in appearance, stability and vascularization on the animal models (Wolff, 2016).

ReCell® is unique technology (Avita Medical: Northridge, CA) that allows a clinician to rapidly promote skin growth based on an idea from what the body is naturally programmed to do. A sample that undergoes ReCell's processes used autologous samples to create Regenerative Epithelial Suspension. Skin grafts produced through ReCell® suspension comprise all four types of skin cells – keratinocytes, melanocytes, fibroblasts and immune system cells, and healing factors needed to recover skins from burn and chronic wounds. They can cover as much area as 80 times its size (Wolff, 2016). ReCell® is currently undergoing Phase 3 clinical trials for the treatment of pigmentation conditions like vitiligo.

3.1.2. 3D printing custom-fit splints

A synthetic vascularized tissue needs endogenous engineering constructs that contain functional vasculature and nutrient channels. 3D printing technology shows a great potential in engineering vascularized tissues and vascular niches, representing synergy between high resolution, high throughput bio-printing of functional channels and instructive bio-ink that promotes perfusable neovascularization and angiogenic sprouting (Lee et al., 2014a, 2014b; Richards et al., 2017).

The similar approach was applied to produce Airway splints that have been custom-fitted to the windpipes of newborns infected with tracheo-bronchomalacia. These additive medical devices are made of silicones and a mold rather than the device itself was created by the 3D printer that allowed the silicone to be polymerized in it (Seegert, 2014). Airway splints precisely fit the shapes of the trachea and improve the performance by preventing the device from sliding around like off-the-shelf stents.

As personalized nanomedicine continues to rise in usage, the future of the 3D printing method seems highly promising. Based on a similar approach, it could be fabricated into 3D heart model that is readily printed for complex cardiovascular surgeries.

3.1.3. 3D printing custom-fit devices for children

The development of a medical device for children represents a tremendous challenge to biomedical community due to differences in size and physiology, varying degree of activity and growth rates (Ulrich et al., 2013). It's not appropriate to simply modify an adult-sized device smaller for children. Moreover, due to a relatively small market, device manufacturers have kept distance on responding to the medical needs for children (Hwang et al., 2014).

A new approach to 3D printing developed at the lab in Northeastern University generates the architecture of the composite consist of ceramics and liquid polymers, a magnetic coating of biocompatible iron oxide, reinforcing its mechanical strength to custom-fit the requirements of the individual device (Martin et al., 2015). By imposing a magnetic field on the liquid, each layer is able to accurately orient the fibers of the ceramics before turning into a solid form by laser.

This composite architecture seems especially useful for pediatric application and partially addresses the issue that there should be some other aspects than size and shape that are considered to be incorporated into a personalized medical device for children (Prendergast et al., 2017).

3.2. Personalized robot for PNMs

3.2.1. Socially-Assistive Robots (SARs) and Care-Provider Robots (CPRs)

Across world, people are getting older and need close attention in various community and personal ways. As age-related diseases also increase in parallel with that trend (Warner et al., 2005), a growing number of people across world will need individual help and assistance to maintain their quality of life, avoid isolation and remain physically and mentally healthy. Personal care has been provided by professional caregivers at home or in a care facility, but mostly they are the patient's spouse or another family member who is also vulnerable to aging

progress. As the percentage of people aged 80 and above is expected to triple by 2060 (WHO, 2016), both professional and relative's care can be replaced with advanced technology including the robot, a semi-humanoid figure equipped with advanced gadgets, such as mobile wheeled motor, audio, cameras, sensors and a touch screen interface (Henkel et al., 2016; Maggioni et al., 2016).

In near future, we will confront novel services to accomplish various daily activities based on the cooperation and help from personalized robots and other agents such as augmented reality (Fiorini et al., 2017). Subsequently, a personal preference and disposition that can provide patients with information, customized medications and special treatment should be ultimately integrated into senior care robots. Along with a concept from a smart-home environment, the robot is able to come in contact with users at needed times, interact with them or provide information via touchscreen or directly talking back in a customized voice (Al-Razgan et al., 2016). They possess a high degree of mechanical flexibility and are able to implement complicate transactions. The versatility of a robotic response depends on diversity of behaviors it can accomplish and on the delicate technology of the regulation methods needed to achieve them (Deimel and Brock, 2016).

Various groups and companies have addressed the robotic solutions, generating Socially-Assistive Robots (SARs) or Care-Provider Robots (CPRs) which could support seniors, children and those in need during daily activities, such acting as companion robots (Stiehl et al., 2005; Zhang et al., 2008), providing complex assistive services like monitor patient's vital signs and provide emergency services (Meyer et al., 2009; Badii et al., 2009; Tran Duc et al., 2016) or as participation in performing specific tasks or private itinerary, such as reading a novel, reminding patients to take their medicine (Iwata and Sugano, 2009; Mukai et al., 2008; Di-Cerbo et al., 2015; Endo et al., 2015).

The principal aspects of the practical experience for Socially-Assistive Robots (SARs) include the culture of the society, the modification and updating of beliefs, and selection of preferable actions, but socialization training of SARs has some intrinsic limitations (Kennedy, 2009). The social and cultural bias will be present within SAR's functions irrespective of repeated update and modification of the interactive features. Moreover, SARs don't have a personal history of social interaction that is integral to provide the robot with the sufficient cultural background and can be obtained by training SARs with augmented reality (AR) or deep-learning based simulated family, as people are naturally brought together to human society.

With advanced technology, the Socially-Assistive Robots (SARs) can personalize themselves for their individual preferences and needs (Hariharan and Shagun, 2015). In the future, the robot can be further customized through augmented reality with which the robot embarks on a voluntary initiation and responses according to patient's environmental conditions including activity and exercise, social gathering, seasoning events and weather status.

3.2.2. Personalized robots in development

3.2.2.1. MOBISERV robot. The MOBISERV team in Europe funded under the European Union's Seventh Framework Programme (FP7) created an easy-to-use interface to configure the robot serving as a care provider, socially-assistive partner, family member – or someone else who knows the user well (Materials provided by European Commission, CORDIS). In trials launched year 2016 in the Netherlands and the United Kingdom, the researchers conducted extensive user evaluation studies with the socially-assistive robot, ranging from usability tests in a home lab, to full-day experience tests in a test home, to multi-day experiences in their own homes.

The prototype MOBISERV robots currently cost around EUR 10,000 to build, but can be lowered to as low as EUR 5000, as technology advances. The MOBISERV team is trying to further enhance their performance as well as conduct user trials on a larger scale.

3.2.2.2. BIG-i robot. BIG-i is the first personalized family robot created by NXROBO that is an innovative robotics company established in 2015 in Shenzhen, China. BIG-i is an interactive and socially-assistive robot with mobility, voice programming, active perception and 3D vision. BIG-i uses clothes for its appearance and soft shielding material for its muscle layer to become more humane to users.

BIG-i receives user's need through voice programming and translates their requirements into text through speech recognition. With the help of semantic analysis, it can understand the trigger conditions, then transfer them to the system. Subsequently, BIG-i will appeal the corresponding sensory organs to detect whether or not the condition is matched. Upon apprehending the positive condition, BIG-i will perform tasks and meet customer needs.

BIG-i will ultimately control user's daily routine, so users can enjoy every moment of their precious life. Upon analyzing the utility and communication frequency between a robot and users, BIG-i will become more and more thoughtful and intelligent through enhanced performance and improved interaction with users.

3.2.2.3. Aethon's Tug robot. In healthcare, Aethon's Tug robot (Pittsburgh, PA) has emerged as a smart autonomous robot which helps patients with medicines and supplies mainly in senior care centers or hospitals. They were adequately socialized to voluntarily interact with patients and safely traverse around obstacles. Tug robot can utilize existing hospital infrastructure and facilities including stairs and elevators, not necessitating extra spaces or equipment, such as separate hallways or large dedicated areas. The flexibility as well as dexterous ability ensure Aethon's Tug robot to be much friendlier to individual patient.

4. Applications of augmented reality (AR) to PNMs

4.1. Background

Virtual reality (VR) is defined as an advanced form of human-computer interaction where the users can correspond with and engage in a computer-generated graphical interface (Brooks Jr, 1999; Choi et al., 2015). VR has been evolved to augment reality (AR) whose real world has been supplemented with environmental conditions, digital information and media, such as computer generated sensory device, 3D models and videos. Recent introduction of Pokémon Go that is a new GPS-based AR game represents a combination of crowd-sourcing and knowledge about the local environment and opens a new era of applying AR to the biomedical field (Bond, 2016).

A key value of augmented reality systems is how precisely they gather augmentations with the real world. This assembling process will be achieved using the software that accurately derives real world coordinates independent of camera images (Azuma et al., 2001) and register computer vision obtained from visual odometry (Maida et al., 2013). Hardware components for augmented reality are processor, sensors, display and input devices (Metz, 2012), whereas technologies used in augmented reality are monitors, optical projection systems, hand held devices, and display systems incorporated into the human body.

AR can be applied to various advanced surgery, such as minimally invasive surgery or image guided real-time surgery, and pharmaceutical medications, such as drug addiction or medication adhesion (Mahei, 2015). Computer-aided design software allows for easy acquisition and transfer of digital imaging and communications in medicine data to various proprietary software, achieving improved operating efficiency (Profeta et al., 2016). The surgeon is ready to review preoperative images on the wearable device screen intraoperatively using 3-dimensional (3D) imaging tools, allowing them to view various images without leaving the operating site during the decision-making process (Markiewicz and Bell, 2011). There will be an increasing demand on the combination of AR technology and the 'Internet of Things' (IOT) to deliver competitive advantage in existing surgical technologies.

An improper treatment of addiction or adherence continues to hamper successful and complete cure for various physical and mental diseases (Magura et al., 2011). Advanced technology mediated interventions seem to be integral to improve patient compliance and medication efficacy (Eticha et al., 2015). As behaviors involved with addiction or adherence occur in the real world, an exposure degree or frequency of medication engagement should be automatically and objectively monitored in real-time through sensors or videos attached to the device. To assure the detailed and accurate medication record, implementation of medication should be simultaneously assessed in the AR context (i.e., big data source expressed as self-taking and frequency of medication activity under the varying environmental conditions) that will lead to efficient therapeutic options.

4.2. Augmented reality for medication adherence

4.2.1. Background and history of medication adherence

Most seniors in chronic diseases often need to take several drugs, necessitating scheduled therapies and concurrent monitoring of health status. The complex procedures involved with drug adherence can induce mental confusion from senior patients and occasionally lead to improper medications (Osterberg and Blaschke, 2005; Losurdo et al., 2016). With an influx of emergency care services for senior patients due to medication adherence, health-care providers have focused on providing them with proper medication options, such as education programmes, reminders, self-monitoring, counselling and family therapy (Haynes et al., 2008) (AGE Platform Europe, 2010).

Revolutionary technology has resolved medication adherence issues through improved physical support and reminder services without influencing therapeutic efficacy (Wahl et al., 2012). The drug dispensers (e-Pill; Philips; PivoTell) or talking pillboxes currently available in the market are relatively advanced but restricted in offering efficient reminder services or social/physical support. Moreover, this approach is unable to provide active interaction and to be corresponded in real-time with other medication providers (Tiwari et al., 2011). At present, there is no ideal strategy available to conclusively resolve the problems involved with medication adherence for senior patients.

In parallel with technical improvements, ‘beyond-the-pill’ (Proteus Digital Health Co., Redwood City, CA) containing the drug Abilify that is aripiprazole used for an antipsychotic medication was just approved from FDA (Pai, 2016). Barton Health (South Lake Tahoe, CA) became the first to implement beyond-the-pill attached with swallowable sensors for tracking of taking medication from chronic disease patients as part of the Proteus Discover Program on drug adherence. By identifying patterns in patients' behavior and personal health habits through the data collected using swallowable sensors, it can help manage patients' medication record in real-time and support physicians to tackle any challenges associated with drug regimens.

4.2.2. Recent progress in augmented reality against medication adherence

Numerous studies validated usefulness of companion robots in resolving the adherence issue of taking medicine (Prakash et al., 2013). A closed-loop medication management system was designed surrounding a healthcare robot with a web-based application (RoboGen) that is available 24 h per day, 7 days per week (Datta et al., 2011). Subsequently, they have set the guidelines for the design of robotic services to simplify the user interface and further improve user compliances (Tiwari et al., 2011; Kaerlein, 2015).

Recently, the cloud-computing paradigm allows users to create a novel personal robot equipped with cloud resources (Sinčák et al., 2015; Kamei et al., 2012; Goldberg, 2014) and provide innovative healthcare services for senior patients (Smith et al., 2013). A personal robot could be further trained for customizing social behavior in a simulated interactive environment, such as an imitated family inhabited with parents and child robots (Fiorini et al., 2017). The caregiver can cope with the medication adherence issues through synergic action of cloud resources and socially assistant robots, which can connect all health care providers via a web portal.

The application of advanced technologies including AR represents a new health-care strategy on the horizon for drug adherence issue (Moschetti et al., 2014) involved with the physical and psychological needs of cognitively impaired senior patients. Patents will get continuous and immediate medication advice in response to the changes in environmental conditions in which they are traced by programmed signal engaged in a computer-generated graphical user interface and monitored through personal gadgets like cellular phones.

4.3. Augmented reality against medication addiction

4.3.1. Background and history of medication addiction

There are two types of addiction; Physical & Psychological addiction. Psychological addiction is often considered much more difficult and time-consuming than recovery from the physical aspects of drug dependency (Ruiz, 2010). For people who may have mild drug use disorder, the symptoms of psychological addiction could be managed using an outpatient treatment program like a group-home setting where counselors provide continued sobriety support, structure, and monitoring on a daily basis (Ruiz, 2010; Black, 2014).

The successful outcomes are obtained from integrated treatment approaches that include interventions of both mental disorder and chemical dependency (Stitzer et al., 2009), and can be further improved by the inclusion of assessment, motivational and behavior interventions, intensive case management, as well as rehabilitation and medication management services (Schaler, 1997).

The primary steps of the recovery processes of drug addiction symptoms include abstinence, detoxification, relapse prevention and rehabilitation (Yang et al., 2015). During the initial stage of abstinence, individual who suffers from drug dependency may need help alleviating the withdrawal effects (Garland, 2014). The process called detoxification is primarily performed in a hospital or other inpatient settings, where close monitoring of medication selected to lessen withdrawal symptoms depending on the drug the person is addicted to should be conducted.

Advanced technology has been utilized to simulate a therapy program that can be hardly duplicated solely by computer programs. However, the use of computer-based approach toward drug addiction still requires an ideal solution to the resource limitations including how to integrate technology into existing treatment frameworks and properly handle emergency situations. Given apparent advantages, such as potentially increased privacy and autonomy afforded by the computerized treatment options, augmented reality (AR) apprehends partial psychotherapy that is guaranteed to address drug addiction issues and can become a routine part of care delivery and therapeutic implementation.

4.3.2. Recent progress in augmented reality against medication addiction

The signal-reactivity therapy has been adapted for the treatment of addictive symptoms due to heroin and alcohol abuse, which frequently requires intimate dealing with physical and psychological dependence (Carter and Tiffany, 1999). The signal-reactivity therapy is intended for patients to control that dependence and elect not to express. However, it is difficult to trigger signals for addiction in a place that doesn't precisely simulate the real world conditions of patients who are mingled with people drinking or taking drugs. That's where virtual reality comes in to actually simulate those environments.

The setup called a “cave” was created by the scientist in Houston University for imposing the person on a more life-like environment (Loria, 2016). They use goggles that turn images projected onto the walls of a room (the cave) into a three dimensional high definition experience.

While two settings that represent two types of users who are going through the treatment come with such restrictions as they can't include

the people or places that will be actually accustomed to a user, they offer a more realistic experience than is possible when an addict is engaging in signal-reactivity therapy in home or an office. It was suggested that augmented reality (AR) can make these moments more actual via effectively signaling these cravings.

AR can utilize advanced gadgets like compatible mobile devices for navigating the physical world where addictive patients are under action or traveling. The software platform, such as Snapchat (Snap Inc.) or Tango (Google co.), can add a new kind of specific vision sensors that are similar to a finger print sensor to mobile device by capturing such advanced features as spatial perception and image recognition. Numerous android device platforms that run C, Java, and Unity can work with AR to enhance its capability of chronical image recognition and spatial perception.

4.4. Augmented-reality for image-guided 3-D surgical navigation

Surgical operation has rapidly adapted minimally invasive surgery (MIS) as the standard care (Nicolau et al., 2011). Although MIS has offered significant benefits, there have been limitations associated with MIS represented mostly by the lack of personalized specification and interactive feedback, especially in robot-assisted surgery that has occupied a great portion of MIS (Hughes-Hallett et al., 2014a).

To address the limitation, interactive feedback was replaced with visualization tools or AR to dissect anatomy (Hughes-Hallett et al., 2015). The first step of operative planning explores 3D reconstructions of preoperative cross-sectional image maneuvered through a tablet-based interface (Hughes-Hallett et al., 2014b), while the second step of execution utilizes optically registered intraoperative ultrasound or magnetic tracers to mitigate the problems of deformation and create freehand 3D reconstructions which are overlaid onto the operative view (Pratt et al., 2013). Visual tools offered a number of potential benefits to the surgical operation process including a reduction in positive surgical margins and improved resection quality (Hughes-Hallett et al., 2015).

Augmented-reality surgical navigation technology further supports the fast growing image-guided MIS market. Owing to intrinsically hindered visibility of the spine during MIS procedures, surgeons relied on real-time imaging and navigation solutions to guide their surgical tools and implants (Philip Media, 2017). A combination of 3D X-ray imaging and optical imaging developed by Philips' engineering team (Bothell, WA) provides surgeons with a unique augmented-reality view of the patient's spine, plan the optimal device path, and subsequently place pedicle screws using the system's fully-automatic augmented-reality navigation during surgical procedures. They can check the overall result in 3D without the need to move the patient to a CT scanner for radiation exposure and with minimal dose to the patient. This breakthrough is able to provide state-of-the-art care and reduce the overall cost for the hospital.

As an alternative approach to visual tools, wearable devices like Google Glass (Google Inc., Mountain View, CA) can serve as a prototype that significantly contributes to construction of image-guided augmented-reality for 3D surgical navigation in the plastic and reconstructive surgery (Sinkin et al., 2016). In those surgeries, Google Glass can potentially incorporate consumer driven personalized services, such as image-guided navigation and preoperative augmented-reality software (Rahman et al., 2016). Moreover, recently updated Google Glass is capable of taking into account the feedback and suggestions from its end users.

Other wearable technologies, such as Microsoft Oculus Rift (Oculus VR, Menlo Park, CA) and HoloLens (Microsoft Corporation, Seattle, WA), are also gaining recognition from the customers (Sinkin et al., 2016). Especially, the Spy Elite (Novadaq Technologies, Inc., Bonita Springs, FL) allows surgeons to visualize fluorescence information directly through the eyepiece and capture and review high-quality images of microvascular flow in tissue perfusion (Liu et al., 2011). The next stage will examine how to merge 2D images visualized on the wearable devices display with the real-time 3D surgical site (Peregrin, 2014).

The use of an image-enhanced operating system could potentially influence 3-D surgery process conducted by surgeons with more challenging anatomy via MIS. The image-guided platform that has been built around the index procedure assisted by mechanically-assistive robots or augmented-reality wearable devices guaranteed the improved physiological perception of anatomy and its clinical application to personalized surgery with the expanded scope.

5. Conclusion

As our understanding of onset and progress of diseases at the genetic and molecular level rapidly progresses, the potential of advanced technologies, such as 3D-printing, socially-assisted robot or augmented reality (AR), that are applied to PNMs to alleviate pathological conditions, have become more prominent. PNMs prepared based on various combinations of nanomaterials and fine-tuned by advanced technologies are efficiently optimized for their interactions with host response or biological systems.

As AR is about to adapt additional new methods, such as speech, voice recognition, eye tracing and motion tracking, to enhanced interaction with host response or biological systems in 3-D space, a combination of multiple approaches via accommodate varying environmental conditions, such as public noise and atmosphere brightness, will be explored. For instance, AR glasses developed by Facebook or Microsoft will serve as new platform that can provide people with the health information they are interested in or various measures through which they can interact with medical services.

As genetic testing and theranostic approaches are necessary to collect the greater number of personal data, we are expected to see a higher degree of personalized medication based on big data and machine learning. Due to the huge volume of personal data, encountering certain ethical conflict and inherent issues surrounding PNMs seems to be also unavoidable. In pace with these advances, regulatory modification may be needed in near future to define the acceptable criteria for PNMs in the approval process by FDA.

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