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Review

Implantable biosensors and their contribution to the future of precision medicine

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ABSTRACT

Precision medicine can be defined as the prevention, investigation and treatment of diseases taking individual variability into account. There are multiple ways in which the field of precision medicine may be advanced; however, recent innovations in the fields of electronics and microfabrication techniques have led to an increased interest in the use of implantable biosensors in precision medicine. Implantable biosensors are an important class of biosensors because of their ability to provide continuous data on the levels of a target analyte; this enables trends and changes in analyte levels over time to be monitored without any need for intervention from either the patient or clinician. As such, implantable biosensors have great potential in the diagnosis, monitoring, management and treatment of a variety of disease conditions. In this review, we describe precision medicine and the role implantable biosensors may have in this field, along with challenges in their clinical implementation due to the host immune responses they elicit within the body.

Introduction

Precision and personalised medicine are interchangeable terms, with similar concepts. Due to concerns among clinicians and scientists that the term “personalised” could be misunderstood, leading patients to believe that unique treatments/drugs were being developed specifically for each individual, the term personalised medicine has now predominately been replaced with precision medicine (Biesecker et al., 2011; Katsnelson, 2013). Precision medicine is defined as the prevention, investigation and treatment of diseases taking individual variability into account. These factors include disease biomarkers, molecular signatures, phenotype, environment and lifestyle (Ghasemi et al., 2016). This approach allows individual patients to be classified into sub-populations that differ in their susceptibility to a particular disease, prognosis and response to treatment (Bu et al., 2016). Precision medicine can therefore help to identify patients most likely to benefit from a specific treatment, thus improving clinical outcomes whilst reducing side effects (Penet et al., 2014).

Even though precision medicine is not a new concept, it has gained increased awareness and momentum in recent years, aided by world leaders such as the former President of the United States Barack Obama, who announced the “Precision Medicine Initiative” at the beginning of 2015. This initiative aimed “to bring us closer to curing diseases like cancer and diabetes – and to give us all access to the personalised information we need to keep ourselves and our families healthier” (Collins and Varmus 2015).

Although the role of precision medicine in everyday treatment is currently limited, dedicated centres, such as The Centre for Personalised Medicine in the UK and The Personalised Medicine Coalition in the USA, should make the integration of precision medicine into everyday healthcare practices more widespread in the coming years (Carrasco-Ramiro et al., 2017). However, cross disciplinary approaches involving engineering and chemistry may be needed to make significant progress. While the application of precision medicine is currently more focused on humans, its concepts are equally applicable in the treatment of veterinary patients.

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Implantable biosensors

The physiology of disease tissue can be markedly different to that of healthy tissue, with diseases such as cancer or diabetes mellitus leading to measurable changes within the body. Methodology that could provide continuous data on the levels of a target analyte, enabling trends and changes in concentrations over time to be analysed, without any need for intervention from the patient or clinician, would be very valuable (Vaddiraju et al., 2010). As such, implantable medical devices have great potential in the diagnosis, monitoring, management and treatment of a variety of disease conditions (Cavallini et al., 2015) (Fig. 1).

Advances in the fields of electronics and microfabrication techniques have caused increased interest in the use of implantable medical devices in precision medicine. Biosensors are analytical devices containing a biological sensing element that transforms a biological response into electrical signals (Turner, 2013; Mehrotra, 2016). Biosensors have many different applications, from environmental monitoring and food safety, to security and defence; however, the use of biosensors for medical diagnostics represents the largest driver for biosensor development and application today (Turner, 2013).

Implantable electrochemical biosensors

Biosensors are composed of two main parts; a bio-recognition element and a transducer. The bio-recognition element of the sensor identifies a target analyte, while a transducer converts the output from the molecular recognition into an electrical signal (Thévenot et al., 2001). Different molecular recognition elements can be employed, including enzymes, nucleic acids, antibodies, proteins and peptides. Electrochemical biosensors have electrodes as their transduction element (Thévenot et al., 2001).

Clark is credited with developing the first biosensor in 1962; this 'enzyme electrode' (Clark and Lyons, 1962) was a concept built on his earlier invention the Clark oxygen electrode (Clark, 1959). Having enzymes as the molecular recognition element depends on the catalytic conversion of an enzymatic substrate to a product. Because enzymes have highly specific binding pockets, enzyme electrodes have high selectivity against their chosen analyte (Zhu et al., 2015). Clark's paper described the electrochemical detection of O_2 or CO_2 by immobilised enzymes. In one example, the enzyme glucose oxidase (GOx) was entrapped on a platinum O_2 electrode over a semi-permeable dialysis membrane, with the amount of O_2 consumed by the electrode acting as an indirect measure of glucose levels (Clark and Lyons, 1962).

Electrochemical biosensors have the potential to offer the sensitive and rapid detection of a wide range of biomarkers; their relative fabrication simplicity, amenability to miniaturisation, along with the reduced cost of instrumentation, has also furthered interest in their development (Kokkinos et al., 2016).

Biosensors and metabolic diseases

One of the first major successful applications of implantable biosensors was in the field of metabolic diseases, specifically diabetes mellitus. Despite advances in insulin therapy delivery and the development of more physiological insulin preparations (Home, 2012), the avoidance of hypoglycaemic episodes still remains a challenge (Cryer, 2015). Blood glucose measurements

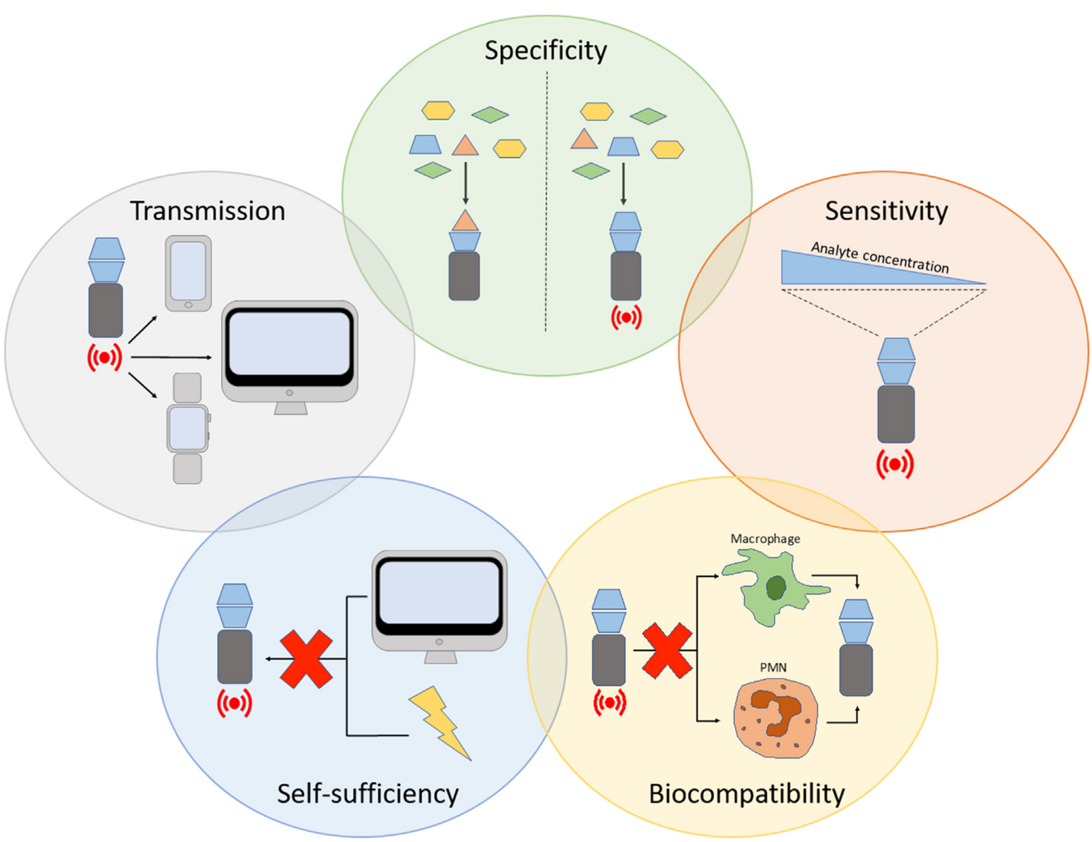

Fig. 1. Diagram showing the criteria that an ideal implantable biosensor should possess. These requirements include: sensitivity and specificity (the biosensor must be able to operate within the therapeutic range of the target substance whilst in the presence of complex solutions e.g. interstitial fluid or blood), biostability and biocompatibility (negative immune reactions may cause the device to become non-functional), self-sufficiency (in terms of power supply and control from external devices) and transmission (the signal output transmitted to an external communication device should be in a meaningful form for ease of use for the patient/clinician).