



Fluorescent Chemosensors for Ion and Molecule Recognition: The Next Chapter

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Over the past 30 years fluorescent chemosensors have evolved to incorporate many optical-based modalities and strategies. In this perspective we seek to highlight the current state of the art as well as provide our viewpoint on the most significant future challenges remaining in the area. To underscore current trends in the field and to facilitate understanding of the area, we provide the reader with appropriate contemporary examples. We then conclude with our thoughts on the most probable directions that chemosensor development will take in the not-too-distant future.

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INTRODUCTION

In 1993 Anthony W. Czarnik published a seminal book on “Fluorescent Chemosensors for Ion and Molecule Recognition”. (Czarnik, 1993). The book was a collection of chapters prepared by leaders in the area of Chemosensor research and provided insight into their research as well as their vision for the future directions of the field. Since that treatise was published, the area of molecular sensing has grown exponentially and the field has expanded to incorporate various other optical-based modalities and strategies e.g., chemiluminescence, photoacoustic/photothermal, and super-resolution imaging. Here we pay homage to that trailblazing book and provide this perspective as an addendum (the next chapter), highlighting what has been achieved (current state of the art), what will be realized soon, and the future challenges (Wu et al., 2017; Tian X. et al., 2021). In doing so, we have judiciously selected key examples that are then discussed to enable the reader to gain an overview of the current state of play in the field. We then conclude this perspective with our thoughts on what directions we expect the development of chemosensors to take over the next several years.

A fluorescent chemosensor was originally defined as “a compound of abiotic origin that complexes to an analyte reversibly with concomitant fluorescence signal transduction” (Czarnik, 1993). This term is now used interchangeably with the term “fluorescent probe”. However, for general understanding, a probe/chemosensor is defined as any compound that incorporates a binding/reactive site and a luminophore, as well as a mechanism for communication between these two sites. This ensures a measurable output is observed upon the probe’s interaction with the target analyte. During the early years, one of the first major hurdles encountered for fluorescent chemosensors was the design of suitable receptors (binding-based units) and locking groups (reaction-based units) (Wu et al., 2019; Chang et al., 2020) that would allow for the selective targeting of a specific species/analyte within a particular sensing environment (e.g., aqueous media). Within the initial reports, poor selectivity was commonly observed and the reported chemosensors were consequently often considered as “proof of concept”. However, these reports inspired researchers to join the effort to develop fluorescent chemosensors for a wide variety of

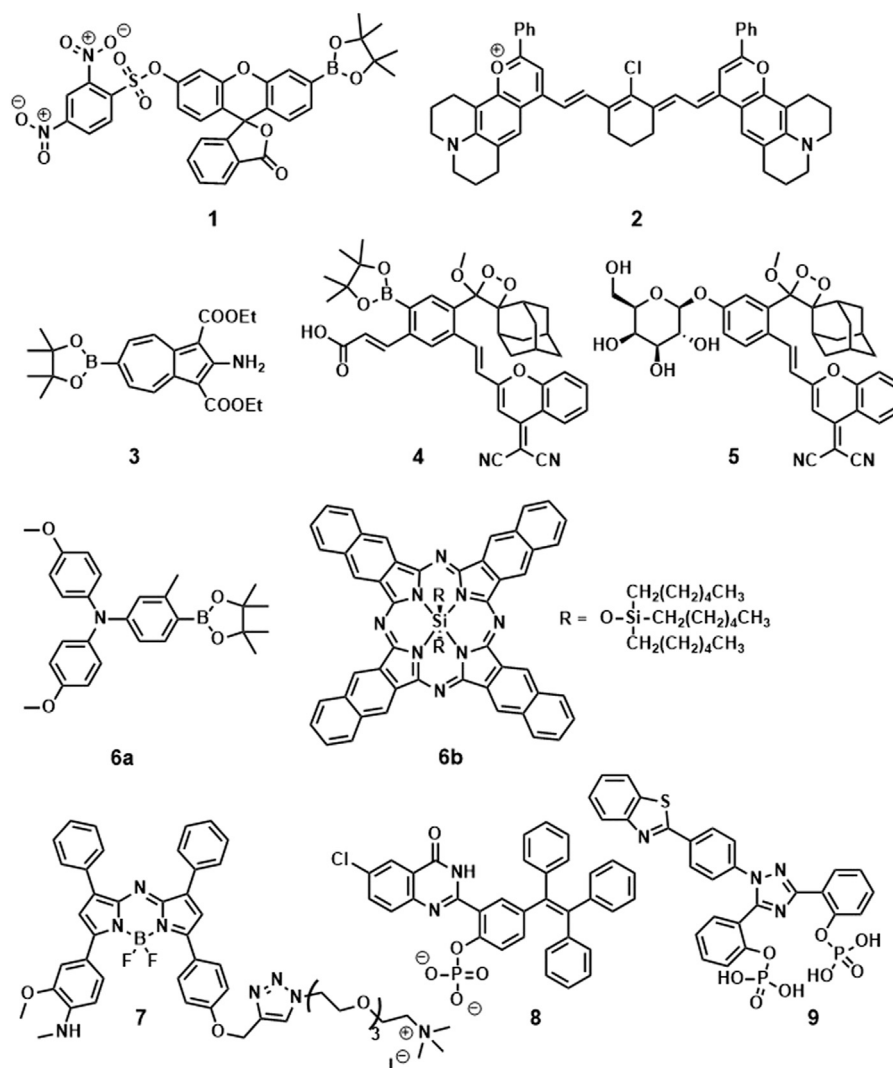


FIGURE 1 | Fluorescent chemosensors 1-9.

interdisciplinary and practical applications, of which we will now briefly highlight some of the most important trends. For detailed discussions on fluorescent chemosensor design and potential applications, we direct the reader to several excellent reviews (Wu et al., 2017; Sedgwick et al., 2018b; Wu et al., 2020; Feng et al., 2021; Han et al., 2021; Ma et al., 2021; Sedgwick et al., 2021a; Tian H. et al., 2021; Wu et al., 2021b).

Currently, researchers have access to a plethora of fluorescent chemosensors that allow for the detection of almost any disease-based biomarker *in vitro* and *in vivo*. These chemosensors are regarded as chemical tools that can be employed to enhance our understanding of various pathological processes through the targeted visualization of key steps and biological intermediates (Han et al., 2021). Moreover, several technological advancements have led to the incorporation of fluorescent chemosensors into various sensor technologies that can provide meaningful quality-of-life improvements for consumers. This includes the use of a fluorescent chemosensor as part of the Eversense device for the

real-time monitoring of blood glucose concentrations in diabetes sufferers (Mortellaro and DeHennis, 2014).

Fluorescent chemosensors have already shown great promise in real-world situations and applications, including but not limited to: the detection of environmental waste pollutants, detection of chemical warfare agents, fluorescence guided surgery, whole body diagnostic imaging, *in vivo* flow cytometry, and eHealth diagnostic devices (point of care (POC) testing) (Christodouleas et al., 2018; Jiao et al., 2020; Wei and Xunbin, 2021). In addition, colorimetric sensors have been established as potentially attractive sensing platforms due to their low cost as well as their capability to respond to stimuli with concurrent colour (UV-Vis) changes that could be discerned using the naked eye (López-Alled et al., 2017; Gwynne et al., 2021a; Gwynne et al., 2021b). This means colorimetric sensors are often seen as ideal diagnostic systems for non-expert users (Liu B. et al., 2020). However, in the context of this perspective, we have solely focused on fluorescent chemosensors. Nonetheless,

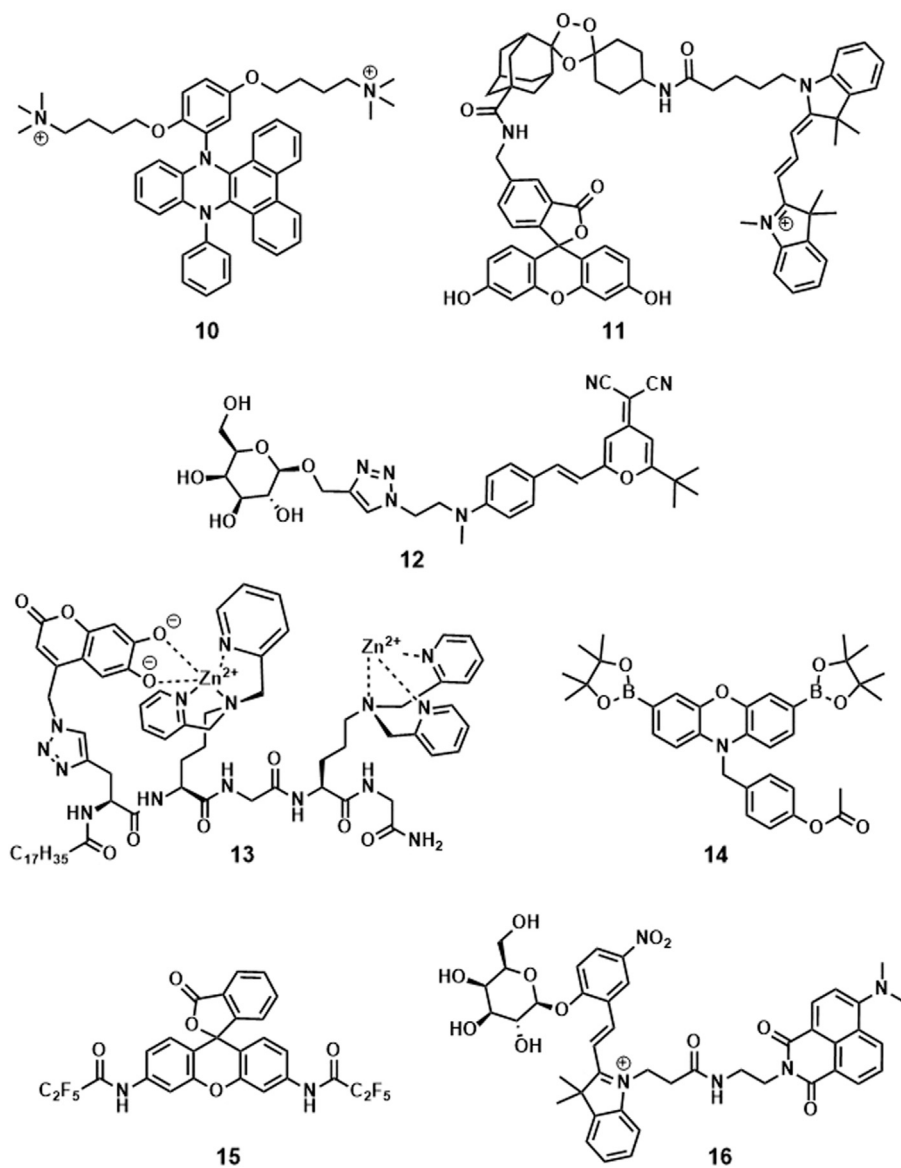


FIGURE 2 | Fluorescent chemosensors 10–16.

fluorescent systems often generate a colorimetric response in addition to a fluorescent output. This is due to the fact that a change in UV absorption (colour) is often coincidental with a change in fluorescence emission for any given chemosensor (Gwynne et al., 2019). Despite these advances, significant improvements to existing technologies needs to be made in order to address the current challenges in the field; these include: facilitating the generation of a measurable signal response by improving the signal to noise ratio, increasing the penetration depth of light to facilitate reliable detection of analytes within biological tissues or solid materials, the tuning of the output emission wavelength, as well as modulating the chemosensor solubility to provide optimized compatibility under various applications, and increasing analyte sensitivity and

selectivity to improve the precision of chemosensors for any desired target. Below we discuss the current state of the art and the various strategies that are being developed to address the current limitations of modern sensing technologies.

CURRENT STATE OF THE ART

Traditionally, efforts to improve analyte selectivity have focused on the synthetic modification of known receptor units. However, at this moment in time, alternative approaches towards achieving target specificity have garnered increasing interest. This in part has been driven by the existence of an extensive library of off the shelf receptor units which has blunted the need to establish

bespoke receptors with enhanced selectivity via synthetic optimization. Consequently, a particularly effective strategy using dual-locked probes (molecular logic gates) has recently emerged (Kolanowski et al., 2018; Wu et al., 2021a). Dual-locked systems are particularly attractive as they provide improved selectivity for the targeted system since they are only activated when at least two or more biomarkers that are associated with the targeted disease are present.

A particularly illustrative example of a dual locked system is our reported probe GSH-PF3 (1) (Sedgwick et al., 2018a; **Figure 1**). This system was designed to activate only when both the reactive oxygen species (ROS) (Wu et al., 2019; Yan et al., 2019) peroxyxynitrite and an important biological antioxidant glutathione (GSH) were present. The underlying design concept exploits the fact that GSH and other biological thiols play key roles in maintaining intracellular redox homeostasis, a process that is often altered within pathological settings (Kolanowski et al., 2018). Probe 1 demonstrated the ability to monitor the redox state of an appropriate cellular model and proved capable of visualizing the effect of a given therapeutic on the cellular redox environment (Sedgwick et al., 2018a). We anticipate that probe designs similar to 1 will allow the screening of drug candidates for a desired therapeutic outcome and thereby facilitate the more rapid identification of promising lead drug candidates. Expanding on this given example, we envision that numerous dual-locked strategies will continue to emerge as selectivity issues can be overcome by adding more than one “selectivity filter” (locking groups) to well-known sensing systems. In addition, these systems have exhibited excellent capability to overcome problems that are commonly associated with the use of multiple independent fluorescent probes during the investigation of relationships between more than one biological species/stimulus. This is of particular interest because the use of separate probes for each specific targeted stimulus can result in erroneous analytical data due to different permeability, distribution, and biocompatibility of each individual probe (Wu et al., 2021a).

The key challenge of reliably achieving a measurable output signal is particularly problematic for *in vivo* imaging due to high background noise and observed autofluorescence, poor penetration depths of light into tissue, as well as significant light scattering. Current strategies aimed at improving signal output include the development of NIR-II systems (absorb/emit: 1,000–1,350 nm), chemiluminescence, (Yang et al., 2020), afterglow luminescence, (Li and Pu, 2019), photoacoustic (PA), (Knox and Chan, 2018), and two photon (TP) methods (Wu et al., 2021b).

NIR-II fluorophores have attracted significant interest as they provide higher image resolution when compared to NIR-I dyes (700–950 nm) (Liu P. et al., 2020). As an example, the group of Sletten developed NIR-II flavylum polymethine dyes such as JuloFlav7 (2), which were demonstrated to achieve high resolution in animal and tissue-based imaging experiments (Cosco et al., 2020). Although significant promise has been observed for these systems as imaging agents, the poor solubility of these NIR-II systems often requires their incorporation into nanoparticle formulations. As such, further

research into overcoming these solubility issues is highly desirable. We would like to emphasize that aqueous solubility is an important design criterion for molecular sensors. This is due to the occurrence of unknown toxicities associated with nanoparticle formulations (De Jong and Borm, 2008) or toxicities associated with the use of organic media for colorimetric systems. We anticipate that the number of water-soluble NIR-II platforms will continue to increase over the coming years. Towards this end, an important strategy to overcome common solubility issues of chemosensors is the introduction of hydrophilic saccharide moieties either as appended motifs to enhance water-solubility or as a locking group to confer additional sensing properties via interaction with the desired target (Cho and Jung, 2015; Gim et al., 2019; Hazarika et al., 2020; Thomas et al., 2020).

In light of the current lack of NIR-II systems, TP imaging provides the ability to excite common fluorescent platforms with a “NIR-II-like” excitation source. Due to this capability, TP is increasingly becoming ubiquitous, however, the development of TP systems is being slowed by the limited availability of suitable TP dyes and as a result there is a lack of appropriate small molecule-based fluorescent chemosensor systems currently available. A recent example of a novel TP system was reported by the group of Lewis using an azulene-based scaffold AzuFluor 483-Bpin (3). Significantly, these AzuFluors present themselves as amenable core units for the development of TP probes (Murfin et al., 2019).

An attractive alternative for improving light penetration is the elimination of the requirement for a light excitation source by using chemiluminescent probes that emit light only when initiated by a suitable chemical reaction. In contrast to conventional fluorescence imaging, the removal of the excitation light source significantly minimizes the issues of background signals and thereby provides a high signal to noise ratio as was shown both *in vitro* and *in vivo*. Significant efforts from the Shabat group (Hananya and Shabat, 2017; Gnaïm et al., 2018; Gnaïm and Shabat, 2019) have demonstrated that the core dioxetane chemiluminescent structure can be modified to function with any appropriate locking group, with proven examples including boronate ester 4 for ROS detection and a galactose unit responsive to β -galactosidase 5. Through their endeavours, an attractive NIR-chemiluminescent scaffold was developed. The reaction of NIR-chemiluminescent probes 4 and 5 with their respective targets led to the emission of NIR light that was shown suitable for *in vivo* imaging (Green et al., 2017).

The group of Pu have explored the use of organic-based afterglow imaging in an effort to enable improved animal and tissue imaging (Dang et al., 2020). Afterglow imaging provides enhanced sensitivity, when compared with traditional methods, as the long-lived emissive species is easily detectable over the comparatively short-lived background auto fluorescence from endogenous biological molecules. This can be seen as analogous to time-gated luminescence with the use of inorganic lanthanide systems (Hananya and Shabat, 2017; Gnaïm et al., 2018; Gnaïm and Shabat, 2019; Bodman and Butler, 2021). Many organic molecules with room-temperature

phosphorescence (RTP) can be seen as suitable afterglow agents. However, most RTP luminogens only emit visible light, which provides shallow tissue penetration depth, thereby constraining possible *in vivo* applications. To overcome this limitation, Pu has developed an RTP nanoprobe with NIR emission for *in vivo* afterglow imaging. The nanoparticle-based probe was constructed using an amphiphilic triblock copolymer (F127), mTPA (6a) as the phosphorescence generator, and an NIR-fluorescent dye NCBS (6b) as the energy acceptor providing redshifted phosphorescent emission at 780 nm (Dang et al., 2020). This phenomenon is known as room-temperature phosphorescence resonance energy transfer (RT-PRET). These redshifted afterglow luminescence probes exhibited minimal background interference and thereby enabled lymph node imaging of live mice. As such, these probes provide excellent insight as a starting point for the construction of other organic-based NIR afterglow imaging agents using RT-PRET.

Another approach capable of achieving enhanced tissue penetration depth is photoacoustic (PA) imaging, where optical excitation is coupled with acoustic detection (light in, sound out), thereby enabling high resolution and deep tissue imaging at centimetre depths (Knox and Chan, 2018; Cheng et al., 2020; Ren et al., 2020; Chen et al., 2021; Lucero et al., 2021). PA probes that can be activated by specific biological species are of particular interest as they have the potential to complement other clinically used diagnostic systems (i.e., Ultrasound) for disease diagnosis. Within this arena, the Chan group has developed nitric oxide (NO) triggered probes for acoustogenic imaging (Lucero et al., 2021). For example APNO-5 (7), could be used for the ratiometric imaging of endogenous NO *in vivo* (BALB/c mice) in a murine lipopolysaccharide-induced inflammation model (Reinhardt et al., 2018).

As seen with the above examples, the response of a chemosensor can be enhanced through the response mechanism. One area that has attracted significant interest over the past decades is Aggregation Induced Emission (AIE), a term which was coined in 2001 by the group of Tang (Luo et al., 2001). Unlike the majority of conventional dyes that undergo aggregation-caused quenching (ACQ), AIE luminogens (AIEgens) show weak or negligible emission in dilute solution but emit intensely in an aggregated state/under conditions of restricted motion (Song et al., 2020). Sensors based on AIE exhibit certain advantages over traditional fluorophores, in fact, the aggregative nature means that the sensor accumulates at a particular location and allows accurate positional biomarker detection. This is particularly relevant because commonly used fluorescent probes/chemosensors are subject to diffusion and can consequently be prone to provide false information on a biomarker's true location.

A noteworthy example is the AIE probe for the monitoring of alkaline phosphatase (ALP) (Sedgwick et al., 2018b) enzyme activity in cells developed by the Zhang group. The precipitation of the unmasked excited state intramolecular proton transfer (ESIPT)-fluorophore HTPQA (8) occurred upon exposure to ALP, which facilitated diffusion resistant monitoring of ALP activity in osteosarcoma cells and tissue (Liu et al., 2017). Another, ALP responsive AIE system,

ExPhos (9), was reported by the Sessler group (Sedgwick et al., 2021b). This system was based on deferasirox (ExJade) an FDA-approved iron chelator, which is used to treat patients with iron overload. Owing to the pathological role of iron, this system enabled the tracking and detection of disease-based biomarkers while providing inherent therapeutic properties (Steinbrueck et al., 2021; Steinbrueck et al., 2020).

Organic fluorophores with dual-emission and large Stokes shifts are desired for many applications including biological imaging. Within this arena, a new luminescence mechanism termed vibration-induced emission (VIE), which possess these desired properties, has recently been established. The VIE mechanism was coined because different emissions are observed from the planar (long-wavelength) and the bent forms (short-wavelength) of the V-shaped *N,N'*-disubstituted-dihydrobenzo [a,c]phenazines (DHPs) (Zhang et al., 2020).

The group of Tian developed probe VN (10) as a VIE system to detect amyloid β (A β) fibrils which are associated with the development of the neurodegenerative disorder Alzheimer's disease (AD) (Dou et al., 2017; **Figure 2**). In fact, probe 10 could be used to detect A β in solution. In the absence of A β fibrils 10 exhibited orange/red emission at 600 nm, however, upon the addition of A β 42 peptide, the blue emission at 470 nm increased. The selective enhancement of blue emission was attributed to binding of 10 with A β 42, limiting the vibration of the excited state. Significantly, 10 could be used to image A β plaques and illustrates the potential of VIE based probes for biological imaging.

Another important approach for the improvement of the output profile of a chemosensor is the use of Förster resonance energy transfer (FRET). With FRET based systems, the apparent Stokes shift of the chemosensor is extended through an energy transfer from the donor to the acceptor, resulting in fluorescence output from the acceptor at a longer wavelength (Wu et al., 2020). A representative FRET system FIP-1 (11) was reported by the Chang group. This iron responsive probe, featuring a 5-aminomethyl fluorescein (5-AMF) donor motif and a cyanine 3 (Cy3) acceptor as the FRET pair, was used for visualising labile iron pools in living systems during ferroptosis therefore allowing for the monitoring of iron signalling in living systems (Aron et al., 2016).

Obviously, combining all these aspects into one molecular species can be a daunting task, that is why ensemble-based approaches towards such systems should be explored. This simple strategy requires the knowledge of host-guest chemistry, the hallmark of the field of supramolecular chemistry. The simplicity of combining molecular sensors with materials/host platforms improves their overall targeting ability for *in vivo* applications, minimizes synthetic effort, and provides a potential route to theranostic applications (incorporation of a therapeutic into the diagnostic supramolecular ensemble) (Hu et al., 2020).

Extensive efforts from the group of He have led to the development of receptor-targeting fluorescence imaging and theranostic systems using graphene oxide (GO) based supramolecular glycoconjugates. (Ji et al., 2015; Dou et al., 2021). Many disease-related processes involve glycoligand-

receptor interactions. GO based supramolecular fluorescent glycoconjugates are constructed using a hydrophobic fluorophore with linked glycoligands. Owing to their design, significantly enhanced cellular and tissue imaging ability of the fluorescent glycoprobe is observed due to glycoligand clustering enhancing interactions with the cell surface receptors. An example is DK1 (12) where GO enhanced clustering to strengthen the interactions between the cancer cell receptors and the glycoprobe (galactose) was observed (Ji et al., 2015). In addition, the composite could be further converted into a theranostic system by co-assembling the glycoprobe and an anticancer drug onto the GO surface. As such, a theranostic supramolecular glycoconjugate could be developed that was able to both image and kill liver cancer cells that overexpress the glycoprotein receptor.

To avoid extensive synthetic endeavours, the receptor and fluorophore do not have to be chemically linked since displacement-based systems remove such a need (Sedgwick et al., 2021a). A particularly interesting example of an intramolecular indicator displacement (IID) system for cell surface phosphatidylserine (PS) has been developed by the group of Jolliffe (Zwicker et al., 2019). With the system P-IID (13), a coumarin indicator is released from the intramolecularly linked receptor in the presence of cell surface PS, resulting in fluorescence “turn-on”. Using this IID system in combination with confocal laser scanning microscopy allowed for the successful monitoring of a key cellular process that is activated during apoptosis in live cells.

As stated previously, the aqueous solubility of imaging systems is often a key challenge and this issue is seen frequently with cyanine and porphyrin-based systems, which are prone to undergo aggregation (Pasternack et al., 2000). As such, nanoparticle formulation is an essential approach to enhance solubility. Within this field, protein-based hybridization is an appealing strategy that exhibits ideal biocompatibility. A prominent example of this approach exploits the host-guest chemistry of human serum albumin (HSA) with highly lipophilic molecules such as cell impermeable and insoluble fluorescent probes (Sheng et al., 2014; Han et al., 2020; Jia et al., 2020; Sen et al., 2020; Sen et al., 2021).

The Pinkment-OAc (14)/HSA supramolecular hybrid was used *in vitro* to detect peroxynitrite (ONOO⁻) with enhanced response (Han et al., 2020). Hybrid 14/HSA was used to monitor ONOO⁻ in RAW 264.7 macrophages and HeLa cancer cells. Importantly, the prepared hybrid exhibited good cell permeability and facilitated the detection of ONOO⁻ *in vivo* in mice. Pinkment-OAc alone was shown to be ineffective for both cellular and *in vivo* imaging, which cemented the significance of protein-based hybridization as a strategy for the enhancement of biocompatibility.

In a separate study, this strategy was used as an effective means to detect enzyme activity. ACS-HNE (15) was used for the selective detection of neutrophil elastase (NE) in RAW 264.7 cells (Jia et al., 2020). Probe 15 exhibited excellent selectivity toward elastase over other biological analytes and enzymes. Using this approach, limitations that arose from the comparatively poor solubility and limited cell permeability of 15 alone could be overcome using the 15/HSA supramolecular hybrid.

Super-resolution-based technologies have revolutionized fluorescence imaging by circumventing the diffraction limit of light and thereby enabling visualization of structures with nanoscale accuracy within a cellular environment (Carvalho et al., 2021). Amongst the super-resolution techniques available we would like to specifically highlight Stochastic Optical Reconstruction Microscopy (STORM) (Rust et al., 2006; Samanta et al., 2019) and photoactivated localization microscopy (PALM) (Betzig et al., 2006) as these techniques use probes with switchable fluorescence emission profiles (photoblinking).

He and co-workers developed a β -galactosidase (β -Gal)-responsive photochromic fluorophore NpG (16), that was able to form an HSA supramolecular hybrid (Chai et al., 2020). 16@HSA hybrid formation enhanced the fluorescence emission (520 nm) and facilitated the visualization of the spiropyran's fluorescence output in aqueous media. Subsequent cleavage of the galactose unit by β -Gal of the 16@HSA hybrid resulted in the formation of NpM@HSA, generating an enhanced red fluorescence emission (620 nm). The formed merocyanine unit experiences photoisomerization (merocyanine \leftrightarrow spiropyran), thereby enabling STORM imaging while displaying excellent photostability/reversibility with minimal phototoxicity. Using STORM and 16@HSA, the subcellular distribution of β -Gal activity between different cell lines could be determined with nanoscale precision.

Given the success of the supramolecular hybrid strategy using HSA with these probes, we anticipate that HSA/fluorescent probe hybrids are one of the best methods to overcome solubility issues associated with hydrophobic fluorescent imaging agents that are designed to detect disease related biomarkers and as such we anticipate that this simple supramolecular approach will be widely adopted by the sensing and imaging community.

WHERE NEXT?

Due to the continuous need for new and effective therapeutics, the development of chemical tools that can be used to evaluate various biological pathways *in vitro* and *in vivo* is more important than ever. Efforts in the sensing community will continue to focus on the development of chemosensors in the endeavour to uncover new biological mechanisms and to identify the role of various biological species. Such chemosensor-based toolkits are crucial to illuminate the origins and progression of disease states. While the development of completely new receptor motifs is rare, we anticipate that fluorescent chemosensors that incorporate novel receptor units will continue to emerge for the investigation of fresh biological targets. One such an example is the development of a thioredoxin reductase selective fluorescent probe developed by Fang and co-workers (Zhang et al., 2014). Significantly, this biomarker is a key target for gold (Au)-based chemotherapeutics and it is anticipated that this tool could be crucial in assisting the development of these attractive drug candidates for clinical use (Yeo et al., 2018). Over the coming years, we expect that similar examples of chemical tools for new biological targets will continue to be developed. However, the

archetypal challenges associated with chemosensor development will need to be successfully addressed in parallel during their development. Those challenges include but are not limited to: aqueous solubility, analyte selectivity, biocompatibility, and laborious time-intensive synthetic optimization.

Due to the complexity of cellular processes, we anticipate that dual-locked systems will continue to be developed and emerge in the literature. This is because such tools can help to improve the fundamental understanding of key biological pathways or help to identify currently unknown relationships between biomarkers that contribute to a specific disease state. Owing to the high signal-to-noise ratio of chemiluminescent probes, we are particularly hopeful that such systems will continue to be developed to help shed light on these difficult problems. Currently, chemiluminescence is a relatively unexplored area; however, the seminal research by the Shabat group has inspired other groups to focus on these potentially game changing systems (Hananya et al., 2016). As a result, we anticipate that new chemiluminescence scaffolds and strategies will continue to emerge over the next several years. However, as with fluorescence-based systems, the major challenge remains the development of aqueous soluble and biocompatible systems.

With regards to *in vivo* applications, we anticipate that NIR-II chemosensors will continue to be developed owing to their enhanced tissue penetration and higher image resolution with respect to systems that depend on visible light (Li et al., 2020). Owing to the “light-in, sound out” approach of PA imaging, we anticipate that PA based chemosensors will remain one of the “hottest” topics in the chemosensor area and will continue to evolve as PA technology improves. The strong interest in PA systems is driven by the potential clinical utility of such PA systems (Attia et al., 2019). Again, the major challenge to PA chemosensor development is the design of systems that avoid both synthetic and solubility issues. Due to the use of a pulsed laser, photostability of current PA systems is a common problem. We have confidence that if current challenges and limitations of NIR-II systems can be overcome, unprecedented opportunities for the investigation of biological process *in vivo* will be possible that have thus far only been realized *in vitro*. Such advancements would allow researchers to solve unknown biological problems and thereby unlock stimulating new biological questions. Moreover, with the recent developments in the area of personalised medicine, (Goetz and Schork, 2018), we anticipate that NIR-II systems will enable a better understanding and hence an improved ability to adjust to differences between individual patients during specific treatment plans. As we write this perspective, very few NIR-II fluorescent and PA examples exist, which we presume to be the result of synthetic challenges coupled with known solubility issues. Therefore, both NIR-II and PA based systems represent a new Frontier for development that is waiting to be explored by a new generation of chemosensor pioneers.

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Within this perspective we have on the whole limited our discussion to systems that selectively detect biological analytes and function as chemosensors, however, many systems that interact with light can also be used for photodynamic therapy (PDT) and photothermal therapy (PTT). These systems are often plagued with off-target toxicities or result in undefined/large tumour margins resulting in unwanted phototoxicities. In recent years, efforts from several research groups have focused on the development of combined and activatable chemosensors with PDT/PTT properties to overcome these challenges. A particularly nice example is the aminopeptidase N responsive PDT agent by Peng and co-workers, which enables the simultaneous detection of APN in tumors and subsequent treatment (Zhou et al., 2020). Given that this approach is still embryonic in nature, we expect that numerous examples will continue to emerge as the area develops.

With reference to the original Czarnik collection, the field of chemosensors has evolved considerably over the past 30 years, and we foresee that the area will continue to develop to meet the ever-changing medicinal needs of individuals over the next 30 years. While it is impossible to predict what will emerge and develop in the future, we are convinced that the field of chemosensors will continue to grow and inspire new generations of researchers who will contribute towards the ongoing efforts and provide fresh and ingenious solutions to the current bottlenecks in chemosensor synthesis, biocompatibility, and solubility.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

TDJ and ACS conceived the perspective and K-CY and AS provided support with referencing and figure preparation.

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