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Progress in the development of olfactory-based bioelectronic chemosensors

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ABSTRACT

Artificial chemosensory devices have a wide range of applications in industry, security, and medicine. The development of these devices has been inspired by the speed, sensitivity, and selectivity by which the olfactory system in animals can probe the chemical nature of the environment. In this review, we examine how molecular and cellular components of natural olfactory systems have been incorporated into artificial chemosensors, or bioelectronic sensors. We focus on the biological material that has been combined with signal transduction systems to develop artificial chemosensory devices. The strengths and limitations of different biological chemosensory material at the heart of these devices, as well as the reported overall effectiveness of the different bioelectronic sensor designs, is examined. This review also discusses future directions and challenges for continuing to advance development of bioelectronic sensors.

1. Introduction

1.1. Artificial chemosensory devices

In mammals, the two principal chemosensory modalities are gustation (taste) and olfaction (smell). Gustation provides basic information about the chemical composition of compounds that includes acidity (sour), the presence of ions (salty), carbohydrate content (sweet), amino acid content (umami), and potential toxicity (bitter). Olfaction, in contrast, probes chemical space in greater detail to uniquely identify either individual or classes of compounds. Together, these sensory inputs provide essential information about the chemical composition of the environment that facilitates many essential biological functions.

The ability of chemosensory systems to probe the chemical nature of the environment in order to identify either advantageous or dangerous objects and conditions has inspired the design platforms that can either replicate or augment these natural systems. Such artificial chemosensory devices have a wide range of applications. These sensors can facilitate security operations, including the detection of either explosives, chemical weapons, or contraband (reviewed in Giannoukos et al., 2016). Security-related applications remains a strong focus and a driver of innovation in the field, but emerging bio-medical applications are also pushing this technology forward. Chemosensors can screen volatile organic chemicals emitted by an organism (the volatilome) and may become key components of non-invasive medical procedures to monitor a patient's metabolic state or diagnose pathological conditions such as cancer (Angle et al., 2016; Broza and Haick, 2013; Di Lena et al., 2016; Fitzgerald and Fenniri, 2016; Gardner and Vincent, 2016; Gui et al., 2017; Liu et al., 2014; Saalberg and Wolff, 2016; Sethi et al., 2013). There are also many industrial applications for artificial chemosensory devices, including quality control processes in food production and manufacturing as well as monitoring workplace environments for toxic or noxious compounds (Loutfi et al., 2015; Mendez, 2016; Rock et al., 2008; Wilson and Baietto, 2009). Moreover, for industries reliant on fragrances, electronic noses can provide a method for standardizing aromas (Son et al., 2017). There are also extensive uses in agriculture where these devices can perform environmental and soil monitoring, pesticide detection, and facilitate waste management (Wilson, 2013). There are many other areas in which artificial chemosensory devices can have a meaningful impact, and several reviews have discussed these potential applications (Dung et al., 2018; Ko et al., 2014; Rock et al., 2008; Wilson and Baietto, 2009).

A reasonable question to ask is why artificial chemosensors are needed when animals can be used to augment human perception of the chemical environment, and when canines, in particular, are considered the standard for such roles. Although dogs are used successfully in many applications, there are several drawbacks or limitations to their

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use, which include: the expense required for maintenance and training/re-training, lack of standardization, their best use is for only volatile compounds, an inability to detect odorless or acutely toxic compounds, as well as impaired performance due to distractions, fatigue, or mood. Other animals, such as rodents and insects, have been proposed as alternatives to dogs (reviewed Oh et al., 2015b). These other species can provide solutions to certain issues, but they also have their set of own complex challenges that tend to offset the benefits they may have relative to the canine standard. Thus, there is a need for artificial chemosensory devices that can provide rapid, sensitive, and selective chemical detection, like natural olfactory systems, but that can also be standardized and reliably function at all times.

The prevailing concept of an artificial chemosensory device is a system containing two basic components: a chemical sensor and a pattern recognition system (Gardner and Bartlett, 1994). Over the past several decades, much of the work with these devices has concentrated on the development of the chemical sensor component. Among the reported sensor designs, two principal divisions can be made: those that incorporate biological material from naturally occurring chemosensory systems (i.e. biological material derived from cells and tissues) and those that completely rely on inanimate components. Bioelectronic sensors are those devices that incorporate components of animal chemosensory systems in an effort to mimic the abilities of natural systems. By contrast, completely inanimate sensors typically use materials such as metal oxides and polymers for the detection of target compounds (Arshak et al., 2004; Zohora et al., 2013). In general, however, completely inanimate sensors lack the ability to probe chemical space with the same range and specificity as natural chemosensory systems.

The development of bioelectronic chemosensors has primarily concentrated on incorporating elements of olfactory systems because there are several features of the olfactory system that make it preferable to the gustatory system. The main olfactory system in mammals relies on a large single family of transmembrane odorant receptor proteins for chemical detection. These receptor proteins represent the largest gene family in vertebrate genomes (ranging from ~ 400 functional receptors in humans to ~ 2000 in elephants; Niimura et al., 2014) and can probe chemical space with finer resolution than the gustatory system. Despite the large size of the odorant receptor protein family, these receptors function the same way by activating a common cyclic adenosine monophosphate (cAMP)-dependent second-messenger intra-cellular signaling pathway to open ion channels and generate an action potential (Fig. 1). There is evidence that a subset of odorant receptors in the main olfactory system can also activate cAMP-independent pathways (Baker et al., 1999; Lin et al., 2004), but this subset is a small fraction of the total olfactory sensory neurons. In contrast to the strong molecular uniformity in the olfactory system, there is considerable variation in the protein receptors and mechanisms for inducing taste sensory information in the mammalian gustatory system. Sweet, bitter, and umami taste modalities are each mediated by different sets of receptor proteins, but all three utilize a common phospholipase C/diacylglycerol-dependent pathway for activating ion channel opening. Candidate protein receptors for sour and salty reception, however, are each a unique class of protein receptors, and they do not rely on second messenger pathways since they can also directly act as ion channels. There are compelling reasons to develop chemosensory devices that model gustation (Ceto et al., 2016; Latha and Lakshmi, 2012; Son and Park, 2018), but the olfactory system's molecular uniformity and the greater ability to probe chemical space is more amenable for developing bioelectronic chemical sensors with maximal sensitivity and range (Fig. 2).

The use of olfactory system components in bioelectronic sensors does not limit these devices to only the detection to volatile chemicals. In fact, mammalian odorant receptors do not directly sample the air since they are located in olfactory sensory neuron cilia that are immersed in a mucosal layer. This arrangement requires odorants to diffuse through the mucosal layer in order to reach their cognate receptors (a process that can be facilitated by odorant binding proteins found in the mucosal layer; Tegoni et al., 2000). Moreover, olfactory systems in aquatic animals, such as fish, do not rely on airborne, volatile odorants (Hamdani el and Doving, 2007; Tierney, 2015). In addition, the expression of mammalian odorant receptor proteins in non-olfactory tissue, such as kidney and sperm (reviewed in Kang and Koo, 2012) further indicates that these receptors are potent sensors of either volatile or liquid chemicals. While the current convention uses the term “electronic nose” or “bioelectronic nose” to describe artificial chemosensors using components of natural olfactory systems, the applications for these systems are not constrained only to the detection of airborne, volatile chemicals and may be aptly named “bioelectronic chemosensors”.

2. Protein-based bioelectronic chemosensors

2.1. Olfactory receptor proteins

Several studies have incorporated molecular elements of natural olfactory systems into bioelectronic sensors (Table 1). Many of these molecular approaches have used olfactory odorant receptor proteins embedded in either membrane fragments, nanodiscs, or nanovesicles. For sensors using receptor proteins derived from cell membrane fragments, an early study used isolated frog olfactory epithelial tissue (Wu, 1999), but most designs have used bacterial or yeast cells that heterologously express odorant receptor proteins (Dacres et al., 2011; Hou et al., 2007; Kim et al., 2009; Lee et al., 2012a, b; Park et al., 2012b; Yoon et al., 2009), although mammalian cells have also been used as a source (Du et al., 2013). Odorant receptor proteins within membrane fractions have typically been solubilized with detergents, such as Triton X-100, to facilitate their incorporation into the sensor. The structure (and consequently, the function) of transmembrane proteins, such as odorant receptors, relies on the phospholipid environment of cellular membranes. Amphiphilic reagents, such as detergents, can solubilize transmembrane proteins embedded in cell membranes, but they also effectively mimic the cell membrane environment so that the odorant receptors can maintain their structure and function. However, even though detergents are amphiphilic reagents offering some control to generate the necessary protein folding, phospholipid membranes provide a stronger support where intermolecular forces allow for the required amino acid sequence alignment providing the proper function. Additionally, olfactory receptors are part of a larger organization of a combination of proteins that synchronize together to provide the detection of individual chemicals. A significant limitation to using isolated, solubilized receptor proteins, however, is that the receptors are separated from other membrane-bound and cytosolic proteins that facilitate odorant binding and signal transduction.

An alternative approach, however, to using detergents is to isolate odorant receptor proteins from cell membrane fragments (e.g. His-tag purification methods) and insert them into nanodiscs (Goldsmith et al., 2011; Yang et al., 2017). Nanodiscs are soluble self-assembling synthetic nanoscale phospholipid bilayer structures containing transmembrane proteins that provide a stable environment for integral membrane proteins like odorant receptors (Bayburt and Sligar, 2010). Nanodiscs are able to maintain the native membrane environment of olfactory receptor proteins but they still separate the receptors cytosolic proteins that facilitate odorant binding and signal transduction. This limitation has been addressed by isolating receptor proteins as part of nanosomes or nanovesicles from yeast or mammalian cells, respectively (Jin et al., 2012; Lee et al., 2015a; Lim et al., 2014; Park et al., 2012a, b; Son et al., 2015; Vidic et al., 2008, 2007, 2006). Nanosomes have been used in chemosensors as small spherical membranes fragments (as small as 50 nm in diameter) generated by multiple rounds of sonication and centrifugation with yeast transformed to co-express an odorant receptor and its cognate $G_{\alpha olf}$ protein (Vidic et al., 2006). Nanovesicles, by contrast, are exosome-like structures that bud off from cells treated

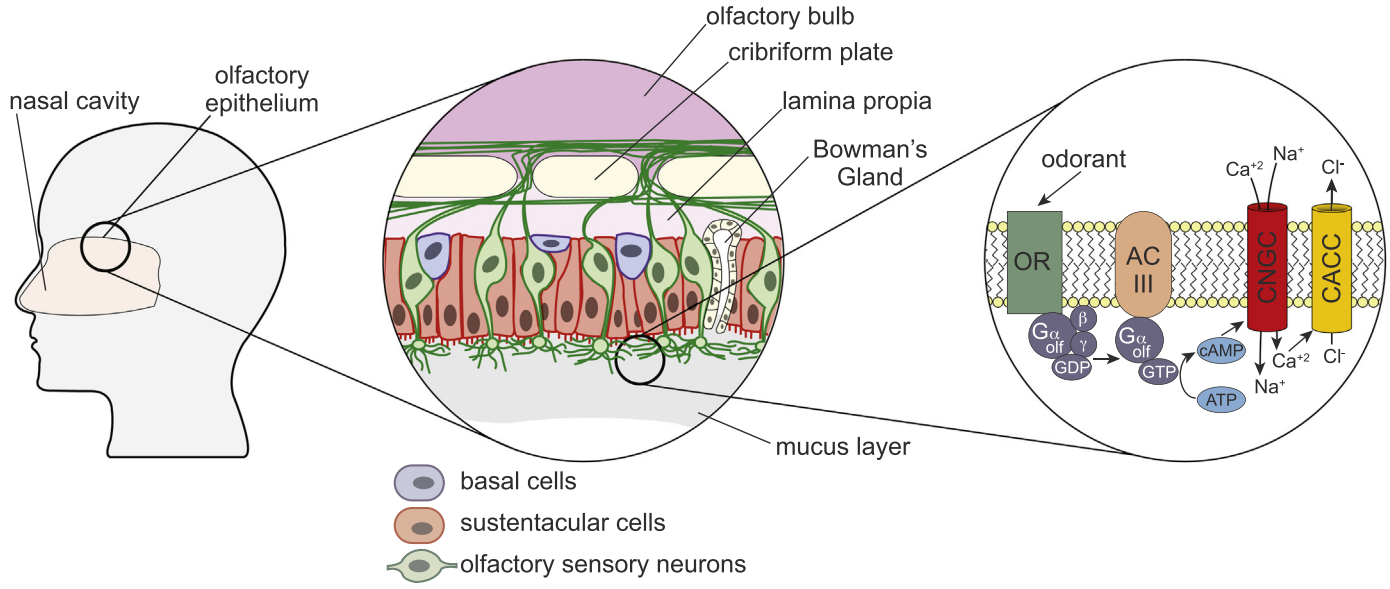

Fig. 1. Olfactory system in humans. A portion of the nasal cavity roof contains the olfactory epithelium, which is separated from the olfactory bulb in the brain by the cribriform plate of the skull. Olfactory epithelial tissue contains several distinct cell types, including: olfactory sensory neurons (green), sustentacular support cells (red), basal cells (including globose and horizontal basal cells; blue), as well as the cells that form Bowman's gland for mucus secretion. Olfactory sensory neurons have apical cilia that project out into the mucus layer, and these cilia are enriched with proteins that mediate odorant detection. At a molecular level, odorants are bound by odorant receptor (OR) proteins embedded in the cilia membrane. Odorant binding induces the $G_{\alpha olf}$ protein to release GDP, bind GTP, and dissociate from the β and γ subunits. The activated $G_{\alpha olf}$ protein forms a complex with adenyl cyclase III, which converts ATP into cyclic AMP (cAMP). The accumulation of cAMP triggers the opening of cyclic nucleotide-gated channels (CNGCs), which allow for an influx of Na^+ and Ca^{+2} across the membrane. The influx of Ca^{+2} enables the opening of Ca^{+2}-activated chloride channels (CACCs) and an efflux of Cl^- across the membrane. Together, the coordinated movement of ions in response to odorant binding depolarizes the olfactory sensory neuron membrane potential and initiates an axon potential that is transmitted down the axon of the olfactory sensory neuron. This action potential is relayed to neurons in the olfactory bulb and processed within the central nervous system as odorant sensory information.

with chemical agents, such as cytochalasins. For bioelectronic chemosensors, the cells are engineered to express odorant receptor proteins so that the nanovesicles incorporate these proteins. A clear advantage of nanovesicle structures is that they contain both transmembrane proteins (such as odorant receptors) as well as cytoplasmic proteins (such as G-protein coupled receptor pathway signaling proteins) so that complete signal transduction can occur within a single nanovesicle. This system creates a simplistic native structure of olfactory receptor transduction found in cells and provides a higher efficiency for successful odorant recognition.

Whether solubilized with detergents or embedded in nanoscale membrane structures, olfactory receptor proteins can be coupled with several different types of detectors. One such design is piezoelectric quartz microbalance electrodes (QMEs) either coated with odorant receptor proteins from cell membrane fractions (Ko and Park, 2005; Sung et al., 2006; Wu, 1999) or functionalized with aptamers to selectively bind odorant receptor proteins (Du et al., 2013). An alternative design is to immobilize odorant receptor proteins on gold electrodes for use with electrochemical impedance spectroscopy (EIS) (Hou et al., 2007). Such sensors have used odorant receptor proteins heterologously expressed in yeast that are then immobilized on an electrode surface functionalized with biotinylated antibodies for the odorant receptor. Sensors using either QMEs or EIS have typically demonstrated sensitivity in the pico- to nano-molar or low parts-per-million ranges for target chemicals in the liquid and gaseous phases, respectively. Other designs include using gold surfaces derivatized with dextrans or self-assembling thiol monolayers to immobilize odorant receptor proteins as part of yeast-derived nanosomes (Vidic et al., 2007, 2006). Binding of a target chemical to the olfactory receptor in this design can be monitored by surface plasmon resonance, but these sensor systems have shown a lower sensitivity with optimal responses only in the micromolar range.

Considerable recent interest has concentrated on developing bioelectronic chemosensors with high sensitivity by coupling odorant receptor proteins with field effect transistors (FETs) (Ahn et al., 2015; Goldsmith et al., 2011; Jin et al., 2012; Kim et al., 2009; Lee et al., 2012a, b; Lim et al., 2014; Park et al., 2012a, b; Son et al., 2015; Yang et al., 2017; Yoon et al., 2009). Nearly all of these devices have relied on nanotubes, although some studies have used graphene (Kwon et al., 2015; Park et al., 2012b). A myriad number of strategies have been used to immobilize the odorant receptor proteins on FETs, which have ranged from immobilizing solubilized proteins from recombinant bacterial cell membrane fractions on derivatized nanotubes, to using nanoscale structures (nanodiscs and nanovesicles) with nanotubes coated with either poly-lysine or modified with nickel-histidine tags or antibodies. In general, these sensors have demonstrated rapid response times and high sensitivity for target chemicals (femtomolar and parts-per-trillion range for liquid and gaseous samples, respectively). Moreover, the relatively small size of these sensors is amenable to the development of compact sensor arrays that could be implemented in field-ready devices.

All of these sensor designs (QME, EIS and FET) have similar issues that limit their practicality, which include a front-loaded workflow that is time-consuming and labor-intensive preparation, as well as variability in sensor performance due to ambient conditions, such as temperature or humidity. An additional challenge for the further development of these sensors is to establish methods for quantifying the amount of odorant receptor protein (either isolated protein or as part of nanostructures) that is incorporated with the sensor. Being able to quantify the amount of material will significantly improve reproducibility in the performance between individual sensors. For FET sensors, differences in the amount of biological material incorporated into the sensor has been suggested to account for some of the variability in the responses between individual electrodes (Lee et al., 2015a).

2.2. Odorant receptor protein-derived peptides

Odorant receptor protein-derived peptides that are capable of

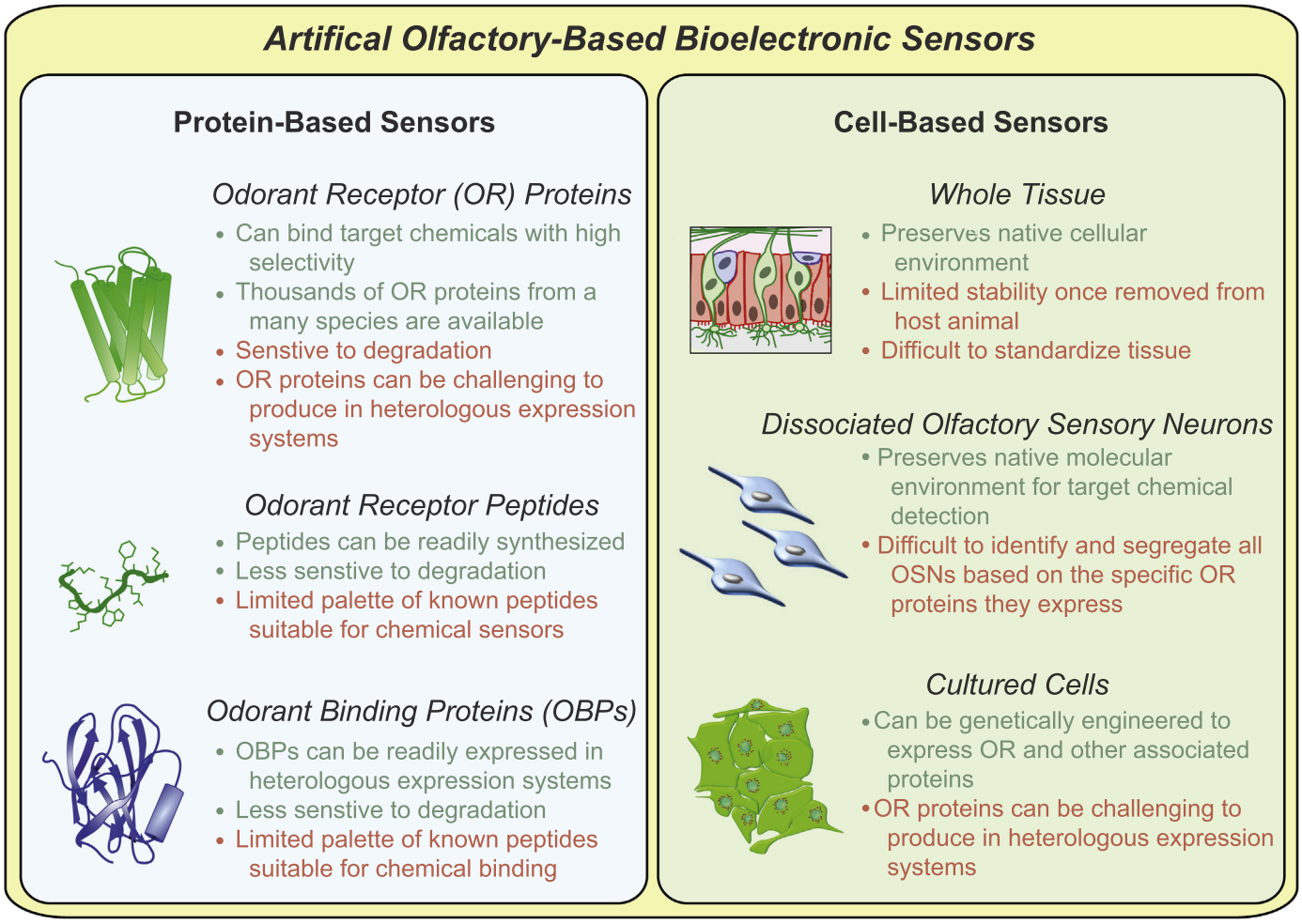

Fig. 2. Summary of biological material from natural olfactory systems that have been used in bioelectronic chemosensory devices. Key advantages and limitations are presented in green and red text, respectively.

interacting with target compounds are an alternative to using the full length receptor proteins for chemosensors (Jaworski et al., 2008; Lee et al., 2018, 2015a; Lim et al., 2013; Lu et al., 2009; Sankaran et al., 2011b). Both *in silico* modelling-based studies of olfactory receptor proteins (Sankaran et al., 2011b; Wu and Lo, 2000) and by directed evolution with phage display screens (Jaworski et al., 2008) have identified peptides capable of interacting with a select set of target chemicals. The use of peptides, rather than full-length proteins, has been proposed to provide a simpler and more stable sensing element (Lee et al., 2015b). In practice, these types of devices have typically paired FETs with peptides non-covalently attached to single-walled carbon nanotubes. These sensors have demonstrated high sensitivity in the parts-per-trillion range for gaseous samples and sub-picomolar concentration for liquid samples. Moreover, unlike sensors using full-length odorant receptor proteins embedded in nano-scale membrane-based structures, peptide-based sensors can reproducibly detect the target compound with minimal loss of signal intensity in multiple independent exposures during a testing session (Lee et al., 2015b; Lim et al., 2013). This reproducibility coupled with the high sensitivity makes this sensor design attractive for further development. Moreover, the wide-spread ability to efficiently synthesize peptides at high yields also makes further development of peptide-based sensors an attractive option. An important limitation for this type of chemosensor, however, is the currently limited palette of peptides available for chemosensory detection. Examining structural features from olfactory receptors is considered but provide similar limitations to full proteins in regards to their performance and detection capabilities. An important goal for moving forward is to identify additional peptides capable of chemoreception so that peptide-based sensors can provide a wider coverage of chemical space. Identifying these additional peptide sequences can be facilitated by examining proteins other than odorant receptors that can specifically bind small molecules. For example, sensors that can detect dioxins have been reported using peptide sequences derived the aryl hydrocarbon receptor protein (Mascini et al., 2005).

2.3. Odorant binding proteins

Odorant binding proteins are secreted globular proteins in vertebrates and insects that facilitate olfaction. The role of these proteins is not completely understood, but they are secreted into the nasal mucous (or chemosensory sensilla lymph of insects) where they are believed to assist the diffusion of volatile chemicals (Pelosi et al., 2014). This ability to interact with target chemicals and augment odorant reception has prompted the exploration of these proteins in chemosensor design (Di Pietrantonio et al., 2015, 2013; Hou et al., 2005; Larisika et al., 2015; Lu et al., 2014, 2015; Manai et al., 2014; Mulla et al., 2015; Palla-Papavlu et al., 2014; Reiner-Rozman et al., 2016; Sankaran et al., 2011a). Mammalian and insect odorant binding proteins have been incorporated into several detector systems that use either surface plasmon resonance, EIS, sonic acoustic wave resonators, or QMEs. The sensitivity of these systems has been relatively low, with detection typically in the micro- to millimolar range or ppm range for liquid and gaseous samples, respectively. Systems with higher sensitivity have been reported with FETs, which includes a water-gated bio-organic

Table 1
Protein-based bioelectronic chemosensors.

Biological material	Detection with	Detection limit	Reference(s)
Olfactory Receptor (OR) Proteins			
Derived from:			
bullfrog	piezoelectric quartz microbalance electrodes	micromolar	Wu (1999)
rat, bacterial cells (nanodiscs) membrane fractions (nanosomes)	carbon nanotubes	picomolar	Goldsmith et al. (2011) and Yang et al. (2017) Vidic et al. (2008)
canine, mammalian cells (nanovesicles)	field effect transistors	femtomolar	Jin et al. (2012), Lim et al. (2014), Park et al. (2012a) and Vidic et al. (2008)
human	piezoelectric quartz microbalance electrodes	nanomolar	Ko and Park (2005), Sung et al. (2006), Wu (1999) and Du et al. (2013)
rat OR (nanosomes)	surface plasmon resonance	micromolar	Vidic et al. (2007, 2006)
rat cell membrane fractions	electrochemical impedance spectroscopy	picomolar, nanomolar (liq) ppm (gas)	Hou et al. (2007)
human, recombinant membrane fractions	field effect transistors	femtomolar (liq) ppt (gas)	Kim et al. (2009), Lee et al. (2012b) and Yoon et al. (2009)
mouse, human	carbon nanotubes	femtomolar, ppb	Ahn et al. (2015), Goldsmith et al. (2011), Jin et al. (2012), Lee et al. (2012a) and Son et al. (2015)
human	graphene field effect	femtomolar	Park et al. (2012b)
Odorant Receptor Peptides			
Derived from:			
cell membrane fractions, mammalian	single-walled carbon nanotubes	femtomolar, ppm	Lee et al. (2018, 2015b) and Lim et al. (2013)
cell membrane fractions, mammalian	gold coated wafer		Jaworski et al. (2008)
cell membrane fractions, mammalian	piezoelectric quartz microbalance electrodes	ppm	Lu et al. (2009) and Sankaran et al. (2011b)
Odorant Binding Proteins (OPBs)			
Derived from:			
honey bee, insect	electrical impedance		Hou et al. (2005), Lu et al. (2014) and Lu et al. (2015)
bovine	sonic acoustic wave resonators	ppm	Di Pietrantonio et al. (2015, 2013) and Palla-Papavlu et al. (2014)
insect	piezoelectric quartz microbalance electrodes	ppm	Sankaran et al. (2011a)
honey bee	field-effect transistor sensors	femtomolar, picomolar	Son et al. (2016), Larisika et al. (2015) and Mulla et al. (2015)
porcine	polycrystalline diamond cantileveers	micromolar, millimolar	Manai et al. (2014)
honey bee	graphene oxide	picomolar	Reiner-Rozman et al. (2016)

field effect transistor coupled to porcine odorant binding proteins that had a nano- to picomolar detection range (Mulla et al., 2015). The highest sensitivity (femtomolar range), however, has been observed with FETs using nanotubes coupled to a peptide derived from an insect odorant binding protein (Son et al., 2016).

The incorporation of odorant binding proteins into chemosensors has several advantages to odorant receptor proteins. A salient advantage is that olfactory binding proteins can be readily expressed and purified in heterologous systems, whereas the expression of most odorant receptor proteins in heterologous systems are a well-established challenge. Moreover, consistent with their native in vivo environment (being secreted into the vertebrate nasal mucous or insect chemosensory sensilla lymph), odorant binding proteins have considerably better stability and resistance than odorant receptors to degradation by temperature, pH, or proteolytic digestion. An important limitation to odorant binding proteins, however, is they do not probe chemical space as extensively as odorant receptor proteins. In mice, for example, there are ~ 1100 odorant receptor genes, but there are only 5 known odorant binding proteins (Shiao et al., 2012). Moreover, odorant binding proteins presumably target hydrophobic molecules in order to facilitate their diffusion across the aqueous-based mucous, which suggests that these proteins have only a limited affinity for polar or charged molecules. This limited range of molecular recognition is an important consideration in chemosensor design because it constrains the number of chemicals capable of being detected by sensors based solely on odorant binding proteins. Protein engineering of odorant binding proteins, however, could expand their range of molecular recognition. In addition, odorant binding proteins can be effective in improving the sensitivity of bioelectronic sensors that use odorant receptor proteins. Studies using surface plasmon resonance sensors with yeast-derived nanosomes containing a human olfactory receptor protein showed that the addition of a rat odorant binding protein significantly increased the overall sensitivity and lowered the detection limit of the sensor (Vidic et al., 2008).

3. Cell-based bioelectronic chemosensors

In addition to the challenges discussed above, the lifetime of the protein-based olfactory components in bioelectronic sensors is an important consideration. Isolated proteins and peptides on sensors are at risk for degradation and/or denaturation that prevents target chemical binding and impairs their chemosensory function. The durability of odorant binding proteins and peptides on bioelectronic sensors is generally considered to be better than odorant receptor proteins, but even these molecular components have limited lifetimes. At a certain point, the inactivation of too many molecular components will render the sensor ineffective and the sensor will need to be replaced. Moreover, sensors that rely on molecular actions initiated by target chemical binding to receptor proteins have additional challenges for continuous monitoring and detection. For example, surface plasmon detectors coated with yeast nanosomes detect the dissociation of the G_{alpha} protein-GTP complex following target chemical binding to receptors embedded in the nanosome membrane (Vidic et al., 2006). Without a continuous exogenous supply of GTP, however, these sensors will cease to function after about 8 h. Similarly, sensors with FETs coupled to nanovesicles detect the influx Ca^{+2} and other ions stimulated by the target chemical binding to receptors proteins (Liu et al., 2014), and these sensors also require maintenance of GTP levels within these nanovesicles. The influx of Ca^{+2} and other ions into the nanovesicles also requires the action of ATP-driven protein pumps to restore ion

Table 2
Cell-based bioelectronic chemosensors.

Biological material	Detection with	Detection limit	Reference(s)
Whole Tissue			
Animal:			
rat	microelectrode arrays	femtomolar	Zhuang et al. (2015, 2013)
mouse	electrical	micromolar	Ibarra-Soria et al. (2017)
transgenic mice	optical	micromolar	Gao et al. (2018)
transgenic mice	optical	micromolar	D'Hulst et al. (2016)
mice	optical	millimolar	Bozza et al. (2004)
Tissue derived from:			
adult rat olfactory epithelium	light-addressable potentiometric	micromolar	Liu et al. (2010a, c)
insect	physicochemical detection		Farbert et al. (1997), Sauer et al. (1992) and van der Pers and Minks (1997)
silkworm antennae	electroantennogram		Kuwana et al. (1999)
insect	electroantennogram		Myrick et al. (2008), Park and Baker (2002) and Park et al. (2002)
insect	field effect transistors	ppm	Schoning et al. (1998), Schroth et al. (1999a, b)
Drosophila	fluorescence	nanomolar	Strauch et al. (2014)
Dissociated Olfactory Sensory Neurons			
Cells derived from:			
post-natal rat	light addressable potentiometric	micromolar	Liu et al. (2006) and Wu et al. (2009)
post-natal rat	multi-electrode arrays	0.1 micromolar	Du et al. (2015)
mammalian	fluorescence and optical imaging		Figueroa et al. (2010)
Cultured Cells			
Cells derived from:			
Xenopus oocytes	electrophysiological	10 nanomolar -1 micromolar	Misawa et al. (2010)
embryonic rat cerebral cortex	electrophysiological		Tanada et al. (2012)
HEK293	fluorescent	micromolar, millimolar	Lee et al. (2006), Oh et al. (2015a), Oh et al. (2014), and Mainland et al. (2015)
HEK293	surface plasmon resonance	micromolar	Lee et al. (2009a, b)
HEK293	microfluidic fluorescence	100 ppb	Lee et al. (2015c)
Yeast	optical-based sensor	femtomolar	Dacres et al. (2011)

concentrations inside the vesicle to pre-stimulation conditions. If ATP levels are not sustained, the action of these pumps will be blocked and sensor function will become impaired.

An efficient strategy to address these challenges is to incorporate living cells capable of chemosensory detection as they have the ability to both regenerate damaged or dysfunctional proteins and produce the necessary molecular cofactors required for continuous monitoring and detection of target chemicals (Table 2). Living cells require conditions within the sensor platform to be suitable to maintain viability, but this is not particularly onerous since many cell cultures can readily be cultured for several weeks or months. Furthermore, homeostatic mechanisms within living cells enable cells to adjust to changes in the environment in order to continue their chemosensory function.

3.1. Chemosensors using whole tissue

Several animal species, with dogs in particular, have been used as living chemosensors in which their behavior is used to alert human handlers of target chemical detection (reviewed in Oh et al., 2015b). As an alternative to monitoring behavior, microelectrode sensors have been inserted into the main olfactory bulb of animals, such as rodents, to show that unique patterns of neural circuit activity can be monitored when animals are exposed to different odorants (Gao et al., 2018; Zhuang et al., 2015, 2013). While this sensor design taps into the high sensitivity and selectivity of a functional in vivo olfactory system, the surgical procedures required to create these animal-sensor platforms is complicated and laborious. In addition, reliably deciphering the detected complex odorant-induced patterns of neural activity in order to identify target chemicals is a major challenge. Computer analysis and neural activity pattern recognition can be calibrated by controlled exposures to individual target chemicals, but whether activity patterns generated by a mixture of compounds can be deconvoluted to identify the presence of a particular target chemical has not been rigorously tested with these bioelectronic sensors. Moreover, variation in the insert point of the microelectrodes within the olfactory bulb is likely to modify the detected patterns of neural activity, which requires each animal to be individually calibrated for target odorants. To overcome these challenges, the reproducibility of microelectrode insertion site can be facilitated by using genetically modified animals that fluorescently label specific olfactory sensory neurons (Gao et al., 2018). Additional considerations are variables that change odorant receptor expression levels. For example, continuous exposure to specific chemicals as well as genetic background differences can significantly change the expression levels of odorant receptors (Ibarra-Soria et al., 2017). These changes in expression may substantially alter neural activity patterns and impede the ability to identify target chemicals.

A potential solution for issues with odorant receptor expression levels has been explored with transgenic mice that over-express specific odorant receptor genes (D'Hulst et al., 2016). These mice expressed selected odorant receptors from transgenes under the control of a synthetic gene promoter containing multiple copies of key cis-regulatory elements found in genomic regions that regulate odorant receptor gene expression. The mice expressed the selected odorant receptor in 1–2% of the total number of olfactory sensory neurons (as opposed to only ~ 0.1% in normal mice), and neurons expressing the transgene suppressed expression of endogenous odorant receptor genes. Detection thresholds for target chemicals were significantly improved, and odorant-induced neural activity was monitored in real-time by crossing these mice with a line carrying the synaptopHuorin fluorescent reporter (Bozza et al., 2004). These mice (or "MouSensors"; D'Hulst et al., 2016) are an intriguing in vivo bioelectronic chemosensor system, and establishing the ruggedness of the optical detection system outside of a laboratory setting as well as its ability to also identify target chemicals in real-time from within a mixture are important goals for further development.

An alternative to using living animals is to use resected olfactory epithelial tissue. An advantage of this approach is that olfactory epithelial tissue includes additional cell types that augment olfactory sensory neuron function by providing metabolic and physical support, as well as the secretion of mucus containing odorant binding proteins (Dennis et al., 2015; Ding and Xie, 2015). A series of reports that coupled olfactory epithelium sections from adult rats with multi-electrode arrays showed that distinct patterns of oscillatory signals from extracellular field potentials can be detected for different odorants (Liu

et al., 2011, 2010b, 2012). The sensitivity of these electrode-based sensors can be enhanced by exposing the tissue sections to zinc nanoparticles (Zhang et al., 2016b). The mechanism for this enhancement in olfactory sensory neuron function is not clear, but it requires that the nanoparticles contain reduced zinc (Zn°) since oxidized zinc blocks this enhancement (Hagerty et al., 2016). Recent studies show that coating zinc nanoparticles with polyethylene glycol can prevent zinc oxidation and substantially prolong nanoparticle effectiveness (Singletary et al., 2017). An alternative approach has been to pair adult rat olfactory epithelium tissue with a light-addressable potentiometric sensor (Liu et al., 2010a, c). This sensor system provides the advantage of being able to monitor the activity of specific regions within the tissue section. For both the multi-electrode array and light-addressable potentiometric sensors, however, the lower limits of detection have not been established. Moreover, these systems face many of the same issues as using living animals, including complex and laborious preparation as well as challenging analyses of recorded signals to identify target chemical detection. An additional challenge is standardization of the resected tissue used for the sensor. Mammalian olfactory receptors are not expressed uniformly throughout the entire olfactory epithelium, rather they are expressed is distinct zones (Mori et al., 2000). Thus, in addition to factors that can alter the expression levels of olfactory receptor proteins (as discussed above), the precise region within the epithelium from which the tissue section is harvested may significantly impact the ability of these types of bioelectronic sensors to detect specific chemicals.

As an alternative to using mammalian olfactory tissue, several studies have developed sensors incorporating insect olfactory organs as the chemosensory component. Early systems concentrated on the detection of insect pheromones as part of efforts to disrupt the mating cycles of pests in farms and vineyards. Portable systems using isolated insect antennae attached to either electroantennogram or single sensillum recording devices demonstrated an ability to reliably measure insect pheromone levels under real-world conditions (Farbert et al., 1997; Sauer et al., 1992; van der Pers and Minks, 1997). Kuwana and colleagues even developed a compact, motorized mobile platform that used silkworm antennae with an electroantennogram recording device (Kuwana et al., 1999). This system could detect target chemicals in the ppb range and guide itself to the target chemical source. A series of papers from the Baker Laboratory reported the development of systems that used electroantennogram devices to simultaneously record from the antennae of multiple insect species (Myrick et al., 2008; Park and Baker, 2002; Park et al., 2002). These sensors could detect distinct activity patterns capable of distinguishing between almost 20 distinct volatile compounds, and a portable device containing this type of sensor could identify individual target chemicals from within mixtures in real-time. Another series of reports describe the development of an insect-based bioelectronic sensor using FETs (Schoning et al., 1998; Schroth et al., 1999a, b). These sensors used antennae from the Colorado potato beetle and could detect target chemicals in the ppb range in real time and were capable of distinguishing between plants damaged by either mechanical force or beetle infestation. A recent insect-based biosensor has reported using optical detection methods with *Drosophila* that are genetically engineered to express a neural activity-dependent fluorescent marker (Strauch et al., 2014). In this proof-of-concept sensor, flies were held in a fixed position to image olfactory sensory neurons on the antennae in real-time. The sensor could detect distinct activity patterns from volatile chemicals produced by cancerous and normal cells. This real-time detection ability is an improvement from previous studies using microelectrodes with antennae from blowflies that could detect target chemicals in the ppb range, but required post-hoc analysis to determine detection (Huotari, 2000). Together, the previous work incorporating insect antennae into bioelectronic chemosensor design has produced some innovative and effective systems. Arguably, the most significant limitation of these devices, however, is the stability of the isolated antennae, which are reported to be good for only 1–4 h after tissue harvest (Kuwana et al., 1999; Myrick et al., 2008; Schutz et al., 2000). Without improving this stability issue, the practical application of these types of bioelectronic sensors will likely be restricted.

3.2. Dissociated olfactory sensory neurons

An alternative strategy to using intact whole tissue is to dissociate resected olfactory tissue and use the cell suspensions to create bioelectronic sensors. Dissociated post-natal rat olfactory epithelial tissue combined with light addressable potentiometric sensors showed reliable detection of extracellular potentials when odorants are presented (Liu et al., 2006; Wu et al., 2009). Similarly, dissociated post-natal rat olfactory sensory neurons immobilized on multi-electrode arrays can detect distinct activity patterns for target chemicals when presented either individually or as mixtures (Du et al., 2015). Other reported sensor designs include microfluidic chambers capable of trapping individual cells and using fluorescence and optical imaging to simultaneously monitor the activity of thousands of olfactory sensory neurons (Figueroa et al., 2010).

Together, these studies provide proof-of-concept demonstrations that functional bioelectronic sensors can be generated with dissociated olfactory sensory neurons. The practicality of these devices, however, is limited for several reasons. A significant impediment is that each olfactory sensory neuron expresses only a single odorant receptor protein, and there are currently no methods available to either isolate each neuron based on its expressed receptor or to organize cells on sensors based on the odorant receptor protein expressed. Current methods can uniquely and simultaneously label a handful of sensory neurons by the co-expression of fluorescent proteins or other markers, but there is no effective method to simultaneously label all $\sim$ 1100 unique olfactory sensory neurons in rodents. To even simultaneously label and organize olfactory neurons cells that differentially express all $\sim$ 60 *Drosophila* odorant receptor proteins is beyond the current abilities. Without an ability to isolate or organize olfactory sensory neurons based on the expression of specific receptor proteins, the pattern of dissociated olfactory sensory neurons on the sensors will remain random and unique. This will likely reduce the reliability and reproducibility for these types of sensors. In addition, it remains to be established whether the long-term culture of dissociated olfactory sensory neurons in bioelectronic sensors affects the expression levels of odorant receptor proteins or the downstream intracellular signaling components that are required for neuron and sensor function.

3.3. Other cell-based systems

A strategy to circumvent issues with dissociated olfactory sensory neurons is to drive expression of select odorant receptor proteins in heterologous cell types. One such proposed alternative is *Xenopus* oocytes (Misawa et al., 2010). Misawa et al. reported a device in which oocytes were injected with RNA to express insect odorant receptor proteins, and the oocytes were immobilized in a fluidic device so that their electrophysiological responses could be monitored. Although the sensor is technically challenging in its design, it was capable of detecting target chemicals in the nanomolar range as well as distinguishing between chemically similar compounds.

A second alternative source is primary neural cell cultures. A proof-of-concept study showed that primary neural cells from the embryonic rat cerebral cortex can be transfected with plasmids to express insect odorant receptors to make a functional bioelectronic sensor (Tanada et al., 2012). All primary neural cell cultures, including the cerebral cortex, however, are heterogeneous and complicated mixtures of many different neuronal and glial cell types. Co-opting the endogenous protein networks in primary neural cells in order to enhance the electrophysiological responses induced by the odorant receptors is an attractive concept, but each of the different primary cell types are bound to

have unique electrophysiological responses. Furthermore, the yield for each cell type will vary between different tissue collections, as will the distribution of these cells types on the sensor. This makes each sensor with primary neural cells unique and likely to make sensor performance challenging to reproduce.

In contrast to primary cell cultures, immortalized cell lines provide a homogenous cell background for bioelectronic sensors. Several studies have reported sensors with immortalized human embryonic kidney (HEK293) cells, a line that has been used extensively to study G-protein intracellular signaling (Krautwurst et al., 1998; Lee et al., 2006, 2009a, b, 2015c; Mainland et al., 2014; Oh et al., 2015a, 2014; Zhuang and Matsunami, 2007). These studies have expressed odorant receptor proteins from several species, including human, rat and *C. elegans*, and have paired the cells with either multi-electrode array, surface plasmon resonance, or optical detection systems. A multi-electrode array sensor system was responsive to target chemical concentrations in the millimolar range, and this sensitivity was increased when G-protein signaling pathway components were also over-expressed (Lee et al., 2009a). Similarly, surface plasmon resonance-based sensors expressing either rat or *C. elegans* odorant receptors were sensitive in the millimolar range (Lee et al., 2006, 2009b). Optical-based sensors, however, have shown the highest sensitivity (high nanomolar/micromolar range) by using various fluorescent and chemiluminescent indicators that monitor ion influx or intracellular signaling pathways activated by this ion influx (Krautwurst et al., 1998; Lee et al., 2015c; Mainland et al., 2014; Oh et al., 2015a, 2014; Zhuang and Matsunami, 2007). Similar findings have been reported with studies using human HeLa cells modified to express several olfactory signaling pathway proteins (Schmiedeberg et al., 2007). Optical-based bioelectronic sensors have also been reported with insect Sf21 cells, which are derived from the armyworm *S. frugiperda* (Mitsuno et al., 2015; Termtanasombat et al., 2016). The cells in these sensors expressed insect odorant receptor proteins and showed sensitivity to target chemicals in the high nanomolar/micromolar range.

Yeast are the only cell type other than mammal or insect cells to have been used to construct a living-cell bioelectronic sensor. Dacres and colleagues reported an optical-based sensor that used *S. cerevisiae* expressing a chimeric receptor based on the *C. elegans* odorant receptor ODR-10 (Dacres et al., 2011). The chimeric receptor protein was engineered to contain both green fluorescent and *Renilla* luciferase proteins as sub-domains within the receptor. Unlike other optical-based systems, this sensor does not rely on the influx of ions resulting from target chemical binding to the receptor. Rather, this sensor relies on a disruption of bioluminescence resonance energy transfer between the GFP and luciferase sub-domains. When an odorant receptor protein binds a target chemical, there is a shift in the relative positioning of the transmembrane helices within the receptor protein, and this structural shift disrupts the resonant energy transfer between GFP and luciferase sub-domains. This chimeric protein-based sensor showed high sensitivity with an EC_{50} in the femtomolar range. A limitation for widespread application of this sensitive bioelectronic sensor, however, is that a chimeric receptor containing both green fluorescent and *Renilla* luciferase proteins must be engineered for each odorant receptor protein to be used.

Together, studies of bioelectronic sensors with cultured cells indicate that these sensors have promising potential. The homogenous cellular environment of cultured cell lines combined with several readily available methods to genetically engineer these cells provides a powerful platform for continued development of this type of bioelectronic sensor. As previously noted, living cells can continuously regenerate odorant receptors, but the expression of mammalian odorant receptor proteins on the cell surface in heterologous cell lines has presented a persistent challenge. Unlike other G-protein coupled receptor proteins, odorant receptors are aberrantly processed in the endoplasmic reticulum of many heterologous cell types, which can substantially reduce the number of functional receptor proteins expressed on the cell surface (Lu et al., 2003). The co-expression of proteins that facilitate the trafficking of odorant receptors to the cell surface, together with the incorporation of intracellular signaling polypeptide sequences on the odorant receptor protein, can substantially improve the cell surface presentation of receptor proteins (Krautwurst et al., 1998; Saito et al., 2004; Shepard et al., 2013; Wu et al., 2012). Alternatively, the co-expression of heat-shock or beta-adrenergic receptors have also been reported to enhance cell surface expression of odorant receptor proteins (Hague et al., 2004; Matarazzo et al., 2005; Minic et al., 2005; Neuhaus et al., 2006). The additional co-expression of select G-protein signaling pathway proteins also increases the sensitivity of heterologous cell responses to target chemicals (Fukutani et al., 2015; Von Dannecker et al., 2005, 2006; Zhuang and Matsunami, 2007). Unlike odorant receptors, odorant binding proteins can be readily expressed in heterologous cell systems. Because odorant binding proteins are secreted, they are not appropriate for a cell-based sensor, but whether their co-expression with odorant receptors can improve the sensitivity of a heterologous cell-based sensor remains to be tested.

4. Summary and conclusions

Bioelectronic sensors strive to achieve the speed, sensitivity and selectivity of natural olfactory systems by incorporating either protein or cellular components of olfactory systems into the sensor design. Current progresses in biology using functions found in biological systems has led to the exploration and development of sensor platforms that provide engineering applications. Together, many studies have demonstrated that olfactory receptor proteins either solubilized with detergents or embedded in nanoscale structures can be coupled to a variety of different detectors in order to produce a functional bioelectronic sensor. Detectors using FET detectors, in particular, have shown rapid responses with high sensitivity. The limited stability of odorant receptor proteins on the sensor, however, is a considerable impediment to producing a field-ready device. Both odorant binding proteins and peptides capable of binding target chemicals potentially offer improved stability while maintaining rapid response times with high sensitivity when coupled to FET detectors. A rigorous comparison of the stability and lifetime between peptides, odorant binding proteins, and odorant receptor proteins on bioelectronic sensors, however, remains to be done. Moreover, continued exploration of odorant binding proteins and peptide sequences that can target specific chemicals is necessary to expand their ability to probe chemical space in similar detail as odorant receptor proteins.

In addition to protein and peptide components, several studies have collectively explored integrating detectors with animals, olfactory tissue, and cells as sensors. Devices implanted or affixed to animals in order to monitor the animal's olfactory neural activity are an interesting attempt to harness and co-opt the strengths of natural olfactory systems, but many technical challenges that require optimizing the biotic-abiotic gap remain to be addressed before such devices will become practical. Functional sensors can also be produced using resected mammalian olfactory tissue, but several technical challenges such as microneedle integration due to size, tissue damage, and accurate location also limit the practicality of these devices. Effective bioelectronic sensors have been reported using resected insect antennae, but isolated antennae remain functional for short periods of time, which restricts the practical application of the devices.

By contrast, live cell-based sensors provide longer-term monitoring capability, as long as culture conditions are maintained. They provide a direct communication response to a single detection event compared to the cascade events between cells in tissue samples. Moreover, genetic engineering methods enable most cells to express individual odorant receptors from any species limiting the issues associated with dissociated cells in order to screen chemical space with depth and selectivity. The target ligands for only a small fraction of animal odorant receptors have been identified (Mainland et al., 2015; Peterlin et al.,

2014), and continued efforts to deorphanize odorant receptors will expand the palette of receptors that can be used by cell-based receptors to probe the chemical environment. In addition, genetically engineered cells provide long-term stability by being able to regenerate odorant receptors and their accessory proteins as well as replicating to expand their total number. The ideal cell type and ideal species for odorant receptors has yet to be established, and it is likely that no one cell type or species of receptor is ideal for every application. Sensors with optical-detection systems have shown that cell-based sensor can also achieve high sensitivity when combined with photodetectors functioning in specific wavelength and intensity ranges. Optical-detection provides a non-invasive method of discriminating chemicals that does not involve direct physical contact with cultured cells and enhances sensing capabilities by maintaining cell viability. Nevertheless, in recent years multi-electrode arrays have several advantages over optical system for cell-based detection, including simplicity, convenience, and a relative low-cost to fabricate. To date, however, cell-based sensors with multi-electrode arrays have not shown the same sensitivity as optical detection systems which could be attributed to the required material properties that are optimal for cell growth and electrical conductivity. Continued genetic engineering of heterologous cell expression systems to increase the magnitude of field potential changes induced by target chemical binding to odorant receptors, however, may increase sensitivity of cell-based multi-electrode array sensors so that they are comparable to their optical counterparts. Together, these attributes over control and exclusive specificity make cell-based sensors attractive for developing sensitive and selective bioelectronic chemosensory devices that also have long monitoring lifetimes.

5. Future directions

The ideal bioelectronic sensor provides the speed, sensitivity, and selectivity of target chemical detection that are found in natural olfactory systems. Current chemical sensors are based on the physical properties of materials such as mass and dielectric properties and do not take into account the three-dimensional structure of specific molecules; a property that is required during recognition in odorant binding proteins and odorant receptor proteins. This functional component captures additional parameters that offers improved deconvolution of chemical species and may assist with probing a larger chemical space and chemical mixtures. Devices using FETs, optical, and MEA detectors have demonstrated that bioelectronic sensors can achieve high levels of sensitivity, but these devices are not likely to replace traditional analytical methods, such as mass spectrometry, especially in a laboratory setting. An advantage of bioelectronic chemosensors, however, is likely to be in their potential for enabling production of compact, lightweight, and portable devices that can benefit several industrial, environmental, military and security field applications. Current manufacturing processes can make small scale sensors with either FETs coated with proteins or peptides, or microfluidic devices with live cells that can be monitored by optical or MEA detectors. Although there are portable gas chromatograph/mass spectrometers already available, these devices do not have the same performance characteristics as benchtop instruments (Beck et al., 2015, 2016; Bednar et al., 2012; Zhang et al., 2016a). As bioelectronic sensor development continues to mature, an important future direction is to rigorously compare these sensors with traditional analytical methods, both benchtop and portable devices, in order to clearly define appropriate applications for artificial chemosensory devices. For many applications, efficient and accurate chemosensory analysis, particularly those outside of a laboratory setting, may be achieved with a combination of bioelectronic and traditional analytical methods.

A second important goal for future work is to establish the stability and operational lifetimes of biological material incorporated into bioelectronic sensors. Cells, proteins and peptides by themselves can undergo long term storage at −80 °C without any appreciable loss of functional activity, but once these materials are incorporated into a bioelectronic sensor their functional lifetime is less certain. As noted above, odorant binding proteins and peptides on bioelectronic sensors are generally considered to be less resistant to degradation than odorant receptor proteins, but this assertion remains to be demonstrated. Multiple studies with devices using nanoscale structures showed that these sensors can be stored at room temperature for several weeks to months with only modest reductions in performance (Goldsmith et al., 2011; Kwon et al., 2015; Lee et al., 2012b; Park et al., 2012b). By contrast, sensors using odorant receptors proteins solubilized with detergent can be stored and remain active for only about 5 days (Goldsmith et al., 2011). In addition to storage shelf-life, the operational lifetimes for continuously monitoring samples with sensors containing either proteins or peptides solubilized in detergent or part of nanoscale structures also remains to be to determined. Live cells on sensors can be cultured for many weeks or months, but the method by which these cells are genetically manipulated will alter the sensor operational lifetime. Transiently transfected cells will eventually degrade or lose transfected plasmids over the several days to weeks, but an effective lifetime for transiently transfected cells on bioelectronic sensors has yet to be reported. By contrast, stably transfected cell lines can in principle maintain their chemosensory function indefinitely, but whether the performance of these cells drift over the course of multiple passages and alter sensor performance is unknown.

Important challenges remain in the development of bioelectronic chemosensors, but this review has also highlighted the substantial progress that has been made in identifying suitable types of olfactory biological material and the detector systems that can achieve the goals of obtaining the speed, sensitivity, and selectivity of target chemical detection found in natural olfactory systems.

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