INTRODUCTION Porphyrins and their general derivatives (porphyrinoids) are pyrrole containing macrocycles with elaborate pi-conjugation pathways that result in vibrant colors observable by the naked eye.The scheme also shows some subsequent biomedical and light?harvesting applications that can be achieved.Type II reactions function by conversion of the ground-state triplet oxygen (3 O2) to its reactive singlet state (1 O2). The other photosensitizer-based therapeutic modalities are newer technologies but are also promising. For example, the purpose of PACT is to treat infections with the ability to also overcome multidrug resistance. In terms of photosensitizers being investigated for these biomedical applications, porphyrinoids have been used the most owing to their unique properties. These include their ability to efficiently absorb visible red light (high extinction coefficients), their long T1 state lifetimes (providing time to form ROS species and in particular generation of 1 O2 with high yield), facile synthetic functionalization, structural diversity, and minimal dark toxicity (Kou et al., 2017; Lin et al., 2020).In addition to classical photophysical and photochemical research (such as electron transfer, solar cells, and artificial light-harvesting) (Hsiao et al., 1996; Aratani et al., 2009; Beletskaya et al., 2009; Tanaka and Osuka, 2015; Zhang and Ying, 2015), researchers have focused on promising biomedical applications where porphyrins serve as photosensitizers (O'Connor et al., 2009) in e.g., photodynamic therapy (PDT), photodynamic antimicrobial chemotherapy (PACT) (Liu et al., 2012; Dosselli et al., 2013; Pereira et al., 2014; Meng et al., 2015; Yuan et al., 2017), photothermal therapy (PTT) (Zou et al., 2017), and as chromophores for biological imaging (Sibrian-Vazquez et al., 2005; Giuntini et al., 2011; Dondi et al., 2016).Further, porphyrin-biomacromolecule conjugation, in tandem with synthetic manipulation of the porphyrin peripheral substituents and metalation state, can result in modulation of key porphyrin features needed for biomedical applications (e.g., multiple absorption bands, emission near the far-red region of the visible electromagnetic spectrum, good photostability, and low dark toxicity).These biomolecules are highly complex and contain multiple reactive functional groups and thus the methods used to selectively attach porphyrins to targeted sites on these biomacromolecules are also instructive for the general tethering of functional entities onto such biomolecules.In many of the photosensitizer-based biomedical applications, the typically hydrophobic porphyrinoids need to be 1) solubilized in water, 2) inhibited from aggregation, and 3) also are required to localize selectively in target cells and tissue (Hamblin and Mroz, 2008).In addition to utilizing naturally occurring reactive groups (e.g., amines and thiols), this manuscript will also discuss key bioorthogonal reactions that can be employed to facilitate porphyrin-biomacromolecule conjugation (Table 1).More than mere aesthetics, biology harnesses the unique photophysical and chemical properties of porphyrinoids to drive immensely important processes including photosynthesis, blood oxygenation, and substrate oxidation.On the other hand, PTT facilitates tumor cell death by a thermal ablation mechanism, where the photosensitizer (i.e., photothermal agent) is designed to produce heat energy upon light irradiation (instead of fluorescence emission and production of singlet oxygen species).The bioorthogonal reactions are judiciously designed, with customized reactive partners, to be highly selective and do not readily react with other biological/chemical entities present in living cells/systems under physiological conditions (ambient temperature and pressure, neutral pH, and aqueous media).This review will focus on the novel methods developed and key applications that are uncovered by covalently linking porphyrinoids to three main

classes of biomacromolecules: oligonucleotides (ONs), peptides and antibodies. Further, bioorthogonal reactions, in general, should meet the criteria of kinetic-, thermodynamic-, and metabolic-stability, without generating materials toxic to living systems (Lang and Chin, 2014; Devaraj, 2018).Scheme 1 illustrates some common functionalities (naturally present or synthetically modified) in porphyrinoids as well as ONs and peptides that have been utilized to generate porphyrin-biomacromolecule conjugates. From the abovementioned therapeutic modalities, PDT has been the most investigated and is used in the clinic to treat various cancers (including tumors of the esophagus, skin, head, neck, bladder, and lung).This modality follows the same principle of PDT in terms of production of ROS that are lethal to microbial pathogens (Meng et al., 2015).Importantly, these photothermal agents can also have applications as contrast agents for photoacoustic imaging (which has deeper penetration in biological tissues) (Zou et al., 2017).Indeed, the green colors in plants are due to the absorption capacity of the porphyrinoid cholorophyll A and its degradation, in the Fall, leads to other chromophores becoming more visible as orange and brown hues.Subsequent irradiation of low-energy, tissue penetrating, light of appropriate wavelength (typically red light) leads to the activation of the photosensitizer from its ground state (S0) to the first excited singlet state (S1).Type I reactions involve hydrogen or electron transfer between the T1 photosensitizer and biomolecules creating reactive radicals and other ROS.In these processes, the pophyrinoid cores interact with and are properly sequestered by, protein macromolecules that tune the activity of the macrocycles.In this method, a photosensitizer first localizes in specific tumor tissue after intravenous injection.Population of the T1 state can lead to two different pathways of creating reactive oxygen species (ROS) necessary to initiate cell death.The S1 state can release its energy by various pathways including emission of light as fluorescence or radiation-less transition.For PDT applications, an intersystem crossing takes place, transferring energy from the S1 state to the longer lived triplet state (T1).Singlet oxygen leads to tissue destruction and apoptosis (O'Connor et al., 2009).The following sections will expound on these conjugation chemistries and applications.Non-covalent interactions of porphyrinoids with biomacromolecules is also an area of active research.The judicious conjugation of porphyrins to biomacromolecules can address these issues.Also, it should be noted that the focus herein will be on covalent tethering.For example, porphyrinoids binding to peptides and proteins have beThe reason for the adoption of PDT in the clinic is because it is generally safe and .has few side effects