Abstract. Carcinogenesis occurs via mutation of critical genes conferring enhanced survival and protection to the ensuing tissue. Current therapies in use garner success due to their specificity for certain intracellular targets. This particularity, whilst beneficial in identifying tumorigenic from normal tissue states, is limited by the variations in geno/phenotypic profiles displayed between tumor tissue types. As such, tissue-specific therapeutic combinations and adjuvants are often required for adequate effect, but present symptomatic complications and occasionally generate secondary carcinogenesis displaying multi-drug resistance (MDR). An accumulation of research over the recent years has suggested that photodynamic therapy (PDT) with macrocycle photosensitizers are a promising alternative. Its administration method and toxicity mechanism present attractive features for potentially overcoming MDR cancers of multiple tissue origins with limited symptomatic onsets. Herein, we highlight these potentials as referenced against existing therapeutics and consider the impact of macrocycle-PDT for broad spectrum application regardless of tumorigenic resistance profiles.

1. Tissue Homeostasis and Cancer Development

Homeostasis within the body is maintained through strict regulation of cellular lifespan. The decision of a cell to grow, divide, repair or die lies within the regulatory function of interacting pathways that govern the cell cycle, while a close interaction between growing, quiescent and dying cells ensures overall cell turnover which is tightly regulated so that tissue mass is maintained at a near steady-state. In cancer, this balance between proliferation and suicide is disturbed. Cancer can therefore be described as the unrestricted tissue expansion due to uncontrolled cell growth (1). From a medical standpoint, this confers nutrient and oxygen depletion on the body resulting in overwhelming physical burden and death.

Biochemically, cells experience daily genetic lesions as a consequence of environmental exposure, normal ‘wear and tear’, errors during new DNA synthesis, and mitosis which are continuously identified at cell-cycle checkpoints and successfully repaired. Genetic mutations arise when these lesions are misrepaired during sequence patch-up or nucleotide excision. Known as point-mutations these include nucleotide deletions, -insertions, -duplications and -rearrangements. Additionally, larger chromosomal alterations encompass amplifications of fragments resulting in multiple gene copies and translocations or rearrangements (gene relocation to another promoter leading to mis-regulated expression) which occur during cell division (2, 3). The position, amount and degree of mutations determine the cellular potential to bypass selection barriers and if so, are carried over to daughter clones. This incurs genetic instability at the nucleotide sequence and/or chromosome, leading to a gradual buildup of multiple mutations (mutational set) and an eventually altered genotype (4). Problems arise when these mutations confer cellular growth, differentiation and survival benefits (4, 5). Termed carcinogenesis, this is identified from other mutational sets by the two key classes of regulatory genes affected;

1. Proto-oncogenes: highly controlled expression of growth factors, their receptors, signal transducers, and transcription factors that collectively promote cell proliferation. Carcinogenesis is generated by over-activated forms (i.e. oncogenes) which flood critical regulatory pathways with a constitutive supply of proliferative signals.
Oncogenes are particularly sensitive to changes in expression rate as their allele pairs exert genetic dominance, i.e. mutation of one confers enhanced expression of the pair (1, 5).

2. Tumor-suppressor genes (TSGs): code for inhibitory products preventing cell proliferation via cell cycle arrest for DNA repair or initiating cell suicide. During carcinogenesis, these are inhibited via inherited mutations of the original genes, epigenetic mechanisms of histone modification and DNA methylation or at the product level via protein interference. The allele pairs are recessive, thereby requiring both genes to be mutated before loss of function occurs (1, 5, 6).

Through these genes, a tissue state converts from a mortal to an immortal (neoplastic) phenotype. This requires a monumental shift in the systemic nature of cellular processes and therefore extends far beyond the pathways directly associated with the mutated gene products. Multiple pathways are branched and interconnected in an intensely complicated way such that, changes in the rate of one confers differential influence over many resulting in marginally identical outcomes. Termed the “Hallmarks of Cancer”, these phenotypic characteristics act as a guide in distinguishing carcinogenesis (extensively detailed in 1, 6-11).

2. Cancer Genotype/Phenotype Complexity and the route of Therapeutic Resistance

Carcinogenesis produces a carcinoma and the generation of a tissue mass comprised of carcinogenic cells is termed tumorigenesis resulting in tumor. Whilst the “hallmarks” are defining end-point features of all static tumor masses, it is the subtle disparities between them which contribute to the complexity of their responses to therapeutics. Therefore, carcinomas can be categorized beyond these “hallmarks” due to histological origin and subsequent genotypic-derived behavioural characteristics (8, 9, 11).

2.1. Classification by Histological Origin. Note that for the purposes of this review, the following classification encompasses static cancers only and omits those of the blood and lymph systems:

1) Squamous Cell Carcinoma (SCC/SqCC): Squamous cells comprise epithelial tissue forming the main part of skin epidermis and internal lining of most cavities. As such SCC encompasses a wide range of tissues including; skin, oral and nasal cavity, digestive tract, lung, bladder, prostate and cervix. Despite their numerous sources, SCC exhibits histological distinctions of atypical shapes, disrupted cytoplasmic keratin/tonofibril characteristics, and tubular patterns. These cancers generally display low risk for metastasis and good survival prognoses (12-14).

2) Basal Cell Carcinoma (BCC): Carcinogenesis of epidermal cells other than squamous, BCC includes majority of skin cancers. Rarely metastatic but invasive to surrounding tissues it is classified based on its dermal location and required therapeutic approach into, superficial, infiltrative and nodular. These three groups are further classified into a wide range of subtypes depending on the body part location and pigmentation ratios (14-17).

3) Adenocarcinoma: Carcinogenesis of heterogeneous epithelial tissue which display exocrine and/or endocrine characteristics but are not necessarily of primary glandular function. Divided into adenoma (benign) and adenocarcinoma (malignant), glandular tissues of the latter are referred to as neuroendocrine tumors and include skin, breast, thyroid, pituitary, pancreas, gall bladder, prostate, ovaries and adrenal glands. Tissues exhibiting glandular traits include lung, oesophagus, liver, kidney, middle and lower digestive tract and uterus, amongst others. The heterogeneous source of adenocarcinomas imparts very few general characteristics for discrimination and may be differentiated to closely resemble their tissue type or not. However, all display aggressive, acute onsets with highly metastatic tendencies resulting in therapeutic complications and poor prognoses (18-21).

2.2. Hetero-cellular Populations. Histological complexity of cancer is further compounded by hetero-cellular compositions and tissue-genotype susceptibilities (8, 11). Externally influenced by the microenvironment of neighboring tissues, tumors are characterized as highly complex “organs” consisting of more than one carcinogenic population. Presence of additional differentiated cell types, each contributing to sustained survival of the tumor mass include cancer stem cells, endothelial cells, specialized mesenchymal cells (pericytes), mesenchymal stem and progenitor cells, immune inflammatory cells, and cancer associated fibroblasts. Understanding its phenotypic nature therefore also requires identifying the influences these impart on the tumorigenic system (6, 8, 9, 11).

2.3. Tissue-specific Genotypic Variations. Tissue types, e.g. lung etc. are all distinguished by unique geno- and phenotypic profiles for cellular function driven by the particular role that tissue needs to fulfill for the larger body system (22). The random combinations of multiple key mutations has been reported to generate a plethora of distinctive cancer genotypes per tissue type with little degree of prediction (4, 5). Therefore, whilst holistically mediated by universal mutations to trademark critical genes, carcinogenesis also demonstrates additional tissue-specific geno- and phenotypic variations that together culminate in the same classic hallmarks observed (22, 23). Over the years, medical advances have identified over 100 distinct cancer tissue types and subtypes for both static tumor masses and monocytic mobile populations (e.g. leukemia and lymphoma). Different
Table I. Tissue-specific deficiencies and surfeits in four cancer genotypic/phenotypic profiles. These highlight some genetic defects/augmentations commonly associated with a particular cancer tissue type.

<table>
<thead>
<tr>
<th>Genotype deficiencies</th>
<th>Phenotype deficiencies</th>
<th>Consequence on survival/cell death</th>
<th>Ref.</th>
<th>Genotype Surfeits</th>
<th>Phenotype Surfeits</th>
<th>Consequence on survival/cell death</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 mutation</td>
<td>Loss of tumor-suppressor protein BRCA1</td>
<td>Un-regulated cell growth, impaired DNA repair</td>
<td>176</td>
<td>AURKA Aurora polymorphism</td>
<td>MDM2 up-regulation</td>
<td>Increased cell survival, metastasis and apoptosis inhibition</td>
<td>177</td>
</tr>
<tr>
<td>BRCA2 mutation</td>
<td>Impaired function of tumor-suppressor complex BRCA2</td>
<td>Reduced genomic stability via loss of gene mutation repair</td>
<td>177</td>
<td>HER2 amplification</td>
<td>HER2 and HER3 GFR overexpression</td>
<td>Activate survival/ proliferation gene transcription</td>
<td>188</td>
</tr>
<tr>
<td>CASP3 mutation</td>
<td>Loss of Caspase-3 enzyme</td>
<td>Impaired execution of apoptosis</td>
<td>178</td>
<td>ESRI mutation</td>
<td>Overexpression of ER (oestrogen receptor)</td>
<td>Stimulated proliferation and DNA replication</td>
<td>188</td>
</tr>
<tr>
<td>Apaf-1 mutation</td>
<td>Loss of Apaf-1 protein for apoptosome formation</td>
<td>Impaired mediation of p53-dependent apoptosis</td>
<td>179</td>
<td>BRAF mutation (V600)</td>
<td>ERK hyperactivation</td>
<td>Hyperproliferation and enhanced survival</td>
<td>103</td>
</tr>
<tr>
<td>PPP6C mutation (R264C)</td>
<td>Dysfunctional PP6 protein component of phosphatase complex</td>
<td>Increased cell cycle and mitotic rates</td>
<td>180</td>
<td>MDM2 up-regulation</td>
<td>Increased inactivation of p53 by E3 Ligase murine double minute-2</td>
<td>Silenced p53 induced senescence and cell death</td>
<td>189</td>
</tr>
<tr>
<td>Fas (CD95) down-regulation</td>
<td>Loss of Fas surface receptor expression</td>
<td>Impaired receptor-mediated apoptosis for pro-survival</td>
<td>181</td>
<td>TERT promoter mutation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMP3 silencing</td>
<td>Reduced, metallo-proteinase inhibitor 3 function</td>
<td>Enhanced angiogenesis and metastasis</td>
<td>182</td>
<td>KRAS mutation</td>
<td>KRAS protein activation</td>
<td>Increased signal transduction and drug resistance</td>
<td>191</td>
</tr>
<tr>
<td>HOXA1</td>
<td>Low Homeobox protein Hox-A1 expression/activity</td>
<td>Inhibited cell cycle arrest and apoptosis, enhanced chemoresistance</td>
<td>183</td>
<td>TOP2A overexpression</td>
<td>Abundant Topoisomerase IIβ</td>
<td>Facilitates transcriptional processes for mitosis</td>
<td>19</td>
</tr>
<tr>
<td>hRAB37 down-regulation</td>
<td>Low Rab37 protein expression</td>
<td>Enhanced metastasis</td>
<td>184</td>
<td>DDR2 mutation (S768R)</td>
<td>Discoidin domain receptor tyrosine kinase 2 up-regulation</td>
<td>Enhanced growth, differentiation and metabolism in SCC</td>
<td>192</td>
</tr>
<tr>
<td>ECRG4 down-regulation</td>
<td>Low ECRG4 tumor-suppressor protein levels</td>
<td>Enhanced lymph node metastasis</td>
<td>185</td>
<td>AURKA polymorphism</td>
<td>Aurora A kinase dysregulation and overexpression</td>
<td>Enhanced cell survival, growth signal, proliferation and metastasis</td>
<td>177</td>
</tr>
<tr>
<td>GPX down-regulation</td>
<td>Low GPX levels for detoxification</td>
<td>Enhanced drug resistance and cell signaling</td>
<td>186</td>
<td>91T → A</td>
<td>HER2 and HER3 GFR overexpression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIRAS1 down-regulation</td>
<td>Reduced receptor signal transduction</td>
<td>Increased cell proliferation and metastasis</td>
<td>187</td>
<td>XPO1 mutation</td>
<td>Overexpressed Exportin 1</td>
<td>Facilitates kinase enzyme transport for cell proliferation</td>
<td>193</td>
</tr>
</tbody>
</table>

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tissues harboring the same carcinoma type incur variations in their characteristics for behavior and treatment sensitivity. Likewise, so do identical tissue types between different individuals (5, 8). The supplementary literature in Table I examples these aspects via a compilation of extensively simplified data between four highly studied cancer tissue-types and aims to merely highlight some of the characteristics responsible for their varying natures. Whilst the features and genes compiled in Table I are far from the only ones exhibited by these tissues, their involvement has
become synonymous with particular tissue types over others. It is the varying combinations of these and other regulated genes displayed within each tissue type that hallmarks its genetic profile, subsequent phenotypic nature and therapeutic response.

3. Implications for Current Therapeutics

This high degree of mutational variation has led to the development of multiple therapeutic approaches for targeting tissue-specific abnormalities. Critical understanding of differential characteristics between cancer tissue types and subtypes has classed therapies into those that: 1) target growth or proliferation aspects via inhibitory and immune-sensitizing agents versus those that, 2) attempt to overcome death resistance via cell damage and death induction (4, 5, 8).

Table II highlights key aspects and applications of currently established systemic cancer therapeutics applied individually, in tandem or as adjuvants to each other. The most commonly used therapeutic branch; Chemotherapy, encompasses an extensive assortment of toxic chemical compounds for oral, intravenous (bloodstream and lymph), intrathecal (spinal column) or regional (organs or abdominal cavity) cancer treatments (24-26). The extent depends on cancer type as drugs exert a particular effect on specific intracellular targets and are therefore categorized according to their mechanism of effect. Development has yielded two alternative chemotherapies namely; “Biological Therapy” (9, 27) and “Immune Therapy” (28, 29). These apply the intricacy and availability of cellular molecules/systems to generate blockades against cancer development and/or initiate defensive responses to its presence.

Radiotherapy (a.k.a. radiation therapy) employs lethal doses of ionizing radiation to the tumor mass, ideally when cells are in the mitotic phase. This damages DNA for cell retardation and death (27, 30). Internal administration utilizes radioisotope therapy and combinations with immuno-agents for targeted Radioimmunotherapy (26, 31-35). Gene therapy aims to restore normal gene function in order to regain growth control or terminate existence. Specific targeting with viral- and non-viral delivery vectors (e.g. surface-coated microspheres) transport genetic variants for genome manipulation enabling direct or indirect therapies depending on the cell function being targeted (11, 27, 36-38).

Whilst prognoses have improved throughout these regimens under study, two critical issues have surfaced regarding cancers of genetic variance:

3.1. Systemic therapies exhibit low tissue specificity. Many chemotherapies, in addition to poor concentration yields generating weak target responses, also exhibit low exclusivity to tumor tissue/cells. This broad specificity to tissues mimicking cancer characteristics (e.g. high proliferative rates of blood, bone, mouth, intestinal tract, nose, nails, hair and sexual organs), or tissues responsible for xenobiotic clearance (e.g. liver and kidney) inadvertently suffer undirected damage upon administration (23). Loss of cell function results in cell renewal shutdown for tissue maintenance, immunosuppression incurring secondary infections, impairment of organ system communications and organ damage, myelosuppression anemia and acute myeloid leukemia (39, 40-45). Similarly, radiotherapies also impart toxicity on normal tissues generating Acute- (epithelial damage, nausea, diarrhea and oedema), and Late- (fibrosis, alopecia, lymphedema, cognitive decline and heart disease) responses (30, 31, 46-51) as well as an increased risk for secondary cancer development (52). Alternatively, gene therapy limitations occur via low specific tumor cell/gene targeting, low transfection efficiency, uncontrolled surrounding tissue damage via toxic product leakage and, onset of flu like symptoms. Additionally, preventing permanent incorporation of genetic changes and other ethical factors are problematic (1, 38, 53).

This combination of being too specific within the cellular system and not specific enough within the organ-tissue system has led to a conundrum of complications. Approaching this from a negative angle one could argue that complete eradication with no recurrence is more a challenge of lucky chance with regards to compatibilities between tissue type, therapeutic application, genetic profile, low heterogeneity, high tissue target-therapeutic agent interaction and a “goldilocks” scenario of therapeutic dosage that is “just right” so as to impart no disabling side effects.

3.2. Therapeutic agents target a single abnormality or family of similar abnormalities. Whilst it is beneficial to design therapies targeting particular abnormalities critical for cell function or who impart influence multiple pathway systems, this approach may, in some cases, be flawed due to:

- Insufficient damage inflicted on one target to overcome survival mechanisms and induce adequate death responses. The intricately interconnected pathway systems displayed by cells is a double edged sword. Many components exhibit multiple functions or interactions across a number of pathway systems whose therapeutic disruption or stimulation could yield broad scale collapse or activation of critical mechanisms for a desired outcome. Conversely, this multi-functionality, many of which are yet to be elucidated, could interfere via protection (26, 54, 55), active damage repair (56, 57) or compensation (58, 59) thereby rendering the treatment largely ineffective. This has prompted the use of drug cocktails and modified chemotherapeutics (e.g. chemoradiotherapy, chemo-radioimmunotherapy) to encompass several targets for crippling of overall cell
functions (5, 22, 25, 31, 60-64). Treatment success is significantly improved but carries a variety of unfavorable consequences and acute life-threatening toxic effects to the body (22, 65).

- Target abnormality might not be present in the carcinoma type or, only be present in specific subpopulations due to tumor heterogeneity.

The diverse genetic variations impart a unique cocktail of resistance traits which complicate design and implementation of successful cancer therapies (8, 23) and exhibition of pretherapeutic resistance hallmarks “innate- or intrinsic-resistance” (22, 66). Melanomas, breast-, prostate-, colon-, and lung cancers express strong variations of this to chemotherapy and radio-therapeutics ensuing high failure rates (8, 22, 67). Occasionally, increasing drug dosage overcomes this.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Target</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkylating Agents</td>
<td>Alkylate proteins and nucleic acids independent of the cell-cycle phase for DNA accessibility, e.g. cisplatin, carboplatin, oxaliplatin.</td>
<td>194, 195</td>
</tr>
<tr>
<td>Anti-metabolites</td>
<td>Broad class of molecular analogues that disrupt proliferation and induce cell death via genomic enzyme competitive-binding or direct nucleotide strand incorporation, e.g. fluorouracil and pentostatin.</td>
<td>194, 196</td>
</tr>
<tr>
<td>Cytoskeletal agents</td>
<td>Natural and semi-synthetic drugs that induce cytoskeletal microtubule dysfunction preventing completion of mitosis, e.g. paclitaxel, docetaxel and vinblastine.</td>
<td>194, 197, 198</td>
</tr>
<tr>
<td>Topo-isomerase inhibitors</td>
<td>Inhibit critical activity of topoisomerase I and II enzymes required for genomic transcription and replication potentials, e.g. topotecan and etoposide.</td>
<td>195, 199</td>
</tr>
<tr>
<td>Cytotoxic antibiotics</td>
<td>Broad group of compounds collectively exert toxic effects on individual cell function components including DNA intercalation, ROS production, metabolic pathway inhibitors and free-energy carriers, e.g. actinomycin, doxorubicin and mitomycin.</td>
<td>200, 201, 202</td>
</tr>
<tr>
<td>Hormone/endocrine agents</td>
<td>A special branch of chemotherapy aiming to impede hormone dependent cancer types by negating stimulatory effects of hormones such as oestrogen and progesterone. Limitations involve the selective targeting of those cancers reliant on hormonal stimulation and the development of secondary endometrial and uterus cancers from its use.</td>
<td>203, 204, 205</td>
</tr>
<tr>
<td><strong>Biological/Immune Therapy:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boosting</td>
<td>Cell-based Vaccination with multiple surface tumor-associated antigens or cancer cell homogenates to increase cytotoxic T-Lymphocyte response efficiency. This involves removing, amplifying and returning a variety of immune cells activated against a particular cancer to augment the immune response.</td>
<td>206, 207, 28</td>
</tr>
<tr>
<td>Restoring</td>
<td>Interferons, interleukins, and other cytokines administered to imitate or influence the natural immune response i.e. Cytokine Therapy.</td>
<td>208, 209</td>
</tr>
<tr>
<td>Directing</td>
<td>Monoclonal antibodies (mAb) synthesized against cell surface proteins typical of cancer. Two types of mAb are applied; naked and conjugated. These sensitize the immune system via antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity inducing membrane protein pore damage, or antagonistic mAb binding of cancer stimulatory receptors for signaling inhibition. Conversely, mAb-drug conjugates with both chemo-drugs and radioisotopes have incurred multiple drawbacks in practical use.</td>
<td>210, 211, 212, 213</td>
</tr>
<tr>
<td><strong>Radiotherapy:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radioisotope Therapy (RIT)</td>
<td>Involves systemic/oral administration of ion radioisotopes for cancer uptake and damage. These include $^{177}$Lu, $^{131}$I, $^{213}$Bi, $^{210}$Po, and $^{90}$Y. For additional targeting, these can be encapsulated in microspheres or conjugated to antibodies and other immuno-agents (Radioimmunotherapy). The latter sports additional sensitization of the immune system to cancer sites.</td>
<td>31, 33, 34</td>
</tr>
<tr>
<td><strong>Gene-Directed Therapy:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct</td>
<td>1) Reintroduce silenced TSGs, e.g. P53 gene enabling apoptosis.</td>
<td>27, 214</td>
</tr>
<tr>
<td></td>
<td>2) Introduce siRNA/microRNA to block malignant oncogene expression e.g. inhibiting overexpression of Bcl-2.</td>
<td></td>
</tr>
<tr>
<td>Indirect</td>
<td>1) Reintroduction of immunogenic cytokine genes increasing tumor susceptibility to external defense responses e.g. MAGE gene.</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>2) Introduction of genes encoding enzymes to convert non-toxic substrates into toxic products e.g. Herpes Simplex Virus Tyrosinase Kinase.</td>
<td></td>
</tr>
</tbody>
</table>
However, this regularly confers increased general toxicity without enhanced efficacy due to the lack of sufficient targets available (26). Recent research has attributed resistance and recurrence to tumor mass heterogeneity. Mesenchymal stromal cells, tumor initiating cells, innate inflammatory immune cells and myofibroblast interactions exert external therapeutic negations via signals for protection and survival (extracellular matrix proteins), epigenetics, oncologic trogocytosis and cancer stem cell conversion. Consequently, therapies may only impart a partial eradication of the tumor (23, 68-72). Similarly, antibody targeting of immunotherapies have fallen short, exhibiting traits of inconsistent surface-antigen expression, limited antibody distribution and tissue penetration due to molecular size through tumor vasculature, low surface-antigen binding incurring weak internalization and superficial cytotoxicity, and the presence of multiple antigens demonstrating competition for immune responses (14, 23, 73).

- **Particular target could incur a quickening of disease development or metastatic potential for escape.**

Many therapeutics inadvertently generate more aggressive tumor phenotypes. Stimulation of key proteins forces an Epithelial-to-mesenchymal transition (EMT). During this, cells transform from polarized epithelial- to highly mobile mesenchymal phenotypes thereby enhancing metastatic potential (74). This has also been associated with therapeutic stimulation of the tumor microenvironment (70, 75-77).

- **Therapy is limited to specific cancers.**

Aspects of tumor heterogeneity, genetic profiles and drug susceptibility enable pairing with certain drug combinations for maximal effect. This however, limits the potential broad applications of available therapies to specific cancer types. Identical treatment regimens are regularly less effective against other cancer tissue types and in some cases, the same tissue type via mutational variation (22, 65). This is most prominently observed in biological- and immune-therapies which are highly cancer-type specific. Here, particular therapies are administered according to the marker profile that identifies possible areas of treatment susceptibility (9, 27) and success requires extensive knowledge of the cancer attributes, mechanisms of resistance and the communication between immune system and tumor cells (78). Furthermore, treatment scenarios may result in eradication of one tumor population but enhanced tumorigenesis of another (23). This has been observed with various radiotherapy administrations where success relies heavily on cancer cell genetic sensitivity and low hypoxic conditions. This non-uniform cellular targeting results in under-targeted subpopulations surviving the initial onslaught (30, 31, 48). Genotype and phenotype identification is, therefore, required to select a therapy or combination of therapies with the highest potential success.

- **Attack on a particular target may induce signaling effects that confer resistance to surviving cells.**

Cancer cells surviving the initial treatment commonly develop resistance by altering their genetic profiles to overcome the target susceptible to the therapy (22, 66). This results in frequent chemoresistance despite its vast application repertoire as summarized in Table I (5, 22, 53, 55, 79, 80). Additionally, these can yield reduced drug affinities or uptake resulting in cancer relapse and tumor recurrence with resistant phenotypes (76, 81), and secondary cancer developments (82, 83). The nature and mechanics behind this phenotype is described in greater detail further on.

In truth, therapeutics have shown remarkable improvements in prognoses, indicating targets selected are critical for cell collapse (84). Efforts in these areas are by no means futile and the limitations thereof are fundamentally due to gaps in the current knowledge and methods for successful application. Whilst these imperfections are being addressed, progress is slow and remains a tedious task of perfecting a specific therapeutic approach for a particular carcinoma of unique genetic profile. Therefore, the need to establish a diversified therapy for broad spectrum application is a much desired alternative.

4. Photodynamic Therapy

Being a treatment modality, Photodynamic therapy (PDT) could potentially fulfill this role. As a unique branch of phototherapy, PDT has become a much researched field with its success driven by the distinctive combination of semi-targeted administration and non-specific damage induction (85, 86).

Essentially, PDT comprises a minimally-invasive, three-component therapy involving the initial topical or systemic administration of a photosynthetic drug (Photosensitizer; Ps) which localizes within target tissue over time (87). Guided irradiation of the area with a high-energy, monochromatic light source of accordant wavelength (usually red/near-infrared) results in photon-based Ps excitation. Upon dissipation, energy transfer generates highly Reactive oxygen species (ROS) resulting in broad scale irreversible photodynamic damage that ideally induces cell death (88, 89, 90). On the molecular level, this process comprises complicated energetic interactions between the Ps electron system, cellular oxygen (O₂), light, potential ROS generating organic or inorganic molecules and target cellular components, the details of which are extensively described elsewhere (88, 90, 91). Of note here, is the emphasis placed on subsequent ROS-generated damage for therapeutic administration.

4.1. **ROS-Generated Non-specific Cellular Damage.** The critical homeostasis of biomolecule concentrations for
healthy cell function include ROS as signaling mediators of multiple cellular pathways that regulate survival, proliferation and cell death (92, 93, 94). However, excessive levels damage various cellular components including protein structure and activity (95), membrane integrity and dysfunction of trans-membrane protein channels (96), and nucleic acid lesions, base modifications and protein-DNA cross linking (8, 95, 97). This broad scale damage is responsible for numerous diseases including carcinogenesis (93, 98, 99). ROS levels are, therefore, tightly regulated (i.e. Redox State) via antioxidant defense mechanisms; free radical scavenger molecules and endogenous antioxidant enzymes (94, 100, 101). In cancer, ROS levels are increased and antioxidant enzyme activities decreased conferring an advantage for proliferation, survival and chemoresistance (8, 98, 99, 102-106). Due to this constitutive oxidative stress, cancer displays increased sensitivities to ROS producing processes such as PDT as these could either increase ROS levels beyond a threshold point for damage-inducing death or stimulate antioxidant enzyme production thereby stunting growth and proliferation (107-109).
Table IV. Summary of current macrocycle classes under popular research. Differential structure and photophysical traits of interest are also highlighted.

<table>
<thead>
<tr>
<th>Macrocycle Classes</th>
<th>Structural Traits</th>
<th>Photophysical / Chemical Traits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Porphyrin Class:</strong></td>
<td>Conjugated pyrrole rings connected by methane bridges</td>
<td>B-band: Single (350-480 nm)</td>
</tr>
<tr>
<td></td>
<td>Exhibits four exo-pyrrole double bonds</td>
<td>Q-band: Multiple (400-850 nm)</td>
</tr>
<tr>
<td><strong>Chlorin Class:</strong></td>
<td>Monomeric porphyrin derivatives</td>
<td>B-band: Single / Twin (350-480 nm)</td>
</tr>
<tr>
<td></td>
<td>Exhibit one (chlorin) or more (bacteriochlorin) reduced exo-pyrrole double bonds</td>
<td>Q-band: Single / Twin (600-700 nm / 720-850 nm)</td>
</tr>
<tr>
<td></td>
<td>Expanded derivatives</td>
<td>Excellent $^1O_2$ yields</td>
</tr>
<tr>
<td></td>
<td>exhibit exo-pyrrole functional groups</td>
<td>Hydrophilic / Lipophilic natures (chlorins and bacteriochlorins)</td>
</tr>
<tr>
<td><strong>Porphyrazine Class:</strong></td>
<td>Additional N in the pyrrole subunits replaces methane bridges with aza-nitrogen bridges</td>
<td>B-band: Single (300-400 nm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q-band: Single / Twin (580-700 nm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excellent $^1O_2$ yields</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydrophobic natures</td>
</tr>
<tr>
<td><strong>Hydroxyquinone Class:</strong></td>
<td>Composed of double bonded bipyrrrole subunits or polycyclic aromatic conjugates</td>
<td>B-band: Single (350-400 nm)</td>
</tr>
<tr>
<td></td>
<td>Bear N-four central core commonly replaced with S or O atoms</td>
<td>Q-band: Single (700-800 nm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Porphycenes are critical intermediates for intracellular formation of natural Ps</td>
</tr>
</tbody>
</table>
4.2. Macrocycle Ps for use in PDT. Whilst there is a vast range of Ps classes to choose from, each showcasing varying abilities for light energy absorption and transfer, one class – Macrocycles - has stood out. Of natural or synthetic origin, these Ps typically harbor a core ring design exhibiting an array of molecular structural varieties. This imparts unique physiochemical and photophysical profiles highlighting potential applications in specific medical niches such as PDT (110). Indeed, PDT only became a fully recognizable therapeutic to pursue following the use of porphyrin macrocycles by Dr. Thomas Dougherty in the 1970-80s (85, 86). Since then, a wide range of second-generation derivatives have been obtained from natural sources or alternatively synthesized. These boast many attractive advantages for PDT application based upon their synthesis methodology and subsequent ring structure attributes (Table IIIA).

Understanding the variations between their photophysical and physiochemical traits is critical, as the nature of these confer the potential of a particular macrocycle Ps for PDT application. Whilst there is currently a plethora of macrocycle classes and subclasses, each categorized largely by their physical structure and to a lesser extent, stable peripheral functional groups, there exist a popularity for certain classes over others. Summarized briefly in Table IV, these classes are among the most studied and highly successful regarding PDT today. Their success is attributed to the generalization that they bear many of the advantages described in Table IIIA.

5. The Case in support of PDT Mechanism for Cancer Treatment

PDT has gained much attention for its expanded application for cancer. Mechanistically, PDT boasts a number of attractive qualities over traditional cancer therapeutics and these are listed in Table IIIIB. Furthermore, these qualities have endorsed its potential use against two cancer scenarios heavily limited to other applications, 1) A single Ps to be applied on multiple cancer tissue types, and 2) PDT could overcome MDR since the use of non-ionizing radiation and multi-targeting oxygen radicals sensitizes cells unresponsive to chemotherapeutics and radiotherapy.

5.1. Treatment of Multiple Cancer Tissue Types/Genetic Variants. PDT has been shown to be an effective anticancer treatment for a range of tissue types. The most common use involves treatment of non-melanoma cancers, cutaneous lymphomas and various non-cancerous skin conditions (111). Additionally, *in vitro* PDT with a single Ps has displayed significant broad spectrum application on differing carcinoma cell lines. Either in a single study or across many
### Table V. Summary of four extensively reported macrocycle Ps (Hypericin, 5-aminolevulinic acid, metallo-phthalocyanine and pheophorbide a) within in vitro studies against cancer. Listing includes the various tissue types investigated and the critical findings reported in each case.

<table>
<thead>
<tr>
<th>Macrocycle Ps:</th>
<th>Reported Studies:</th>
<th>Findings:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypericin (Hyp):</strong> Phenanthroperylene quinone of natural origin from the plant St. John’s wort (Hypericum perforatum). (245)**</td>
<td>Glioblastoma brain (U373 MG, LN229, T98G)</td>
<td>Hyp-PDT gave varying degrees of cell line sensitivity, narrow dosage differences enabled std. inhibitory (ID$_{50}$) values of between 0.15-0.22 J/cm$^2$ at 2.5 μM hypericin for all.</td>
</tr>
<tr>
<td></td>
<td>Oesophageal: SCC (Kyse-140) Adenocarcinoma (OE-33)</td>
<td>Hyp-PDT comparisons indicated significant apoptotic cell death induction for both tissue types in a dose-dependent manner.</td>
</tr>
<tr>
<td></td>
<td>Cervical (HeLa) Breast (MCF-7) Lung (A549)</td>
<td>PDT with Hyp derivatives (improved hydrophilicity) revealed significant photocytotoxities of all cell types. This was linked to those derivatives whose modifications improved cellular uptake.</td>
</tr>
<tr>
<td></td>
<td>Ovarian (NuTu-19)</td>
<td>Hyp loading into polyacetic/polyacetic-co-glycolic acid nanoparticles revealed enhanced delivery and phototoxicity at lower drug loading percentages.</td>
</tr>
<tr>
<td><strong>Head &amp; Neck SCC (FaDu)</strong></td>
<td></td>
<td>Hyp-PDT induced significant metabolic reductions coupled to excessive apoptosis with no population recovery observed over an 8 day period.</td>
</tr>
<tr>
<td><strong>Nasopharyngeal cancer cells</strong></td>
<td>Bladder (T24)</td>
<td>Hyp-PDT induced apoptosis occurring predominantly but not exclusively via the Fas/FasL receptor pathway.</td>
</tr>
<tr>
<td></td>
<td>Ovarian (SKBR)</td>
<td>Hyp-PDT cell death was augmented by co-addition of metabolic reducing drugs against HER2, Akt, P-Erk1/2 and Survivin.</td>
</tr>
<tr>
<td><strong>SCC non-melanoma</strong></td>
<td></td>
<td>A number of significant findings by the group of L.M. Davids revealed significant photocytotoxicities of all cell types. This was linked to those derivatives whose modifications improved cellular uptake.</td>
</tr>
<tr>
<td><strong>cutaneous cancer (NMCC)</strong></td>
<td>Bladder (T24)</td>
<td></td>
</tr>
<tr>
<td><strong>Melanoma: pigmented</strong></td>
<td>Leukemia (HL60)</td>
<td></td>
</tr>
<tr>
<td><strong>(UCT Mel-1) non-pigmented</strong></td>
<td>Leukemia (HL60)</td>
<td></td>
</tr>
<tr>
<td><strong>5-aminolevulinic acid (ALA):</strong></td>
<td>Oesophageal SCC (Eca-109)</td>
<td>Reported that the efficacy to induce apoptotic responses following proliferatory inhibition and cell cycle arrest hinged on uptake time and ALA-PDT dosage parameters.</td>
</tr>
<tr>
<td>ALA and its derivatives are harmless prodrugs in the heme synthesis pathway that produces protoporphyrin IX (PpIX). Excitation of PpIX induces the resulting phototoxicity. Addition of ALA boosts subsequent PpIX production thereby enhancing the PDT effect. (162, 215)</td>
<td>Colon (HCT116)</td>
<td>Both Zawaka-Pankau et al., and Yow et al., studies attributed growth suppression and apoptosis to stimulation of pro-death p53 genes and mechanisms. Zawaka-Pankau et al., further linked this to PDT-induced disruption of the p53 negative regulator HDM2.</td>
</tr>
<tr>
<td></td>
<td>Liver (HepG2)</td>
<td>Reported that under individually established IC$_{50}$ conditions for culture lines, either necrosis or apoptosis could be induced with no indications of PDT resistance between them.</td>
</tr>
<tr>
<td></td>
<td>Leukemia (HL60)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Breast (MCF-7, T47D) Bladder (HT1197)</td>
<td>Analysis of critical cellular parameters under LD$_{50}$ conditions indicated that both tissue types were predominantly necrotic whilst RT4 cells displayed increased susceptibility.</td>
</tr>
<tr>
<td></td>
<td>Rat Carcinoma (WRC) Urothelial (RT4) Colon (HT29)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glioblastoma brain (U87, U373) Prostate (PC-3, DU145), Murine prostate (TRAMP-C1, -C2)</td>
<td>A complex study comparing low and high-dose ALA-PDT between culture lines reported similar gene upregulation for cell stress and cell cycle arrest and variable death responses across all culture lines.</td>
</tr>
<tr>
<td></td>
<td>PDT-derived variants of: Lung (CL1-5) Melanoma (A375) Breast (MDA-MB-231)</td>
<td>Regarding metastatic potential, the study observed surviving populations to display lowered migration and invasiveness and reduced mitochondrial function. This they stated could be passed down to progenator cells thereby aiding against metastasis.</td>
</tr>
<tr>
<td></td>
<td>Gastric: (KKLS, NKPS, TMK-1, MKN45, MKN28)</td>
<td>Comparisons revealed critical enzymes responsible for PpIX generation were also responsible for ALA-PDT susceptibility. Differential susceptibility between lines was due to high influx transporter and low efflux transporter protein levels.</td>
</tr>
</tbody>
</table>

Table V. Continued
Table V. Continued

| Metallo-Phthalocyanines: | Extensively researched, with common varieties harboring core metal ions aluminium (AlPc), silicon (Pc4) and zinc (ZnPc). Due to tendencies for hydrophobicity and self-aggregation, is a commonly associated modification | AIPc-PDT: Epidermoid carcinoma (A431) | Sulphonated AIPc-PDT induced both mitochondrial dysfunction associated with ATP loss and consequent cell death. | |  | Oesophageal (SNO) | Within our laboratory, two separate studies comparing efficiencies of sulphonated AlPc with novel sulphonated GePc (germanium metal ion core) exhibited superior phototoxicity with AlPc regarding proliferation inhibition, metabolic retardation and cytotoxic responses leading to cell death. | |  | Breast (MCF-7) | Comparisons of two AIPc derivatives bearing either chloride or tetrasulphonate chloride resulted in both derivatives inducing apoptotic cell death of HeLa whilst only cytoplasm and nuclear alterations in CHO-K1 cells unassociated with stress and death. | |  | Cervical: | Non-cancer (CHO-K1) | | |  | Carcinoma (HeLa) | | |  | Breast: Casp. 3 | and that these deficiencies do not appear to prevent cell death by Pc4-PDT. | |  | Vector exp. | P44-PDT efficiency reported to be augmented via enhanced silica nanoparticle encapsulation Ps delivery systems. This was observed for both tissue types exhibiting apoptotic responses. | |  | Casp. 3 (MCF-7/c3) | | |  | Breast (MCF-7) | Following Pc4-PDT, authors observed presence of apoptotic caspase-3 to be of little consequence as both culture lines underwent photodamage of anti-apoptotic Bcl-2 and induction of cell death. | |  | Breast (MCF-7) | Reported routine induction of cell death in apoptotic deficient cell lines and that association within PCL nanoparticles enhances overall population | |  | Prostate (DU-145) | | |  | Melanoma: Human (A375) | and that these deficiencies do not appear to prevent cell death by Pc4-PDT. | |  | Murine (B16-F10) | | |  | Breast (MCF-7/c3) | | |  | Melanoma: | Human (A375) | A comparative study indicated photoxic responses and cell death | | |  | Breast (MCF-7/c3) | across all tissue types at differential concentrations despite the initial priming of an adaptive response to ZnPc-PDT. | |  | Prostate (DU-145) | Multiple studies show lung carcinoma responding well to ZnPc-PDT via decreased population proliferation and DNA damage (Manoto & Abrahamse) and that association within PCL nanoparticles enhances overall population cell death due to improved solubility (da Volta Soares, et al.). | |  | Lung carcinoma | | |  | Breast (MCF-7) | A water-soluble Zn(II)Pc derivative induced an atypical apoptotic pathway as cell death markers were possibly linked to the involvement of calpains. | |  | Oesophageal (SNO) | Reported to undergo a form of caspase independent apoptosis in response to ZnPc-PDT. | |  | Breast (MCF-7) | Parallel studies with ZnPc both resulted in mitotic catastrophe responses along with cell cycle arrest and apoptosis. | |  | Breast (MCF-7/c3) | ZnPc derivatives bearing diverse ionic charges were shown to hold efficient photoactivities where charges influenced membrane affinity. | |  | Lung (A549) | | |  | Nasopharyngeal carcinoma (KB) | | |  | Cervical (HeLa and SiHe) | | |  | Colon (HT29) | Research group at The Chinese University of Hong Kong has reported on the effects of Pa-PDT including cell cycle arrest and late stage apoptosis at under 1 μM dosage (Tang et al.), significant inductions of apoptosis via mitochondrial damage, singlet oxygen and intrinsic pathway mediators (Tang et al.), and induced mitochondrial-mediated apoptosis with dual loss of autophagy. This was achieved via ERK pathway suppression resulting in an anti-tumor effect (Bui-Xuan et al.). | |  | Liver resistant (R-HepG2) | Reported mitochondrial damage and associated apoptosis following Pa-PDT. | |  | Uterine (MES-SA) | Reported autophagic induction which culminated in cell death over time. This was attributed to its prolonged activity which crippled cell function beyond recovery. | |  | Breast (MDA-MB-231) | Using closely related pyropheophorbide; MPPa resulted in an apoptotic population majority suggesting subtle differences between a Ps and its derivatives may confer significant variations in death responses. | |  | Pancreatic adenocarcinoma | Comparison revealed greater survival inhibition of A431 epidermoid carcinoma cell over normal keratinocytes culminating in caspase-independent apoptosis further suggesting a cancer specificity by Pa-PDT. | |  | Prostate (PC-3) | | |  | Prostate (PC-3-M) | | |  | Prostate (PC-3-M) | | |  | Epidermoid carcinoma (A431) | Non-cancer keratinocytes | Non-cancer keratinocytes | | 

Horne and Cronje: Cancer, Therapeutic Implications and PDT (Review)
related studies, a wide variety of promising macrocycle Ps has imparted broad tissue-based susceptibility to PDT. A summary in Table V highlights this point across four well known Ps. Studies such as these have prompted many subsequent in vitro trials with hopes of establishing clinically viable modalities for each Ps. Examples of these are well described in the following list and represent but a small portion of the work done thus far (112-119).

5.2. Treatment of MDR Cancer Types. Therapeutic modalities are typically administered in triplicate-line regimens encompassing different molecular agents. Therapeutic resistance occurs when tumor cells exhibit defenses against these molecular agents (120). The level of resistance portrayed is related to the range of therapeutic recognition by the tumor cell. Resistance after exposure to one agent (1st-line of treatment) is termed “acquired resistance”. Should the cancer cell exhibit additional resistance to unrelated agents (2nd- and 3rd-lines), this is termed “cross or multi-drug resistance” or MDR (22, 66). The latter encompasses a broad range of unrelated therapeutic agents making it one of the principle causes for treatment inefficiency and relapse, thereby presenting a complicated obstacle to current therapeutics (120).

MDR imparts therapeutic incompatibility via either heightened protection or inactivation of fatal targets through manipulation of coordinated intracellular defense mechanisms (121). A principal facilitator associated with this phenotype is the drug efflux trans-membrane systems and their associated transporter proteins termed multi-drug resistance proteins (MRPs). These expel xenobiotic or harmful molecules from the cytoplasm in an ATP-dependent manner (122-124). As such, many highly mutagenic and kinetic cancer tissue types exhibit an over-expression or -activation of these protein systems (22, 55, 125, 126). Of particular interest are the P-glycoprotein (P-gp) efflux systems that have been well documented over the years in association with cancer therapeutic resistance (80, 127-129). Encoded by the ABCB1 gene and regulated by the proto-oncogene Ras (130), P-gp is alternatively known as ATP-binding cassette sub-family B member 1 (ABCB1). Multi-drug resistance protein 1 (MDR1) or cluster of differentiation 243 (CD243). Bound within the plasma membrane, P-gp has a broad substrate specificity allowing for recognition and expulsion of multiple xenobiotic components of dissimilar structures via a unique binding pocket. Associated conformational changes are driven by ATP hydrolysis (124, 126, 128, 131, 132).

PDT has been suggested to potentially overcome MDR by either knocking-down drug efflux activities or through suggested non-recognition of the Ps for removal (120). An extensive review by Detty et al., (2004) (133) briefly touched on this concept by stating that whether drug efflux systems recognized Ps structures for removal or not could be mutually beneficial. Non-recognition would allow successful PDT administration to the cell without efflux interference whilst recognition could result in PDT damage of the efflux systems thereby enabling increased efficiency of other therapeutics. Indeed, some early studies highlighted sufficient accumulation of macrocycle Ps classes within a range of cell types despite P-gp expression (134, 135). These studies also reported knockdown of resistance to chemotherapeutic drugs and an indication that MDR phenotypes may not express cross-resistance to PDT. This potential has also been carried over to second generation macrocycles including; mTHPC-PDT on doxorubicin-resistant MCF-7 cells (136), Pheophorbide a (Pa)-PDT on R-HepG2 cells bearing MDR activity (137), and phthalocyanine (AISPc)-PDT on colchicine-resistant 3T3 cells (138).

Whilst this is promising for P-gp efflux evasion, there are related transport systems also associated with cancer development and drug resistance. These most commonly include the ATP-binding cassette sub-family G member 2 (ABCG2) also known as the Breast cancer resistance protein (BCRP) (139) and the ATP-binding cassette sub-family C member 1 (ABCC1) also known as Multidrug resistance-associated Protein 1 (MRP1) (140). In particular, BCRP has been shown to exhibit active substrate recognition for a variety of photosensitizers including; Pa (141), Pa methyl ester (MPPa), Clorin e6, ALA (142, 143), HPPH (144, 145), and Photofrin (146).

To curb this, more recent studies report on combination treatments with various BCRP drug efflux inhibitors. Of these, tyrosine kinase inhibitors have become popular since the success of Imatinib Mesylate (commercially known as Gleevec®) as a chemotherapeutic (147). Extension of their inhibitory effects to overcome MDR has been extensively explored (148) and a few studies have extended this concept to prevent Ps efflux during PDT (144, 145, 149). Likewise, similar PDT enhancements have also been reported using alternative inhibitors such as microbial metabolites; Fumitremorgin C and its analog Ko-134 as well as proadifen against both the ABCG2 and P-gp efflux systems (146, 150, 151).

Unfortunately this approach, whilst effective, is not considered ideal. Whilst there are many therapeutic agents available for drug efflux transporter inhibition (151, 152), many have been shown to harbor low selectivity and therefore reduced potency as well as significant contraindications for the necessary release of toxic metabolites and complicated co-treatment dosage adjustments between themselves and chemotherapeutic agents (153). This has been demonstrated in a few in vivo trials which have reported Imatinib Mesylate and some related inhibitors to bear severe toxicities including hypertension, oesophagitis, gastritis and cardiotoxicity (154-156).
Table VI. Summary of current macrocycle Ps approved for clinical trials and adjuvant therapies. For each, definitive aspects highlighting reasons for their success are given. Additionally, cancer types and other tissue disorders under application are listed.

<table>
<thead>
<tr>
<th>Macrocycle Ps</th>
<th>Therapeutic Traits</th>
<th>Clinical Applications</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Porphyrin Class:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Photofrin™ (Porphyrin mixture)</td>
<td>Comprised of a mixture of active porphyrin oligomers linked by ether and ester functional groups</td>
<td>Cancers treated: breast, malignant and non-malignant cervical, bladder, oesophageal, and various types and stages of lung and gastric cancer</td>
<td>133 162 237 286</td>
</tr>
<tr>
<td><strong>Chlorin Class:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foscan®/Temoporfin (meso-Tetrahydroxy-phenylchlorin)</td>
<td>Synthetic chlorin, lipophilic. High $^{1}O_{2}$ quantum yield</td>
<td>Approved for PDT of head and neck cancer. Clinical trials: ovary-, breast-, prostate-, oesophageal-, lung-, gastric- and skin cancers</td>
<td>85 162 165 240</td>
</tr>
<tr>
<td>Tookad® (Pd(II)bacteriopheophorbide derivative)</td>
<td>Lipophilic with exceptional $^{1}O_{2}$ quantum yield due to the heavy-atom effect.</td>
<td>Phase III clinical trials for prostate cancer</td>
<td>288 287</td>
</tr>
<tr>
<td>Photochlor (pheophorpbide: HPPH)</td>
<td>Lipophilic</td>
<td>Clinical trials: oesophageal cancer, Barrett’s oesophagus, BCC and lung cancer</td>
<td></td>
</tr>
<tr>
<td>Verteporfin (VP) (Benzoporphyrin derivative-monoacid ring A: BpD-MA)</td>
<td>High $^{1}O_{2}$ quantum yield High efficacy allows for lower dosages</td>
<td>Approved for age related macular degeneration Clinical trials: leukemic bone marrow purging, ocular disease, human psoriasis, lung- and bladder cancer, canine osteosarcoma</td>
<td>162 237 287 289</td>
</tr>
<tr>
<td><strong>Hydroxyquinone Class:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levulan™ (ALA porphycene)</td>
<td>Precursor compounds utilizing heme synthesis pathways for generation of Protoporphyrin X</td>
<td>Treatment of pre-cancerous actinic keratosis. Detection: various neoplasms of the brain, oesophagus, bladder, uterus and skin Detection of papillary bladder cancer</td>
<td>92 162 165</td>
</tr>
<tr>
<td>Hexvix™ and Metvix™ (MAL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phthalocyanine Class:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Photosense® (Sulphonated Aluminium Phthalocyanine)</td>
<td>Constitutes a mixture of di- and tri-sulphonic derivatives collectively exhibiting the largest molar absorption coefficient ($=20\times10^{4}$ M$^{-1}$ cm$^{-1}$) of all 2nd generation Ps</td>
<td>Phase III clinical trials: SCC of skin, breast, oropharyngeal, lung and larynx</td>
<td>162</td>
</tr>
<tr>
<td><strong>Texaphyrin Class:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xcytrin™ and Motexafin (Gd(III) texaphyrins)</td>
<td>Large internal cores enable complexing with many trivalent metal ions</td>
<td>Currently used as MRI agents, radiosensitizers and chemosensitizers. Phase III clinical trials: brain tumors and metastases is underway</td>
<td>162 223</td>
</tr>
<tr>
<td>Lutrin® and Antrin (Lu(III) texaphyrins)</td>
<td></td>
<td>Approved for PDT of prostate- and cervical- cancers. Clinical trials: breast cancer, melanoma and Kaposi’s sarcoma</td>
<td>289</td>
</tr>
</tbody>
</table>

A promising alternative is the association of Ps with nanoparticles. This combination has been widely investigated and found to aid PDT greatly via targeted delivery, increased uptake concentrations and retention times, shielding of drug recognition and efflux as well as inducing an occasional Photochemical internalization (PCI) effect when the nanoparticle complexes are stored within the cells lysosomal compartments. Studies are extensive and in surplus prompting the release of many comprehensive reviews on the field (157-160). Ranging from silica nanoparticles and block co-polymers to polymeric micelles and dendrimers, the intricacy and extensiveness of this field is beyond the scope of this review but hold much promise against MDR.

5.3. Current Applications of Macrocycles within Clinical PDT for Cancer. Due to its research advancements, PDT with certain Ps are clinically available in some countries alone or as adjuvant therapy to traditional treatments,
applicable for multiple small or superficial cancerous tumors and certain non-malignant pathologies characterized by cellular overgrowth (85, 90, 161, 162). The range of macrocycle Ps utilized span the multiple subclasses described in Table V and are briefly highlighted for their applications in Table VI.

6. PDT Shortcomings and Focal Points of Consideration

Like any therapeutic, PDT is far from a perfect process demonstrating its own limitations for effect however. A few limitations regarding PDT include;
- Selective recognition of certain Ps structures by drug efflux systems reduces cancer cell concentration and retention time thereby weakening PDT toxicities,
- Clinical association with local inflammatory pain. Higher nerve density augments this however the main cause is not well understood,
- Excitation light is scattered and absorbed by tissue macromolecules thereby reducing dosages available for subcutaneous PDT,
- Currently, only static cancer can be treated effectively. Disseminated tumors, leukemias and lymphomas require a remodeled approach for PDT administration,
- Of major concern, many Ps exhibit hydrophobic natures incurring considerable aggregation within aqueous environments. This lowers systemic administration and photoactivity.

In free form, mode of Ps uptake is closely associated with a complex coordination of properties regarding size, charge, lipo-/hydrophilicity, aggregation state and cell type (163-166). Requirement of a balanced hydro- and lipophilicity enabling dual biocompatibility with aqueous biological solutions and lipid membranes has placed focus on Ps peripheral modification. Whether it is the addition of simple functional groups (e.g. SO₄) or large long chain or bulky substituents, these are commonplace facilitators of solubility, with the added benefit of increasing targeted uptake and redirected subcellular localization (167-171). Adversely, associations with nanoparticle drug delivery systems have become a promising solution to many of these structural flaws.

Despite these drawbacks, PDT remains a promising alternative to current therapies. Its overall efficiency is multifactorial with respect to tissue, Ps and light properties. Tissue properties including fluctuations in composition, tumor depth/type, extent of microvasculature, cell cycle phase, cellular metabolic state, cellular concentration of molecular oxygen, ROS production yield and type and duration of inflammatory and immune responses are all unalterable. It is therefore necessary that Ps properties (type, tissue accumulation potential, intracellular localization, absorption spectrum, and total dosage) and light properties (source, fluence rate, wavelength, and depth of tissue penetration) are manipulated to compensate for a suboptimal PDT environment (88, 120, 172-175). As such, research efforts are being made to improve the overall effect of PDT in order to gain a solid standing in the therapeutic field.

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