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Review

Role and Application of Biocatalysts in Cancer Drug Discovery

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Abstract: A biocatalyst is an enzyme that speeds up or slows down the rate at which a chemical reaction occurs and speeds up certain processes by 10^8 times. It is used as an anticancer agent because it targets drug activation inside the tumor microenvironment while limiting damage to healthy cells. Biocatalysts have been used for the synthesis of different heterocyclic compounds and is also used in the nano drug delivery systems. The use of nano-biocatalysts for tumor-targeted delivery not only aids in tumor invasion, angiogenesis, and mutagenesis, but also provides information on the expression and activity of many markers related to the microenvironment. Iosmapinol, moclobemide, cinepazide, lysine dioxygenase, epothilone, 1-homophenylalanine, and many more are only some of the anticancer medicines that have been synthesised using biocatalysts. In this review, we have highlighted the application of biocatalysts in cancer therapies as well as the use of biocatalysts in the synthesis of drugs and drug-delivery systems in the tumor microenvironment.

Keywords: biocatalyst; enzymatic catalysis; cancer; immune system; chemotherapy; nanomedicine

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1. Introduction

Biocatalysis has become an essential component of modern organic synthesis, both in the commercial and academic spheres of activity and in green synthesis. Its success may be attributed in large part to the creation of cutting-edge methodologies for the discovery of novel enzymes and the application of a high-throughput laboratory. Biocatalysts can be used for preparation on a grammes (g) to kilogrammes (kg) scale. It has also become an alternative to chemical catalysis in recent years, and it is currently being used in a diverse field [1–5]. Over the last two decades, the number of biocatalytic tools, such as newly developed catalysts with specifically tuned features and novel ideas for reaction, has expanded tremendously [5,6]. The initial stages in biocatalysis include identifying the target reaction, searching for biocatalysts, characterizing those biocatalysts, and using them in different fields. Biocatalysts are also used in recombinant enzyme systems; from the extraction of natural sources to gene mining using bioinformatics techniques, the screening of biocatalysts has evolved rapidly. They are effective in reactions having multiple steps as they offer an environment that is protective of enzymes (Figure 1) [7–10].

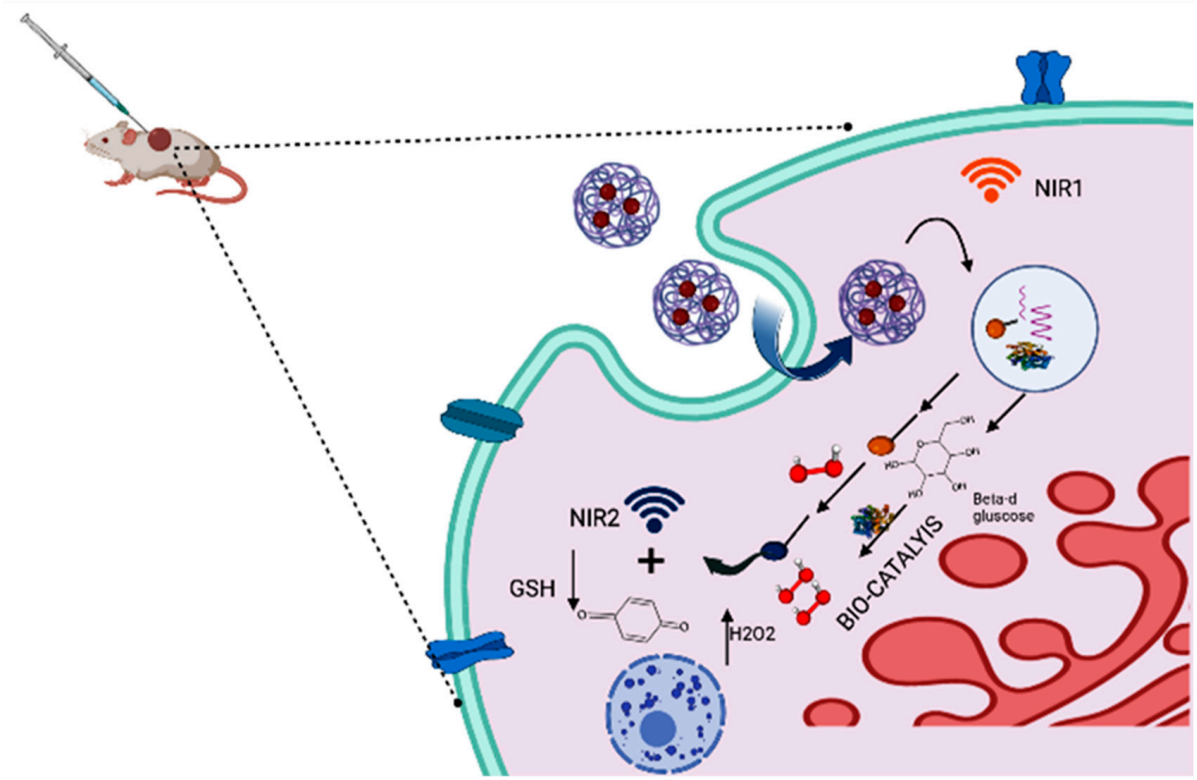


Figure 1. Mechanistic pathways of biocatalyst.

Biocatalysts can be identified using genomic and metagenomic techniques, such as sequence-based methods that search for biocatalysts homologous to presently known biocatalysts, and PCR-based techniques that use primers designed in accordance with methods to conserve regions of known enzymes or functional metagenomics, where genomic libraries are constructed, such as fosmid- and cosmid-based repositories with 25–40 kb DNA inserts, and screened with the DNA used directly from environmental metagenomes. In order to successfully construct biocatalysts, it is necessary to engage in rational planning and selectivity [8,11] in enzymes to catalyse chemical reactions in industrial processes such as the manufacture of drug substances, flavours, fragrances, chemicals, and polymers. The incorporation of biocatalysis into conventional chemical manufacturing will result in increased longevity of the process, less environmental toxicity, and a decrease in the production cost [12–14]. In this review, we have highlighted the role and application of biocatalysts in cancer therapies as well the use of biocatalysts in the synthesis of drugs and drug-delivery systems in the tumor microenvironment.

2. Role of Biocatalyst in Tumor Tissue

Tumor tissue has a variety of enzyme expression patterns, which is useful for creating effective enzyme-responsive nano-drug delivery systems. Designing a stimulus-responsive mechanism that can only deliver the potential drug in the tumor microenvironment (TME) is one way to get a drug to accumulate in tumors. The enzyme substrate which is found in the TME can be used to connect the drug to its carrier [15–17]. An alternative is to encapsulate the drug in a carrier that can be precisely broken down by these enzymes in the TME. The benefit of this approach includes fast-released drug molecules, superior tumor tissue penetration, and effectiveness. The GPX4 enzyme can be inhibited by the Fe3+ ion and tannic acid to initiate ferroptosis and inhibit tumors [18]. Carboxyl-esterase-responsive albumins coated with folate form a nanocluster (FHP) useful for precision cancer theranostics and is enzyme-triggered [19].

2.1. MMPs as Biocatalyst

Matrix metalloproteinase (MMP) enzyme can be used as a tumor-specific catalyst to promote the release of active drugs in prostate tumor tissues since they are overexpressed in a wide range of tumors. Formononetin, an isoflavone, is found to have anti-migration properties when tested on MDA-MB-231 and 4T1 breast cancer cells. MMP-2 and MMP-9 might be inhibited by formononetin via the PI3K/Akt pathways. This study's findings demonstrated improved perfusion and hypoxia reduction by removing tumor microenvironment barriers in the tumor location [20–22]. Using the pancreatic stellate cell type in BALB/c nude mice, matrix-metallopeptidase-2-sensitive and RGD-peptide-modified liposomes are found to contain gemcitabine and pirfenidone [23]. In another finding, the treatment of pancreatic-tumor-bearing animals with an intravenous injection of a therapeutic drug carrier containing monomethyl auristatin E, which was aimed at albumin where β-glucuronidase was highly expressed, produced a remarkable effect [24].

2.2. Polysaccharides

A significant role is played by polysaccharides during enzyme-targeted treatment of colorectal cancer. These polymers are natural, biodegradable, and biocompatible, and also function as drug-delivery systems. Colonic enzyme-responsive oligoesters and cross-linked nanoparticles that are based on dextran and transport 5-FU were created. It was observed that the compound released no drug under the pH conditions of the small intestine and stomach but released 75% of the drug after 12 h of glucanase incubation [25].

2.3. Prostate-Specific Antigen

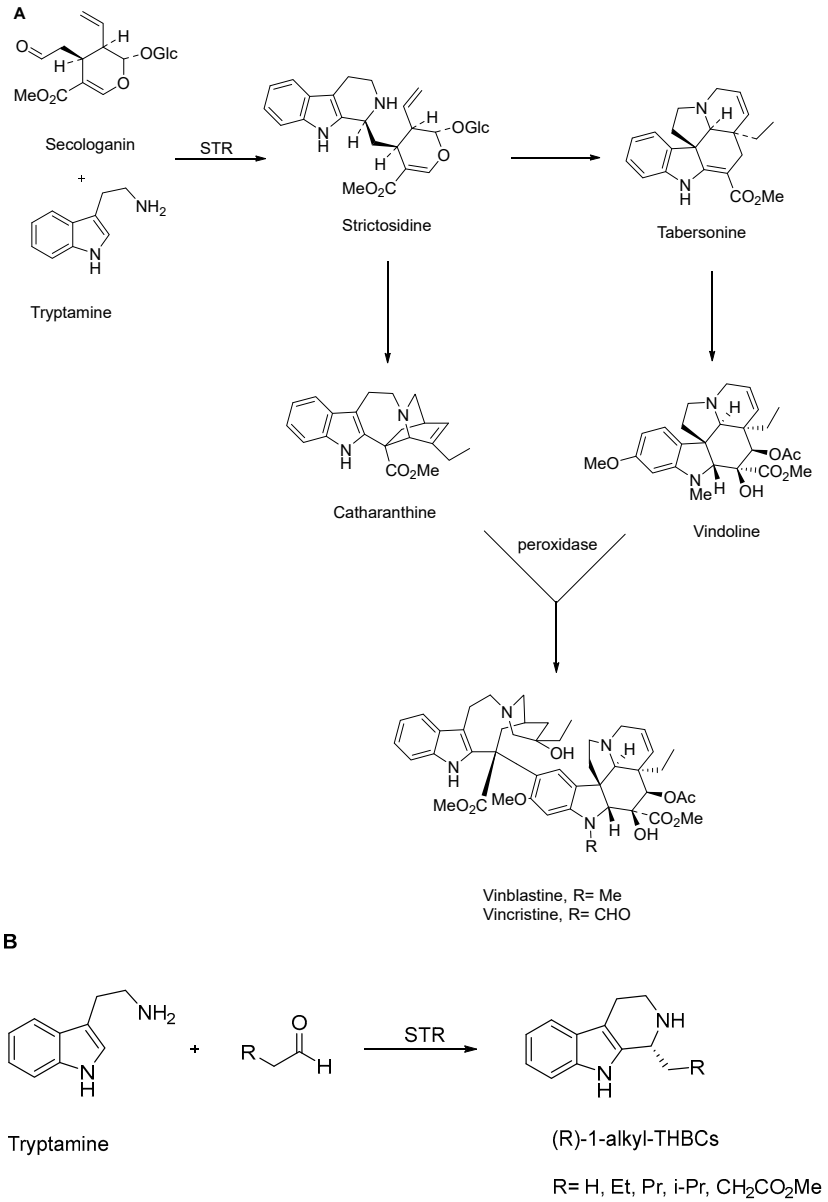
Prostate-specific antigen (PSA) is a 33 kDa mono-chain glycoprotein and a serine protease that is androgen-regulated and a member of the glandular Kallikrein family. The FDA authorized a PSA test for prostate cancer progression assessment in 1986. A novel target drug delivery method for prostate cancer treatment might be created using a substrate-drug combination. The 7-mer peptide group (His-Ser-Ser-Lys-Leu-Gln-Leu) could be cleaved by PSA, and a prodrug was designed by conjugating this peptide to doxorubicin [26–29]. Cathepsins A, B, C, D, E, F, G, H, L, K, O, S, V, and W are overexpressed in various forms of human cancer and belong to the family of endopeptidases. Cathepsins B, C, F, H, L, K, O, S, V, W, and X are cysteine proteases; cathepsins D and E are aspartic proteases, and cathepsins A and G are serine carboxypeptidases [30,31]. Prostate cancer cells overexpress the protein sub-MMPs, and the amount of expression is connected with the development of tumors. All cathepsins are developed in an inactive state, and the low pH of lysosomes can activate the majority of its members [32].

2.4. Indoleamine 2,3-Dioxygenase as Biocatalyst

With an inherent biocompatibility, absence of toxicity, and specific catalysis against -d-glucose, glucose oxidase (GOx) has garnered an increased amount of attention as a biocatalyst in the field of biomedicine. It does this by catalyzing the transformation of glucose into hydrogen peroxide and gluconic acid in an effective manner, hence increasing the concentrations of these chemicals in the microenvironment of the tumors [33]. Influencing immunological responses and contributing to the progression of cancer, indoleamine 2,3-dioxygenase (IDO) is an essential enzyme in the breakdown of tryptophan. In the preclinical research phase, increased efforts have been made to construct IDO-inhibitor nanomedicines for tumor-targeted delivery. In the clinical research phase, efforts have also been increased to optimise the IDO-inhibitor-based combination therapy [34,35]. Because they play such an important part in tumor invasion, angiogenesis, and metastasis, proteases are a good candidate for use as a target for imaging probes in the early identification and treatment of cancer but also provide information on the activity and expression of a variety of markers linked with the microenvironment of the tumors [35,36].

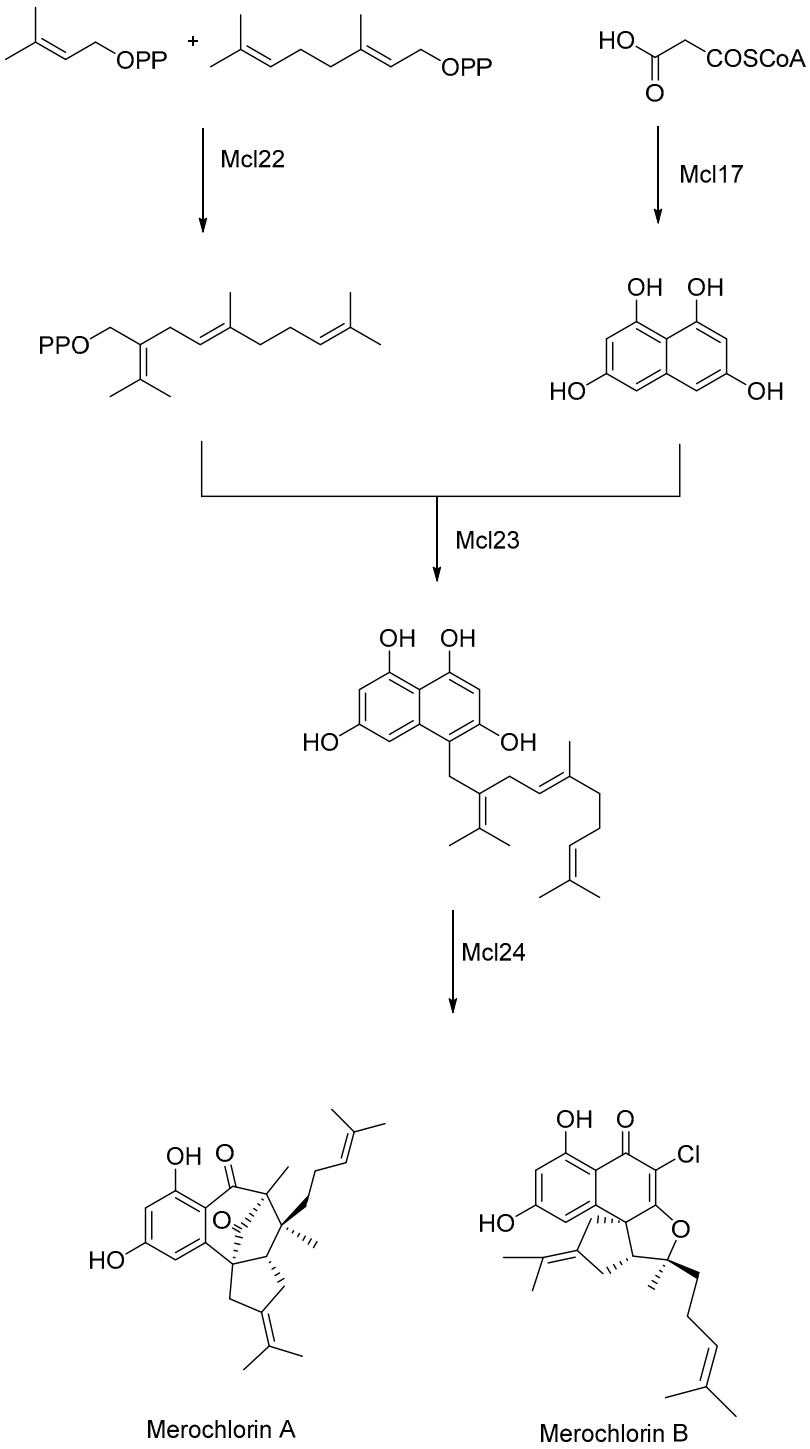
3. Biocatalyst in Natural Product Synthesis

It has been demonstrated that biocatalysts are useful for synthesizing various compounds. Benzylisoquinoline alkaloids, which are generated from phenylalanine or tyrosine, are among the most significant plant alkaloids (BIAs). The first complete synthesis of the anticancer drug noscapine was in yeast. This was accomplished by the expression of 430 enzymes originating from a wide variety of sources. Vincristine and camptothecin are two anti-cancer drugs that also utilize biocatalysts for its synthesis. Strictosidine, the major intermediate of MIAs, is produced by strictosidine synthase (STR), an enzyme that creates C–C bonds. Strictosidine is converted from the monoterpenoid secologanin and tryptophan-derived tryptamine [37–39] (Scheme 1).



Scheme 1. Synthesis of monoterpenoid indole alkaloids. In part (**A**), using the strictosidine synthase (STR) enzyme, tryptophan-derived tryptamine and monoterpenoid secologanin are converted into the essential intermediate of MIAs, strictosidine. Strictosidine then goes through many transformations to create several MIA subclasses. In part (**B**), it is demonstrated that a few STRs formed (R)-1-alkylTHBCs in medium to high optical purity by substituting secologanin with several simple aliphatic aldehydes [37–39].

Meroterpenoids are a kind of hybrid terpenoids that possess a wide range of bioactivities, such as anticancer, antioxidant, and antibacterial properties. However, the entire synthesis of these molecules by enzymatic means is very difficult to accomplish. The first thorough enzymatic synthesis of halogenated meroterpenoids was referred to as merochlorin A and B (Scheme 2) [40].



Scheme 2. Enzymatic total synthesis of the meroterpenoids merochlorin A and B. Mcl17 is a type III polyketide synthase, Mcl22 is a prenyl diphosphate synthase, Mcl23 is an aromatic prenyltransferase, and Mcl24 is a vanadium-dependent chloroperoxidase [39,40].

4. Biocatalysts Used in Nanoparticles for Tumor-Targeted Delivery

Different biological characteristics are significantly impacted in tumorous tissues compared to normal tissues that can detect these changes and deliver the drug to a particular site [41]. Achieving successful precise therapeutic administration and reducing the toxicity of traditional chemotherapeutic drugs in off-target tissues are both benefits of the drug-delivery systems' tumor-targeting and stimulus-response behavior. The administration of drugs using nanoparticles is a new method. The nanoparticle's hydrophilic nature helps them to avoid detection by the reticuloendothelial systems, their submicrometric size promotes their uptake by cells via phagocytosis, and their intrinsic stability avoids breakdown in the blood circulatory system.

In addition, they may have a large surface area, a precise distribution of pore sizes, and, if necessary, specialized surface acid–base characteristics for site-specific adaptation. Docetaxel, gemcitabine, paclitaxel, and carboplatin can be quite successful. Cisplatin has the drawback of causing nephrotoxicity, ototoxicity, hepatotoxicity, cardiotoxicity, and neurotoxicity in non-target tissues, necessitating tumor-site-specific drug administration to prevent this toxicity from occurring. By reacting with carboxyl ions such as cisplatin-poly (methacrylic acid), cisplatin-PEOpoly (aspartic acid or glutamic acid), or cisplatin-PEG-b-poly (aspartic acid), researchers have created a variety of complexes with cisplatin [42–45].

4.1. Site-Specific Drug Delivery

Nanomedicine-based drug delivery systems are becoming more popular for the treatment of cancer [46]. This is due to the fact that these systems have stimuli-responsive smart nanocarriers, which result in better site-specific drug delivery and enhanced drug solubility. The drug within the nanocarriers is shielded from the physiological environment while it is being transported to the target location by the nanocarriers [47].

There are a number of different approaches that have been taken to allow receptor targeting and intelligent drug release by nanocarriers with stimulus sensitivity. The levels of numerous matrix metalloproteinase (MMP) enzymes are much greater in tumorous tissue. These enzymes are helpful for the regulated release of drugs from nanocarriers and may be found in higher concentrations in tumorous tissue. There is an overexpression of MMP enzymes, which are proteases that govern metastasis, tumor invasiveness, and angiogenic pathways in tumor cells. The MMP enzymes have the potential to degrade a wide variety of proteins that are found in biological systems, including gelatin, collagen, fibronectin, and others. For the purpose of developing a therapeutic strategy for the treatment of lung cancer, gelatin nanoparticles that are sensitive to MMP and mannose receptors were synthesized and tested for their capacity to target particular receptors and release medicines at the appropriate time. Cisplatin was complexed with the gelatin matrix (CG-NP) and surface-decorated with con-A with the aim of assessing how effectively lung cancer cells react to stimuli and the pattern of their release. Cisplatin was also used to determine the pattern of their release (CCG-NP) [48–50].

4.2. Enzyme-Responsive Drug Delivery System

In order to target cancer, the nanosystem will become an enzyme-responsive drug delivery system to selectively target tumor cells. A class of heparanase-based, systematically released nanoparticles were enhanced with β-cyclodextrin-grafted heparin (NLC/H (D + F + S) NPs) and co-loaded with the TGF-β receptor inhibitor, doxorubicin, and ferrocene. Breast cancer metastasis was prevented by intracellular and extracellular hybrid mechanisms of the produced nanoparticles. In order to activate the ferroptosis pathway, doxorubicin and ferrocene loaded in NLC/H (D + F + S) NPs efficiently increase intracellular ROS levels. The augmented ROS also stimulated the apoptosis pathway and lowered MMP-9 expression to work in conjunction with ferroptosis for tumor treatment [51–53].

Mesoporous silica nanoparticles (MSNs) produce a matrix-metalloproteinase-responsive drug-delivery system. MSNs were immobilized with the substrate peptide PLGLAR by an amidation process. Additionally, to prevent the mesopores of polysulfonic mucopolysaccharide,

bovine serum albumin was employed as an end cap. When combined with immunotherapy, MSNs reacted to the overexpressed matrix metalloproteinases in the tumor resulting in the regulated release of the loaded drug and adverse effects [54].

4.3. Photothermal Therapy

Photothermal treatment (PTT) is a strong and non-invasive therapeutic alternative for treating many different forms of cancer. It is an acid-triggered self-destructing nano-biocatalyst for triple therapy (starvation, chemical, and photothermal combination), and these techniques are used to kill cancer cells. An enzyme-responsive nanomedicine called Pd-DOX@TGMs is injected in the microenvironment of the tumors with palladium and doxorubicin nanoparticles. The combination of chemotherapy and photothermal treatment resulted in an increase in the release of molecules such as adenosine triphosphate, calreticulin, and high mobility group box 1 protein. These chemicals increased the immunogenicity of the tumor cells that had died. More notably, the combination treatment activated the immune checkpoint defense (ICD), which in turn successfully inhibited the PD-L1 checkpoint and effectively reversed the immunosuppressive microenvironment [55,56].

The biocatalyst used in different drugs and their combination in various drug delivery system are summarized in Table 1.

Table 1. Drugs and their combinations used to develop drug-delivery systems with biocatalysts for cancer therapy.

Drugs	Drug-Delivery System	Biocatalysts Used	Results (Targeted Site/Nanomedicine Produces)	Ref.
Doxorubicin	Mesoporous silica nanoparticle	MMP-13	Reduced side effects as a targeting moiety and end-capping agent.	[54]
Doxorubicin + verapamil	Transferrin-conjugated PEGylated liposome	cytochrome P450 oxidase	To treat leukemia, efficacy for liposomal loading was observed to be 95% and 70% of DOX and VER, respectively.	[57]
Gemcitabine + doxorubicin	HPMA-Gem-Dox	MMP-2	In prostate cancer, it was observed that polymers in the form of liposomes could be utilized to deliver multiple chemotherapeutic drugs at the in vivo tumor sites simultaneously.	[58]
Unmethylated CpG-ONTs + doxorubicin	Aptamer-G4 PAMAM dendrimer conjugates	cytochrome P450 oxidase	Chemo-immunotherapy system to treat prostate cancer.	[59]
Doxorubicin + siRNA	RGDfK-G3 poly-lysine dendrimer	cytochrome P450 oxidase	Compared to free doxorubicin at high doses, the nanoparticle formed showed higher cytotoxicity in glioblastoma U87 cells.	[60]
Doxorubicin + Msurvivin T34A plasmid	Liposome	cytochrome P450 oxidase	Inhibit tumor growth in the Lewis lung-carcinoma-bearing C57BL/6 mice.	[61]
Topotecan + vincristine	PEG-liposome	Strictosidine synthase (STR) to produce the intermediate Strictosidine, and peroxidases for the production of Vincristine.	Delivery of the drugs simultaneously at a defined ratio to the cancer site showed more efficiency.	[62]

Table 1. *Cont.*

Drugs	Drug-Delivery System	Biocatalysts Used	Results (Targeted Site/Nanomedicine Produces)	Ref.
Vincristine + verapamil	PLGA	Strictosidine synthase (STR) to produce the intermediate Strictosidine and peroxidases for the production of Vincristine.	Treatment of drug-resistant human hepatocellular carcinoma in vivo.	[63]
Doxorubicin	Liposome	cytochrome P450 oxidase	Doxil® (US FDA approved nanomedicines)	[64]
Vincristine	Liposome	Strictosidine synthase (STR) to produce the intermediate Strictosidine, and peroxidases for the production of Vincristine.	Marqibo (US FDA approved nanomedicines)	[65,66]
Indoximod (NLG-8189) IDO1 inhibitors	Ce6-conjugated hyaluronic acid, Indoximod-conjugated polylysine, and aPD-L1.	2,3-dioxygenase (IDO) pathway inhibitorS 1-mt	Increase the effectiveness of immunotherapy, prevent tumor metastasis, and postoperative regeneration and regrowth.	[67]
Doxorubicin	HPMA copolymer	MMP-2	Increased entry of DOX in DU-145 cells in the presence of MMP-2 observed in prostate cancer cells.	[68]
Doxorubicin	Mesoporous silica nanoparticle	MMP-2	The photothermal molecules indocyanine green (ICG) and DOX were detected using PEG-MSN.	[69]
Cisplatin	Mesoporous silica nanoparticle	MMP-9	Cleave heptapeptide connected to a biotin group, which is coated on the outside of MSNs, as a result of the heptapeptide sequence's selective proteolysis.	[70]

5. Tumor Microenvironment and the Role of Biocatalyst in Its Improvement

5.1. Tumor Microenvironment and Other Cells

The tumor microenvironment (TME) is a complex network that is made up of extracellular matrix (ECM), stromal cells (including fibroblasts, adipocytes, neural and neuroendocrine (NE) cells, endothelial cells (ECs), and pericytes), immune and inflammatory cells, and other cell types that drive the progression of cancer cell fate from invasion to intravasation and metastasis. Both stromal and epithelial processes are reversible at the interface between the stroma and the inflammation, making this a dynamic area. During the transition into a microenvironment that is tumorigenic, molecules such as growth factors, cytokines, chemokines, enzymes, matrix proteins, and metabolic intermediates are all examples of the types of molecules that are exchanged within this dynamic space [71].

The tumor microenvironment (TME) and cancer cells interact in both ways, which results in the recruitment, activation, and reprogramming of stromal and immune/inflammatory cells in the extracellular space as well as their continued presence. Alterations in the genetic and epigenetic make-up of tumor cells, as well as the dynamic interaction between tumor cells and the TME that surrounds them, both play a role in regulating the genesis and progression of tumors. Tumor cells, stromal cells (such as stromal fibroblasts), endothelial cells, immune cells (such as microglia, macrophages, and lymphocytes), and the non-cellular components of the extracellular matrix (collagen, fibronectin, hyaluronan, and laminin) are all examples of the many different types of cells that are found in the tumor microenvironment (TME) [72].

5.2. Macrophages and Myeloid Suppressor Cells

Tumor-associated macrophages (TAMs) block lymphocyte activity by producing inhibitory cytokines such as IL-10, prostaglandins, or reactive oxygen species. Myeloid suppressor cells (MSCs) are immature dendritic cells origin in the bone marrow and display the surface markers CD34, CD33, CD13, and CD15. MSCs are seen in human cancers inducing iNOS in neighboring cells and producing an abundance of arginase 1, an enzyme that is involved in the metabolism of L-arginine. This enzyme works in tandem with iNOS to boost production of superoxide and nitric oxide, which in turn promotes the development of tumors and reduces the activity of immune cells, resulting in the formation of a novel ecosystem during the process of a tumor's growth. Produced by tumors, they also shape, regulate, and influence the cellular and molecular processes occurring in their surrounding tissues (Figure 2). [73,74].

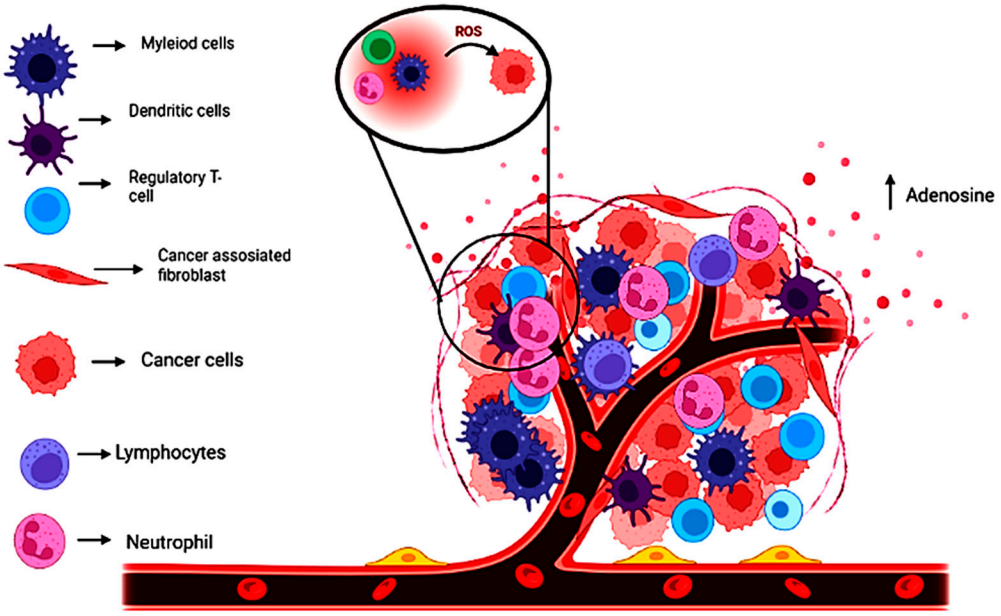


Figure 2. Immune cell trafficking and reactive oxygen species (ROS) generation in tumor microenvironment. ROS are responsible for the generation and suppression of immune cells, as well as the growth of tumors.

The tumor cells, which serve as the central node of the tumor microenvironment (TME), use complex signaling networks to control the behavior of both cellular and non-cellular components. This allows the tumor cells to co-opt healthy cells for their own purposes. Because of these cross-talks, tumors grow and continue to spread, patients have poor treatment responses, and they acquire resistance to a number of different medications (MDR).

5.3. Non-Malignant Cells

Throughout the entire process of the development and spread of cancer, the nonmalignant cells present in the tumor microenvironment (TME) are essential in encouraging carcinogenesis. Recent discoveries in the field of tumor biology have illuminated the importance of conducting research into the myriad of interactions that take place between cancer cells and the microenvironment in which they reside in order to achieve a comprehensive understanding of the various mechanisms that underlie the growth and spread of tumors. Tissue degeneration, carcinogenesis, and the evolution of tumors may all be traced back to interactions between tumor cells and the non-cellular (ECM) and cellular components of the tumors microenvironment (TME). On the other hand, interactions in reactive non-neoplastic cells, genetically-altered tumors cells, and extracellular matrix (ECM) effectively control the majority of the stages of tumorigenesis. These stages include clonal evolution, cancer

heterogeneity, epithelial–mesenchymal transition (EMT), migration, invasion, metastasis development, neovascularization, apoptosis, and chemotherapeutic drug resistance [75,76].

5.4. Bioenzymes and Their Role in Carrying Biocatalysts as Nanomedicines

Bioenzymes as a form of alternative therapeutics have great advantages as compared to conventional small-molecular drugs which include greater bioactivity, better specificity, lower risk of adverse effects, and negligible resistance in case of numerous cancer treatments. In preclinical studies, it was shown that enzymes both directly induce the death of cancer cells and improve the efficacy of chemotherapy. However, enzymes often have some disadvantages such as low stability, a short blood circulation characteristic, and poor membrane permeability. Because of these problems, the enzymes' bioavailability and their potential for use in the treatment of cancer in vivo are severely restricted, which is a significant constraint, even if it is sometimes necessary to inject enzymes on a daily basis in order to get the therapeutic advantages. The use of nanomedicines in more widespread amounts has led to a substantial improvement in the efficiency of cancer therapy [77].

A successful treatment for tumors was created using biocatalytic processes, based on which appropriate nanocatalysts can be chosen. For example, the pH-dependent enzyme-like activity of ferromagnetic nanoparticles (Fe_2O_3 or Fe_3O_4 NPs) has been shown in vitro and in vivo. Under neutral pH conditions, these iron oxide nanoparticles (IONPs) exhibited catalase-like activity by catalytically decomposing H_2O_2 into non-toxic H_2O and O_2. More surprisingly, under acidic conditions, they displayed peroxidase-like activity by disproportionately converting H_2O_2 into extremely deadly reactive oxygen species (ROS)—hydroxyl radicals (OH) [78–80]. Therefore, IONPs are thought to be promising tumor-therapeutic nanozymes, since their site-specific creation of the hydroxyl radicals might promote the apoptosis and death of cancer cells in the moderately acidic microenvironment of the tumor, while leaving the normal cells unharmed. However, even when catalysed by Fe_3O_4 NPs, the intracellular H_2O_2 level in tumor cells is too low to allow IONPs to create sufficient amounts of hydroxyl radicals to achieve a desirable catalytic performance. Therefore, a plan must be devised to increase the concentration of H_2O_2 within tumors. [81–83].

5.5. Biocatalyst Used for In Vitro/In Vivo Studies in Cancer Therapy

The goal of the current cancer therapy approaches is to increase the effectiveness of treatment against tumors by inducing undesirable tumor metastasis or other significant impacts on the environment of normal tissues. When compared to non-cancerous cells, TME exhibits dramatically different metabolic rates, intermediates, and pH. Thus, in vitro and in vivo cancer therapy with TME-responsive nanocatalysts have recently been carried out.

5.6. Enzyme-Based Nanomedicines for Tumor Microenvironment

Enzyme-based nanomedicines have the capacity to affect the microenvironment of tumors, which has the potential to boost the efficiency of anticancer therapy. This ability is in addition to the fact that these medicines may directly kill cancer cells. Since traditional cancer therapeutic procedures may have unanticipated negative effects on nearby normal tissues and/or promote tumor spread, targeting the tumor microenvironment (TME) has been used as a means of increasing the anti-tumor therapeutic efficiency of cancer therapy. When compared to non-cancerous cells, tumor microenvironment (TME) cells have significantly different metabolic rates, intermediates, and pH levels. In point of fact, it has been hypothesized that the potential cancer treatment could be realized with minimal effects on non-target cells if the inherent characteristics of the TME in the presence of nanocatalysts could initiate the Fenton reaction (Figure 3). This is because the TME is thought to be the environment in which cancer cells thrive [84,85].

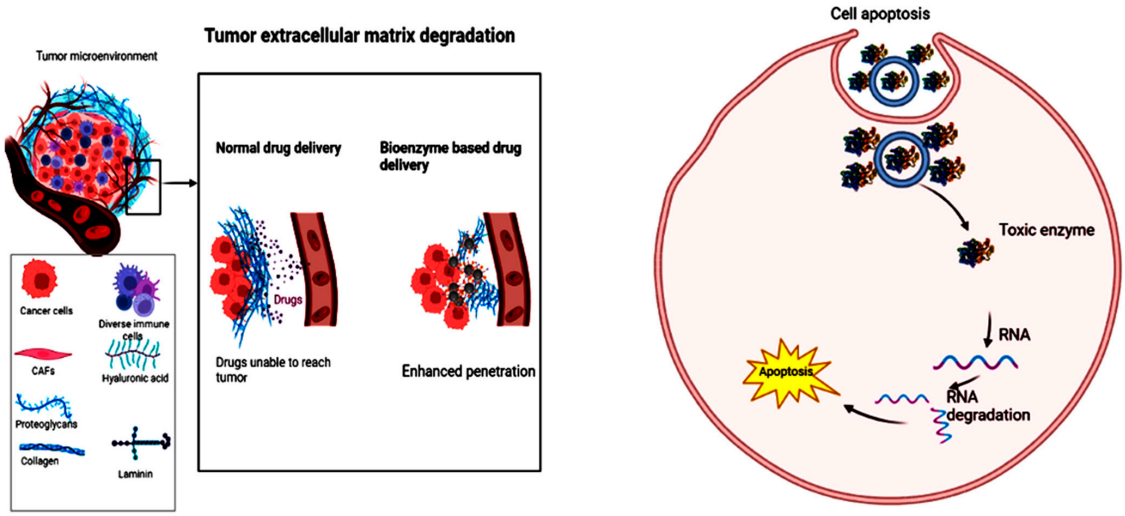


Figure 3. Cancer associated fibroblasts (CAFs) are a complex and abundant cell type within the tumor microenvironment. These fibroblasts help to remodeling the extracellular matrix in tumor microenvironment and decrease drug penetration in tumor tissue. Bio enzymes base nanomedicine enhanced the penetration insides the tumor tissue and cause apoptosis.

5.7. Magnetic Nanocatalysts in TME

In an acidic TME, magnetic nanocatalysts can actually accelerate the Fenton reaction, which produces an abundance of deadly OH. In cancer cells, ferroptosis occurs as a result of the Fenton reaction. This process is dependent on iron (Fe) and reactive oxygen species (ROS). In cancerous cells, the H_2O_2 molecule acts as a reactant to begin ferroptosis, and the Fe^{2+} plays the role of the catalyst in this process. It is widely known that acidic conditions are preferable for the Fenton reaction; hence, because of its acidic nature, TME may be considered a useful component for starting the Fenton reaction. This is because acidic conditions are favorable for the Fenton reaction [81–83]. It has become increasingly common for researchers to work on the conception and development of nanostructure-based biocatalytic reactions that are capable of inducing ferroptosis in a wide range of cancers.

Nanostructures based on iron are good candidates for selective accumulation in tumor regions through active as well as passive targeting mechanisms. The ferroptosis process cannot begin until these nano-based platforms have been degraded into either ferric iron (Fe^{2+}) or ferric iron (Fe^{3+}) in the endocytic organelles of cancer cells. In general, this catalytic process results in an imbalance between the production and removal of reactive oxygen species (ROS), which may ultimately lead to severe oxidative-stress-induced apoptosis. The disproportionation of hydrogen peroxide may be caused by the stimulation of an intratumoral Fenton reaction [86,87].

Ferroptosis-based nanocatalysts that contain the potential to change endogenous H_2O_2 to OH is an excellent technique for the treatment of cancer. In addition, since OH has a greater potential for oxidation than singlet oxygen does, the formation of these species is in high demand for the Fenton reaction. The short half-life of OH, on the other hand, makes it difficult for it to permeate into further-away areas and this indicates that it can only cause a small number of oxidative processes, such as protein oxidation, lipid oxidation, and DNA damage. Given the evidence so far, it is plausible to draw the conclusion that tumor-selective Fenton-based nanocatalysts should be the main focus of cancer treatment. Recently, it has been discovered that reducing oxidative stress, which is brought on by reactive oxygen species (ROS), may be an effective cancer treatment strategy [86,87].

5.8. Glucose-Oxidase-Based Enzyme-Catalyzed Technique

The glucose-oxidase-based enzyme-catalyzed technique has received a lot of interest recently due to its unique catalytic properties in the depletion of b-D-glucose with ROS

generation, inherent biocompatibility, and lack of toxicity [34,86]. Most of the published glucose-oxidase-based biocatalytic methods have mainly concentrated on encapsulating the enzyme inside tumor-specific nanocarriers to increase its stability, lengthen the amount of time it remains in the blood circulation, and improve its capacity to target tumors.

Although significant progress has been made, there is still no acceptable GOD-based design method for predicting in vivo behaviors and controlling glucose oxidase's therapeutic effectiveness in clinical trials. There is a significant gap in the field. Boosting cellular glutathione (GSH) levels lowers oxidative stress; this is an established fact [86,88–90].

Therefore, it is advantageous to develop functional nano systems that can reduce the quantity of glutathione present in cells in order to improve therapeutic efficacy. The cascade mechanism consisting of GOD-catalyzed H_2O_2 production followed by GSH depletion has also been suggested as a way to manage oxidative stress. As a result, adding GSH scavengers and glucose-oxidase-catalyzed hydrogen peroxide (H_2O_2) generation to a nanotherapeutics system has the potential to greatly improve the effectiveness of the therapy. The increased oxidative stress brought on by the cascade system, however, is a double-edged sword for applications that take place in vivo and inevitably damages healthy tissues [91,92].

It is still difficult to predict and control the therapeutic effects of the glucose-oxidase-catalyzed cascade process in either in vitro or in vivo situations because of the dynamic nature of oxidative stress. In this context, it is envisaged that the interaction of GOD-induced oxidative stress with optical imaging/sensing may result in synergistic therapeutic efficacy with real-time feedback data (Figure 4) [93–95].

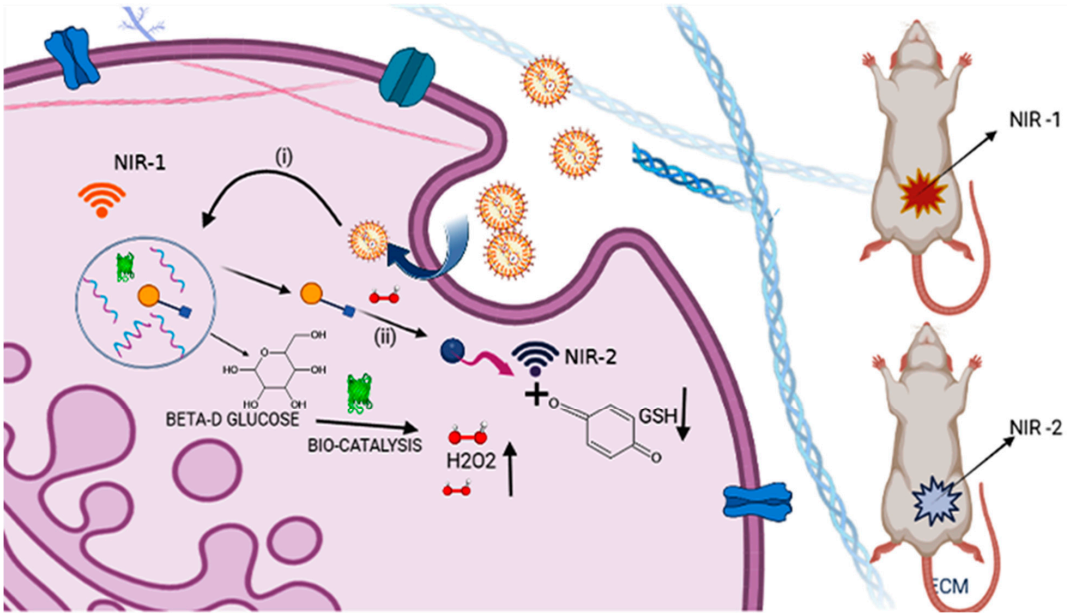


Figure 4. Cascade tumor-specific nanotheranostics integrated with the in vivo real-time tracking of biocatalysts and synergistic treatment. The acidic cellular microenvironment causes nanoparticle dissociation. Then glucose oxidase (GOD) turn-on emission at 825 nm and released near-infrared (NIR-1). The released GOD catalyzes the oxidation process of oxygen and glucose, producing a huge quantity of H_2O_2 and halting tumor progression. A high concentration of H_2O_2 causes a dual-channel reaction (a dramatic shift from 825 to 650 nm, NIR-2) that suppresses glutathione (GSH)levels, resulting in synergistic tumor therapy.

Guo et al. investigated in vivo real-time monitoring of tumor-specific biocatalysis for combination cancer therapy using cascade nanotheranostics. In order to significantly improve the efficiency of synergistic therapy while giving real-time feedback data, the scientists created a tumor-specific cascade nanotheranostic system (BNG) that integrates

dual-channel fluorescence sensing and oxidative stress catalysed by glucose oxidase (GOD). While the nanotheranostic system in the blood circulatory system was completely silent, the near-infrared (NIR) fluorescence at 825 nm was increased when the GOD enzymes were released specifically in the cancer site. Then, GOD catalyzes the generation of H_2O_2, which triggers a cascade reaction that depletes GSH and results in an optical output of NIR fluorescence at 650 nm, allowing for a synergistic approach to the therapy of cancer [95].

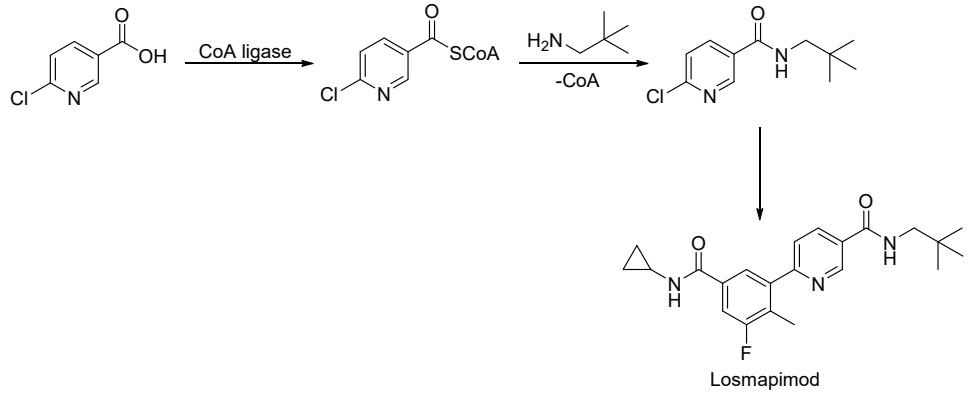
Duan et al. investigated glucose-oxidase–polycation–iron nanoconjugates as a self-activated cascade biocatalyst in cancer immunotherapy. This study found that glucose-oxidase–polycation–iron nanoconjugates also had a self-activated cascade biocatalysis that breaks down glucose and generates very damaging hydroxyl radicals, in addition to increased cellular absorption and cancer retention. For more effective immune checkpoint blockade therapy, they successfully initiate the immunogenic cell death pathway [86,96].

5.9. Other Biocatalytic Reactions

Al Hilfi et al. studied that biocatalysis of new-generation SB-T-taxane precursors that are effective against paclitaxel-resistant cancer cells. According to the findings, the cells utilized the bacteria's stores of acetyl CoA and n-propionyl CoA to create the synthetic chemical cyclopropane carbonyl CoA and the naturally occurring products acetyl CoA and n-propionyl CoA, which were subsequently utilized by the acyltransferase to acylate 10-O-deacetylbaccatin III in vivo [97]. Polyethylene-glycol-conjugated, ferrous-ion-containing two-dimensional (2D) ultrathin LDH monolayer nanosheets (PEG/Fe-LDH) have been created by Zhang et al. The multilayer PEG/Fe-LDH quickly dissolved to efficiently create Fe2+ when the NPs were administered and transported into particular tumor cells and tissues. The intracellular Fenton catalytic reaction might create deadly hydroxyl radicals quickly for tumor eradication by stimulating the dissociation of intratumoral H_2O_2 molecules [98].

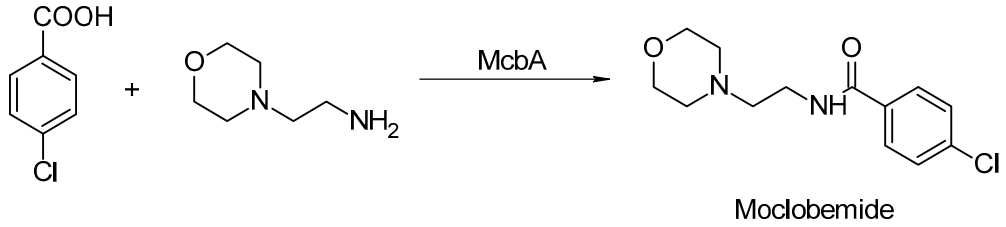
6. Biocatalyst Used for Synthesis of Different Compounds

Philpott et al., 2018, attempted to form amide bonds with the help of ATP-dependent CoA ligases along with N-acetlytransferases [99]. He scanned a large amount of these enzymes as well as their substrate spectra. By integrating these enzymes, a wide range of amide products was formed (Scheme 3). They synthesized their reaction using *E. coli* as a whole-cell biocatalyst. Losmapimod is a clinical drug used to overcome resistance in non-small-cell lung cancer [100].



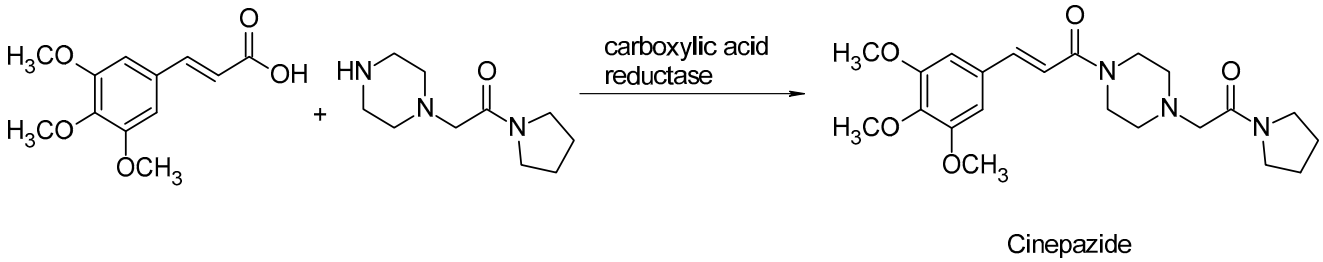
Scheme 3. Synthesis of losmapimod *via* CoA ligase (Coenzyme-A ligase). CoA ligase and N-acetlytransferases can easily adjust to the dynamic and transitional environmental pressures through evolutionary processes. By combining CoA ligase and N-acetlytransferases with favourable substrate profiles, biocatalytic mechanisms can be reliably constructed to allow access to structurally diverse secondary and tertiary amides in high yield [99].

Petchey et al. studied the tolerance of substrate using various carboline derivatives. Another research suggested favourable outcomes regarding the enzyme's substrate range [101,102] (Scheme 4). Based on their study, future protein engineering could enhance the characteristics and substrate acceptance of the enzyme [102]. Moclobemide is a monoamine oxidase inhibitor that is used in the treatment of prostate cancer [103].



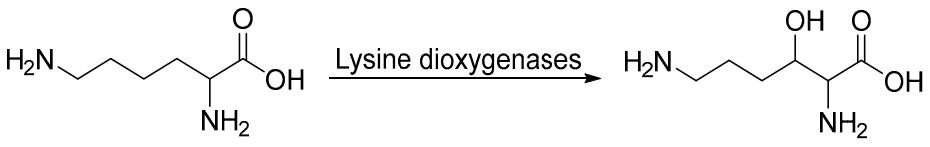
Scheme 4. ATP-based amide bond synthetase (ABS) McbA was exploited in the synthesis of the monoamine oxidase A inhibitor moclobemide, through the reaction of 4-chlorobenzoic acid with 1.5 equiv of 4- (2-aminoethyl) morpholine.

Lubberink et al. employed a truncated version of a carboxylic acid reductase from Mycobacterium marinum denoted CARmm-A [104]. A recovery framework, i.e., polyphosphate kinase class III, was used to optimise the reaction and overcome the issue of stoichiometrically needed ATP. Because of this, many products could now be attainable in one single step, which includes cinepazide, a vasodilator that is also a breast cancer drug [105] (Scheme 5).



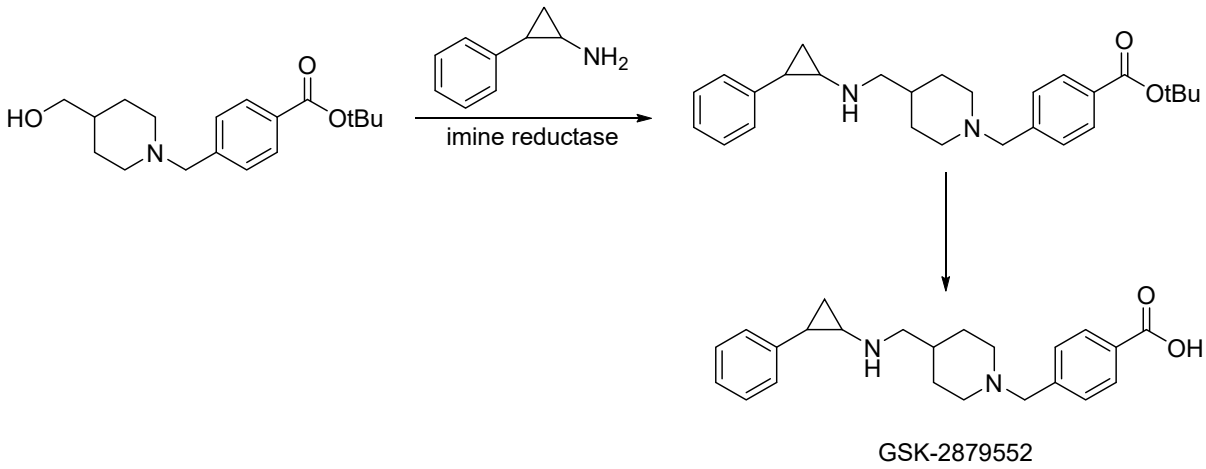
Scheme 5. Synthesis of cinepazide by the truncated carboxylic acid reductase [104].

Lysine dioxygenases help in the process of hydroxylation of the amino acid L-lysine [106–108] (Scheme 6). They are employed in combination with the chemoenzymatic production of the potential APIs tambromycin [109] and cepafungin I [110], that are investigated for their use in the treatment of cancer.



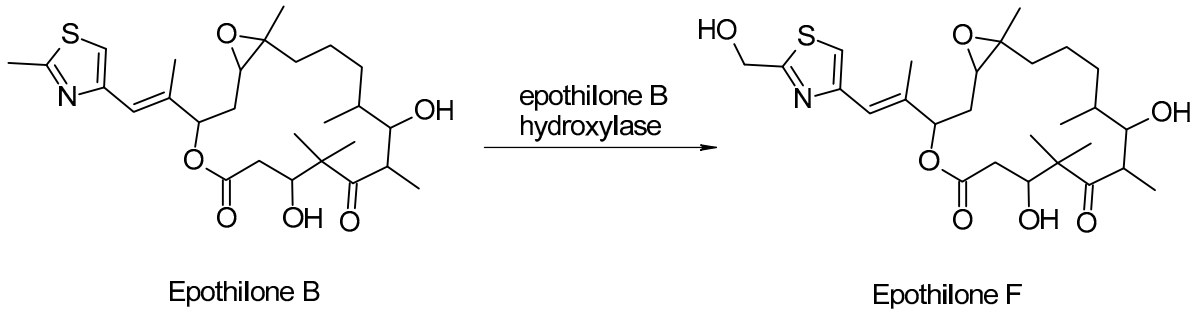
Scheme 6. Biocatalysis via lysine dioxygenases [108].

GSK-2879552, an experimental drug, was synthesized using an imine reductase [111,112] (Scheme 7). Clinical trials for this drug's mechanism in small-cell lung cancer, acute myeloid leukaemia, and myelodysplastic syndrome were explored but then they were later terminated [112].



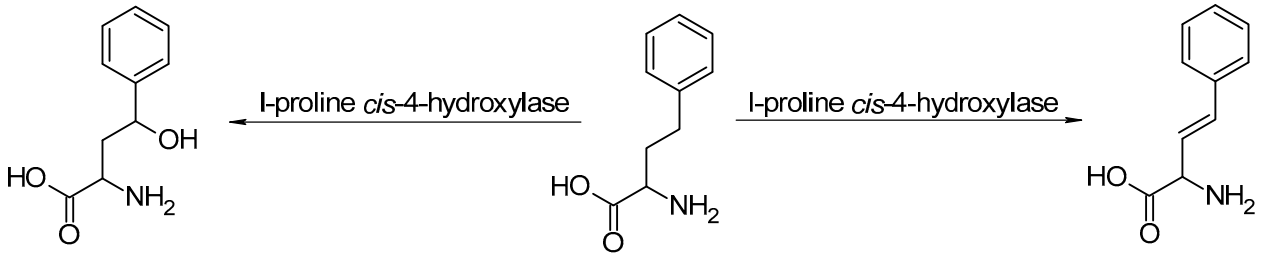
Scheme 7. Enzymatic catalysis for the synthesis of GSK-2879552 [112].

Several clinical studies have examined the synthesis of epothilone analogs in order to enhance antitumor efficacy [113–116] (Scheme 8). A variety of purposes have been served by cloning epothilone B hydroxylase. To obtain higher yields, it is used to hydroxylate epothilone B to epothilone F [117].



Scheme 8. Hydroxylation of epothilone B to epothilone F [116].

Meyer et al., 2021, created L-proline cis-4-hydroxylase to hydroxylate a new substrate [118,119] (Scheme 9). This hydroxylated resultant is an intermediate in the production of kynurenine monooxygenase inhibitors used in the treatment of cancer.



Scheme 9. Hydroxylation of l-homophenylalanine [119].

Therapeutic peptides, for example, anticancer agent bleomycin, are biosynthesized by large enzyme complexes, which are made by non-ribosomal peptide synthetases [120,121].

7. Summary and Challenges

In recent years, biocatalysts have become one of the most studied supports due to their distinct structural properties and multivalent functionalization along with exceptional

chemical, mechanical, and electrical characteristics. A recent development in nanomaterial production has led to new options for investigating their potential application as nanoscaffolds for biocatalysis. In comparison to traditional immobilized enzymes, nanobioconjugates exhibit greater functional stability and greater catalytic activity. Although nanobiotechnology has made great strides in recent years, it still faces significant challenges before it can fully take advantage of nanomaterials as biomolecule carriers. There is an urgent need to better understand how nanomaterials may affect proteins, enzymes, and other biomolecules. An effective nanobiocatalytic system requires, for example, in-depth research into the effect of structure on manufactured nano supports and the effect of functionalization or activation agents on the loading efficiency and orientation of proteins confined to the nanoplatform. Moreover, the field of industrial biocatalysis and biotransformation, organic synthesis, enzyme-mediated biosensing, and biofuel and energy production may benefit from the re-engineering and design of new nano-based materials with fine-tuned structural properties and functionalities exhibiting minimum toxicity, high biocompatibility, and insignificant environmental effects, in addition to the selection of suitable immobilizations method.

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References

1. Burton, S.; Cowan, D.; Woodley, J. The search for the ideal biocatalyst. *Nat. Biotechnol.* **2002**, *20*, 37–45. [CrossRef]
2. Mansi, K.; Kumar, R.; Kaur, J.; Mehta, S.; Pandey, S.K.; Kumar, D.; Dash, A.K.; Gupta, N. DL-Valine assisted fabrication of quercetin loaded CuO nanoleaves through microwave irradiation method: Augmentation in its catalytic and antimicrobial efficiencies. *Environ. Nanotechnol. Monit. Manag.* **2020**, *14*, 100306. [CrossRef]
3. Bell, E.L.; Finnigan, W.; France, S.P.; Green, A.P.; Hayes, M.A.; Hepworth, L.J.; Lovelock, S.L.; Niikura, H.; Osuna, S.; Romero, E.; et al. Biocatalysis. *Nat. Rev. Methods Prim.* **2021**, *1*, 46. [CrossRef]
4. Alcántara, A.R. Biocatalysis and Pharmaceuticals: A Smart Tool for Sustainable Development. *Catalysts* **2019**, *9*, 792. [CrossRef]
5. Yang, G.; Ding, Y. Recent advances in biocatalyst discovery, development and applications. *Bioorganic Med. Chem.* **2014**, *22*, 5604–5612. [CrossRef] [PubMed]
6. Wang, P. Nanoscale biocatalyst systems. *Curr. Opin. Biotechnol.* **2006**, *17*, 574–579. [CrossRef]
7. Turner, N.J.; Humphreys, L. *Biocatalysis in Organic Synthesis: The Retrosynthesis Approach*; RSC: London, UK, 2018.
8. Wahler, D.; Reymond, J.-L. Novel methods for biocatalyst screening. *Curr. Opin. Chem. Biol.* **2001**, *5*, 152–158. [CrossRef]
9. Almonacid, D.E.; Yera, E.R.; Mitchell, J.B.; Babbitt, P.C. Quantitative comparison of catalytic mechanisms and overall reactions in convergently evolved enzymes: Implications for classification of enzyme function. *PLoS Comput. Biol.* **2010**, *6*, e1000700. [CrossRef]
10. Silverman, R.B. *Organic Chemistry of Enzyme-Catalyzed Reactions*; Academic Press: Cambridge, MA, USA, 2002.
11. Es, I.; Vieira, J.D.G.; Amaral, A.C. Principles, techniques, and applications of biocatalyst immobilization for industrial application. *Appl. Microbiol. Biotechnol.* **2015**, *99*, 2065–2082. [CrossRef]
12. Dash, A.K.; Mukherjee, D.; Dhulap, A.; Haider, S.; Kumar, D. Green chemistry appended synthesis, metabolic stability and pharmacokinetic assessment of medicinally important chromene dihydropyrimidinones. *Bioorganic Med. Chem. Lett.* **2019**, *29*, 126750. [CrossRef]
13. Li, M.; Qin, J.; Xiong, K.; Jiang, B.; Zhang, T. Review of arginase as a promising biocatalyst: Characteristics, preparation, applications and future challenges. *Crit. Rev. Biotechnol.* **2021**, *42*, 651–667. [CrossRef] [PubMed]
14. Gao, X.; Feng, J.; Song, S.; Liu, K.; Du, K.; Zhou, Y.; Lv, K.; Zhang, H. Tumor-targeted biocatalyst with self-accelerated cascade reactions for enhanced synergistic starvation and photodynamic therapy. *Nano Today* **2022**, *43*, 101433. [CrossRef]
15. Mahato, R.; Tai, W.; Cheng, K. Prodrugs for improving tumor targetability and efficiency. *Adv. Drug Deliv. Rev.* **2011**, *63*, 659–670. [CrossRef] [PubMed]

16. Wang, L.; Zhu, B.; Deng, Y.; Li, T.; Tian, Q.; Yuan, Z.; Ma, L.; Cheng, C.; Guo, Q.; Qiu, L. Biocatalytic and Antioxidant Nanostructures for ROS Scavenging and Biotherapeutics. *Adv. Funct. Mater.* **2021**, *31*, 2101804. [CrossRef]
17. Deryugina, E.I.; Quigley, J.P. Matrix metalloproteinases and tumor metastasis. *Cancer Metastasis Rev.* **2006**, *25*, 9–34. [CrossRef]
18. Liu, T.; Liu, W.; Zhang, M.; Yu, W.; Gao, F.; Li, C.; Wang, S.-B.; Feng, J.; Zhang, X.-Z. Ferrous-Supply-Regeneration Nanoengineering for Cancer-Cell-Specific Ferroptosis in Combination with Imaging-Guided Photodynamic Therapy. *ACS Nano* **2018**, *12*, 12181–12192. [CrossRef] [PubMed]
19. Li, C.; Li, Y.; Li, G.; Wu, S. Functional Nanoparticles for Enhanced Cancer Therapy. *Pharmaceutics* **2022**, *14*, 1682. [CrossRef]
20. Pellikainen, J.M.; Ropponen, K.M.; Kataja, V.V.; Kellokoski, J.K.; Eskelinen, M.J.; Kosma, V.-M. Expression of Matrix Metalloproteinase (MMP)-2 and MMP-9 in Breast Cancer with a Special Reference to Activator Protein-2, HER2, and Prognosis. *Clin. Cancer Res.* **2004**, *10*, 7621–7628. [CrossRef]
21. Li, H.-C.; Cao, D.-C.; Liu, Y.; Hou, Y.-F.; Wu, J.; Lu, J.-S.; Di, G.-H.; Liu, G.; Li, F.-M.; Ou, Z.-L.; et al. Prognostic value of matrix metalloproteinases (MMP-2 and MMP-9) in patients with lymph node-negative breast carcinoma. *Breast Cancer Res. Treat.* **2004**, *88*, 75–85. [CrossRef]
22. Zhou, R.; Xu, L.; Ye, M.; Liao, M.; Du, H.; Chen, H. Formononetin Inhibits Migration and Invasion of MDA-MB-231 and 4T1 Breast Cancer Cells by Suppressing MMP-2 and MMP-9 Through PI3K/AKT Signaling Pathways. *Horm. Metab. Res.* **2014**, *46*, 753–760. [CrossRef]
23. Ji, T.; Li, S.; Zhang, Y.; Lang, J.; Ding, Y.; Zhao, X.; Zhao, R.; Li, Y.; Shi, J.; Hao, J.; et al. An MMP-2 Responsive Liposome Integrating Antifibrosis and Chemotherapeutic Drugs for Enhanced Drug Perfusion and Efficacy in Pancreatic Cancer. *ACS Appl. Mater. Interfaces* **2016**, *8*, 3438–3445. [CrossRef]
24. Renoux, B.; Raes, F.; Legigan, T.; Péraudeau, E.; Eddhif, B.; Poinot, P.; Tranoy-Opalinski, I.; Alsarraf, J.; Koniev, O.; Kolodych, S.; et al. Targeting the tumour microenvironment with an enzyme-responsive drug delivery system for the efficient therapy of breast and pancreatic cancers. *Chem. Sci.* **2017**, *8*, 3427–3433. [CrossRef] [PubMed]
25. Abid, M.; Naveed, M.; Azeem, I.; Faisal, A.; Nazar, M.F.; Yameen, B. Colon specific enzyme responsive oligoester crosslinked dextran nanoparticles for controlled release of 5-fluorouracil. *Int. J. Pharm.* **2020**, *586*, 119605. [CrossRef] [PubMed]
26. Barve, A.; Jin, W.; Cheng, K. Prostate cancer relevant antigens and enzymes for targeted drug delivery. *J. Control. Release* **2014**, *187*, 118–132. [CrossRef]
27. Lövgren, J.; Rajakoski, K.; Karp, M.; Lundwall, Å.; Lilja, H. Activation of the Zymogen Form of Prostate-Specific Antigen by Human Glandular Kallikrein 2. *Biochem. Biophys. Res. Commun.* **1997**, *238*, 549–555. [CrossRef]
28. Balk, S.P.; Ko, Y.-J.; Bubley, G.J. Biology of Prostate-Specific Antigen. *J. Clin. Oncol.* **2003**, *21*, 383–391. [CrossRef] [PubMed]
29. Cary, K.C.; Cooperberg, M.R. Biomarkers in prostate cancer surveillance and screening: Past, present, and future. *Ther. Adv. Urol.* **2013**, *5*, 318–329. [CrossRef] [PubMed]
30. Mohamed, M.M.; Sloane, B.F. multifunctional enzymes in cancer. *Nat. Rev. Cancer* **2006**, *6*, 764–775. [CrossRef]
31. Tan, G.-J.; Peng, Z.-K.; Lu, J.-P.; Tang, F.-Q. Cathepsins mediate tumor metastasis. *World J. Biol. Chem.* **2013**, *4*, 91–101. [CrossRef]
32. Palermo, C.; Joyce, J.A. Cysteine cathepsin proteases as pharmacological targets in cancer. *Trends Pharmacol. Sci.* **2008**, *29*, 22–28. [CrossRef]
33. Fu, L.-H.; Qi, C.; Lin, J.; Huang, P. Catalytic chemistry of glucose oxidase in cancer diagnosis and treatment. *Chem. Soc. Rev.* **2018**, *47*, 6454–6472. [CrossRef] [PubMed]
34. Sharma, A.; Tonk, R.; Shekhar, R.; Dohare, S.; Kumar, D. Need to focus on inhibitory activity of benzimidazole analogues against indolamine 2,3-dioxygenase-1 (IDO-1). *EXCLI J.* **2022**, *21*, 904–905. [CrossRef] [PubMed]
35. Guo, Y.; Liu, Y.; Wu, W.; Ling, D.; Zhang, Q.; Zhao, P.; Hu, X. Indoleamine 2,3-dioxygenase (Ido) inhibitors and their nanomedicines for cancer immunotherapy. *Biomaterials* **2021**, *276*, 121018. [CrossRef] [PubMed]
36. Mumtaz, T.; Qindeel, M.; Asim.Ur.Rehman; Tarhini, M.; Ahmed, N.; Elaissari, A. Exploiting proteases for cancer theranostic through molecular imaging and drug delivery. *Int. J. Pharm.* **2020**, *587*, 119712. [CrossRef] [PubMed]
37. Li, Y.; Li, S.; Thodey, K.; Trenchard, I.; Cravens, A.; Smolke, C.D. Complete biosynthesis of noscapine and halogenated alkaloids in yeast. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E3922–E3931. [CrossRef]
38. Pan, Q.; Mustafa, N.R.; Tang, K.; Choi, Y.H.; Verpoorte, R. Monoterpenoid indole alkaloids biosynthesis and its regulation in Catharanthus roseus: A literature review from genes to metabolites. *Phytochem. Rev.* **2015**, *15*, 221–250. [CrossRef]
39. Yi, D.; Bayer, T.; Badenhorst, C.P.S.; Wu, S.; Doerr, M.; Höhne, M.; Bornscheuer, U.T. Recent trends in biocatalysis. *Chem. Soc. Rev.* **2021**, *50*, 8003–8049. [CrossRef]
40. Teufel, R.; Kaysser, L.; Villaume, M.T.; Diethelm, S.; Carbullido, M.K.; Baran, P.S.; Moore, B.S. One-Pot Enzymatic Synthesis of Merochlorin A and B. *Angew. Chem. Int. Ed.* **2014**, *53*, 11019–11022. [CrossRef]
41. Ashfaq, U.A.; Riaz, M.; Yasmeen, E.; Yousaf, M.Z. Recent Advances in Nanoparticle-Based Targeted Drug-Delivery Systems against Cancer and Role of Tumor Microenvironment. *Crit. Rev. Ther. Drug Carr. Syst.* **2017**, *34*, 317–353. [CrossRef]
42. Kowalczuk, A.; Stoyanova, E.; Mitova, V.; Shestakova, P.; Momekov, G.; Momekova, D.; Koseva, N. Star-shaped nano-conjugates of cisplatin with high drug payload. *Int. J. Pharm.* **2011**, *404*, 220–230. [CrossRef]
43. Nishiyama, N.; Kataoka, K. Preparation and characterization of size-controlled polymeric micelle containing cis-dichlorodiammine platinum(II) in the core. *J. Control. Release* **2001**, *74*, 83–94. [CrossRef] [PubMed]
44. Yokoyama, M.; Okano, T.; Sakurai, Y.; Suwa, S.; Kataoka, K. Introduction of cisplatin into polymeric micelle. *J. Control. Release* **1996**, *39*, 351–356. [CrossRef]

45. Tseng, C.-L.; Su, W.-Y.; Yen, K.-C.; Yang, K.-C.; Lin, F.-H. The use of biotinylated-EGF-modified gelatin nanoparticle carrier to enhance cisplatin accumulation in cancerous lungs via inhalation. *Biomaterials* **2009**, *30*, 3476–3485. [CrossRef] [PubMed]
46. Sharma, A.; Shambhwani, D.; Pandey, S.; Singh, J.; Lalhlenmawia, H.; Kumarasamy, M.; Singh, S.K.; Chellappan, D.K.; Gupta, G.; Prasher, P.; et al. Advances in Lung Cancer Treatment Using Nanomedicines. *ACS Omega* **2022**, *8*, 10–41. [CrossRef]
47. Du, J.; Lane, L.A.; Nie, S. Stimuli-responsive nanoparticles for targeting the tumor microenvironment. *J. Control. Release* **2015**, *219*, 205–214. [CrossRef]
48. Nezhad-Mokhtari, P.; Arsalani, N.; Ghorbani, M.; Hamishehkar, H. Development of biocompatible fluorescent gelatin nanocarriers for cell imaging and anticancer drug targeting. *J. Mater. Sci.* **2018**, *53*, 10679–10691. [CrossRef]
49. Farooq, M.A.; Aquib; Farooq, A.; Khan, D.H.; Maviah, M.B.J.; Filli, M.S.; Kesse, S.; Boakye-Yiadom, K.O.; Mavlyanova, R.; Parveen, A.; et al. Recent progress in nanotechnology-based novel drug delivery systems in designing of cisplatin for cancer therapy: An overview. *Artif. Cells Nanomed. Biotechnol.* **2019**, *47*, 1674–1692. [CrossRef]
50. Vaghasiya, K.; Ray, E.; Singh, R.; Jadhav, K.; Sharma, A.; Khan, R.; Katare, O.P.; Verma, R.K. Efficient, enzyme responsive and tumor receptor targeting gelatin nanoparticles decorated with concanavalin-A for site-specific and controlled drug delivery for cancer therapy. *Mater. Sci. Eng. C* **2021**, *123*, 112027. [CrossRef]
51. Stern, R.; Jedrzejas, M.J. Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action. *Chem. Rev.* **2006**, *106*, 818–839. [CrossRef]
52. Chao, K.L.; Muthukumar, L.; Herzberg, O. Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis. *Biochemistry* **2007**, *46*, 6911–6920. [CrossRef]
53. Zhang, J.; Yang, J.; Zuo, T.; Ma, S.; Xokrat, N.; Hu, Z.; Wang, Z.; Xu, R.; Wei, Y.; Shen, Q. Heparanase-driven sequential released nanoparticles for ferroptosis and tumor microenvironment modulations synergism in breast cancer therapy. *Biomaterials* **2020**, *266*, 120429. [CrossRef] [PubMed]
54. Liu, Y.; Ding, X.; Li, J.; Luo, Z.; Hu, Y.; Liu, J.; Dai, L.; Zhou, J.; Hou, C.; Cai, K. Enzyme responsive drug delivery system based on mesoporous silica nanoparticles for tumor therapy in vivo. *Nanotechnology* **2015**, *26*, 145102. [CrossRef]
55. Liu, K.; Yan, S.; Liu, Z.; Wang, D.; Yang, Q.; Jiang, X.; Chen, L.; Tang, H. New anti-tumor strategy based on acid-triggered self-destructive and near-infrared laser light responses of nano-biocatalysts integrating starvation–chemo–photothermal therapies. *Cancer Nanotechnol.* **2022**, *13*, 11. [CrossRef]
56. Wen, Y.; Chen, X.; Zhu, X.; Gong, Y.; Yuan, G.; Qin, X.; Liu, J. Photothermal-Chemotherapy Integrated Nanoparticles with Tumor Microenvironment Response Enhanced the Induction of Immunogenic Cell Death for Colorectal Cancer Efficient Treatment. *ACS Appl. Mater. Interfaces* **2019**, *11*, 43393–43408. [CrossRef] [PubMed]
57. Wu, J.; Lu, Y.; Lee, A.; Pan, X.; Yang, X.; Zhao, X.; Lee, R.J. Reversal of multidrug resistance by transferrin-conjugated liposomes co-encapsulating doxorubicin and verapamil. *J. Pharm. Pharm. Sci.* **2007**, *10*, 350–357.
58. Lammers, T.; Subr, V.; Ulbrich, K.; Peschke, P.; Huber, P.E.; Hennink, W.E.; Storm, G. Simultaneous delivery of doxorubicin and gemcitabine to tumors in vivo using prototypic polymeric drug carriers. *Biomaterials* **2009**, *30*, 3466–3475. [CrossRef]
59. Lee, I.-H.; An, S.; Yu, M.K.; Kwon, H.; Im, S.-H.; Jon, S. Targeted chemoimmunotherapy using drug-loaded aptamer–dendrimer bioconjugates. *J. Control. Release* **2011**, *155*, 435–441. [CrossRef]
60. Kaneshiro, T.L.; Lu, Z.-R. Targeted intracellular codelivery of chemotherapeutics and nucleic acid with a well-defined dendrimer-based nanoglobular carrier. *Biomaterials* **2009**, *30*, 5660–5666. [CrossRef]
61. Xiao, W.; Chen, X.; Yang, L.; Mao, Y.; Wei, Y.; Chen, L. Co-delivery of doxorubicin and plasmid by a novel FGFR-mediated cationic liposome. *Int. J. Pharm.* **2010**, *393*, 120–127. [CrossRef]
62. Zucker, D.; Barenholz, Y. Optimization of vincristine–topotecan combination — Paving the way for improved chemotherapy regimens by nanoliposomes. *J. Control. Release* **2010**, *146*, 326–333. [CrossRef]
63. Song, X.R.; Zheng, Y.; He, G.; Yang, L.; Luo, Y.F.; He, Z.Y.; Li, S.Z.; Li, J.M.; Yu, S.; Luo, X.; et al. Development of PLGA Nanoparticles Simultaneously Loaded with Vincristine and Verapamil for Treatment of Hepatocellular Carcinoma. *J. Pharm. Sci.* **2010**, *99*, 4874–4879. [CrossRef] [PubMed]
64. Hamilton, A.; Biganzoli, L.; Coleman, R.; Mauriac, L.; Hennebert, P.; Awada, A.; Nooij, M.; Beex, L.; Piccart, M.; Van Hoorebeeck, I.; et al. EORTC 10968: A phase I clinical and pharmacokinetic study of polyethylene glycol liposomal doxorubicin (Caelyx®, Doxil®) at a 6-week interval in patients with metastatic breast cancer. *Ann. Oncol.* **2002**, *13*, 910–918. [CrossRef] [PubMed]
65. Bedikian, A.Y.; Silverman, J.A.; Papadopoulos, N.E.; Kim, K.B.; Hagey, A.E.; Vardeleon, A.; Hwu, W.-J.; Homsi, J.; Davies, M.; Hwu, P. Pharmacokinetics and Safety of Marqibo (Vincristine Sulfate Liposomes Injection) in Cancer Patients with Impaired Liver Function. *J. Clin. Pharmacol.* **2011**, *51*, 1205–1212. [CrossRef] [PubMed]
66. Silverman, J.A.; Deitcher, S.R. Marqibo®(vincristine sulfate liposome injection) improves the pharmacokinetics and pharmacodynamics of vincristine. *Cancer Chemother. Pharmacol.* **2012**, *71*, 555–564. [CrossRef] [PubMed]
67. Li, Q.; Zhang, D.; Zhang, J.; Jiang, Y.; Song, A.; Li, Z.; Luan, Y. A Three-in-One Immunotherapy Nanoweapon via Cascade-Amplifying Cancer-Immunity Cycle against Tumor Metastasis, Relapse, and Postsurgical Regrowth. *Nano Lett.* **2019**, *19*, 6647–6657. [CrossRef] [PubMed]
68. Peng, Z.-H.; Kopeček, J. Enhancing Accumulation and Penetration of HPMA Copolymer–Doxorubicin Conjugates in 2D and 3D Prostate Cancer Cells via iRGD Conjugation with an MMP-2 Cleavable Spacer. *J. Am. Chem. Soc.* **2015**, *137*, 6726–6729. [CrossRef]
69. Lei, Q.; Qiu, W.-X.; Hu, J.-J.; Cao, P.-X.; Zhu, C.-H.; Cheng, H.; Zhang, X.-Z. Multifunctional Mesoporous Silica Nanoparticles with Thermal-Responsive Gatekeeper for NIR Light-Triggered Chemo/Photothermal-Therapy. *Small* **2016**, *12*, 4286–4298. [CrossRef]

70. van Rijt, S.H.; Bölükbas, D.A.; Argyo, C.; Datz, S.; Lindner, M.; Eickelberg, O.; Königshoff, M.; Bein, T.; Meiners, S. Protease-Mediated Release of Chemotherapeutics from Mesoporous Silica Nanoparticles to *ex Vivo* Human and Mouse Lung Tumors. *ACS Nano* **2015**, *9*, 2377–2389. [CrossRef]
71. Barnestein, R.; Galland, L.; Kalfeist, L.; Ghiringhelli, F.; Ladoire, S.; Limagne, E. Immunosuppressive tumor microenvironment modulation by chemotherapies and targeted therapies to enhance immunotherapy effectiveness. *Oncoimmunology* **2022**, *11*, 2120676. [CrossRef]
72. Charles, N.A.; Holland, E.C.; Gilbertson, R.; Glass, R.; Kettenmann, H. The brain tumor microenvironment. *Glia* **2011**, *59*, 1169–1180. [CrossRef]
73. Goldie, J.H. Drug Resistance in Cancer: A Perspective. *Cancer Metastasis Rev.* **2001**, *20*, 63–68. [CrossRef] [PubMed]
74. Zeng, X.; Ruan, Y.; Chen, Q.; Yan, S.; Huang, W. Biocatalytic cascade in tumor microenvironment with a Fe2O3/Au hybrid nanozyme for synergistic treatment of triple negative breast cancer. *Chem. Eng. J.* **2022**, *452*, 138422. [CrossRef]
75. Iorio, M.; Ganesh, N.U.; De Luise, M.; Porcelli, A.M.; Gasparre, G.; Kurelac, I. The Neglected Liaison: Targeting Cancer Cell Metabolic Reprogramming Modifies the Composition of Non-Malignant Populations of the Tumor Microenvironment. *Cancers* **2021**, *13*, 5447. [CrossRef] [PubMed]
76. Baghban, R.; Roshangar, L.; Jahanban-Esfahlan, R.; Seidi, K.; Ebrahimi-Kalan, A.; Jaymand, M.; Kolahian, S.; Javaheri, T.; Zare, P. Tumor microenvironment complexity and therapeutic implications at a glance. *Cell Commun. Signal.* **2020**, *18*, 59. [CrossRef] [PubMed]
77. Du, F.; Liu, L.; Li, L.; Huang, J.; Wang, L.; Tang, Y.; Ke, B.; Song, L.; Cheng, C.; Ma, L.; et al. Conjugated Coordination Porphyrin-based Nanozymes for Photo-/Sono-Augmented Biocatalytic and Homologous Tumor Treatments. *ACS Appl. Mater. Interfaces* **2021**, *13*, 41485–41497. [CrossRef]
78. Yang, J.; Yao, H.; Guo, Y.; Yang, B.; Shi, J. Enhancing Tumor Catalytic Therapy by Co-Catalysis. *Angew. Chem.* **2022**, *134*, e202200480. [CrossRef]
79. Pavel, M.; Gradinariu, G.; Stancu, A. Study of the Optimum Dose of Ferromagnetic Nanoparticles Suitable for Cancer Therapy Using MFH. *IEEE Trans. Magn.* **2008**, *44*, 3205–3208. [CrossRef]
80. Pavel, M.; Stancu, A. Ferromagnetic Nanoparticles Dose Based on Tumor Size in Magnetic Fluid Hyperthermia Cancer Therapy. *IEEE Trans. Magn.* **2009**, *45*, 5251–5254. [CrossRef]
81. Hou, H.; Huang, X.; Wei, G.; Xu, F.; Wang, Y.; Zhou, S. Fenton Reaction-Assisted Photodynamic Therapy for Cancer with Multifunctional Magnetic Nanoparticles. *ACS Appl. Mater. Interfaces* **2019**, *11*, 29579–29592. [CrossRef]
82. Shen, Z.; Liu, T.; Li, Y.; Lau, J.; Yang, Z.; Fan, W.; Zhou, Z.; Shi, C.; Ke, C.; Bregadze, V.I.; et al. Fenton-Reaction-Acceleratable Magnetic Nanoparticles for Ferroptosis Therapy of Orthotopic Brain Tumors. *ACS Nano* **2018**, *12*, 11355–11365. [CrossRef]
83. Chi, H.; Zhu, G.; Yin, Y.; Diao, H.; Liu, Z.; Sun, S.; Guo, Z.; Xu, W.; Xu, J.; Cui, C.; et al. Dual-Responsive multifunctional "core–shell" magnetic nanoparticles promoting Fenton reaction for tumor ferroptosis therapy. *Int. J. Pharm.* **2022**, *622*, 121898. [CrossRef] [PubMed]
84. Zhao, Y.; Xiao, X.; Zou, M.; Ding, B.; Xiao, H.; Wang, M.; Jiang, F.; Cheng, Z.; Ma, P.; Lin, J. Retracted: Nanozyme-Initiated In Situ Cascade Reactions for Self-Amplified Biocatalytic Immunotherapy. *Adv. Mater.* **2020**, *33*, e2006363. [CrossRef] [PubMed]
85. Zhao, Y.; Ji, T.; Wang, H.; Li, S.; Zhao, Y.; Nie, G. Self-assembled peptide nanoparticles as tumor microenvironment activatable probes for tumor targeting and imaging. *J. Control. Release* **2014**, *177*, 11–19. [CrossRef] [PubMed]
86. Duan, F.; Jin, W.; Zhang, T.; Zhang, F.; Gong, L.; Liu, X.; Deng, X.; Gao, W. Self-Activated Cascade Biocatalysis of Glucose Oxidase–Polycation–Iron Nanoconjugates Augments Cancer Immunotherapy. *ACS Appl. Mater. Interfaces* **2022**, *14*, 32823–32835. [CrossRef]
87. Zhou, Y.; Fan, S.; Feng, L.; Huang, X.; Chen, X. Manipulating Intratumoral Fenton Chemistry for Enhanced Chemodynamic and Chemodynamic-Synergized Multimodal Therapy. *Adv. Mater.* **2021**, *33*, 2104223. [CrossRef]
88. Shao, L.; Gao, X.; Liu, J.; Zheng, Q.; Li, Y.; Yu, P.; Wang, M.; Mao, L. Biodegradable Metal–Organic-Frameworks-Mediated Protein Delivery Enables Intracellular Cascade Biocatalysis and Pyroptosis In Vivo. *ACS Appl. Mater. Interfaces* **2022**, *14*, 47472–47481. [CrossRef]
89. Wang, R.; Yan, C.; Zhang, H.; Guo, Z.; Zhu, W.-H. In vivo real-time tracking of tumor-specific biocatalysis in cascade nanotheranostics enables synergistic cancer treatment. *Chem. Sci.* **2020**, *11*, 3371–3377. [CrossRef]
90. Presnell, C.E.; Bhatti, G.; Numan, L.; Lerche, M.; Alkhateeb, K.S.; Ghalib, M.; Shammaa, M.; Kavdia, M. Computational insights into the role of glutathione in oxidative stress. *Curr. Neurovascular Res.* **2013**, *10*, 185–194. [CrossRef]
91. Secret, E.; Kelly, S.J.; Crannell, K.E.; Andrew, J.S. Enzyme-Responsive Hydrogel Microparticles for Pulmonary Drug Delivery. *ACS Appl. Mater. Interfaces* **2014**, *6*, 10313–10321. [CrossRef]
92. Jobin, P.G.; Butler, G.S.; Overall, C.M. New intracellular activities of matrix metalloproteinases shine in the moonlight. *Biochim. et Biophys. Acta (BBA) Mol. Cell Res.* **2017**, *1864*, 2043–2055. [CrossRef] [PubMed]
93. Gu, D.; Liu, Z.; Wu, H.; An, P.; Zhi, X.; Yin, Y.; Liu, W.; Sun, B. Dual catalytic cascaded nanoplatform for photo/chemodynamic/starvation synergistic therapy. *Colloids Surfaces B Biointerfaces* **2020**, *199*, 111538. [CrossRef] [PubMed]
94. Cao, Z.; Zhang, L.; Liang, K.; Cheong, S.; Boyer, C.; Gooding, J.J.; Chen, Y.; Gu, Z. Biodegradable 2D Fe-Al Hydroxide for Nanocatalytic Tumor-Dynamic Therapy with Tumor Specificity. *Adv. Sci.* **2018**, *5*, 1801155. [CrossRef]
95. Guo, Z.; Ma, Y.; Liu, Y.; Yan, C.; Shi, P.; Tian, H.; Zhu, W.-H. Photocaged prodrug under NIR light-triggering with dual-channel fluorescence: In vivo real-time tracking for precise drug delivery. *Sci. China Chem.* **2018**, *61*, 1293–1300. [CrossRef]

96. Sharma, A.; Kumar, A.; Pandey, S.; Kumar, D. Importance of photophosphatidylserine and Tim-3 in photoimmunotherapy. *RSC Med. Chem.* **2022**, *13*, 1274–1275. [CrossRef] [PubMed]
97. Al-Hilfi, A.; Walker, K.D. Biocatalysis of precursors to new-generation SB-T-taxanes effective against paclitaxel-resistant cancer cells. *Arch. Biochem. Biophys.* **2022**, *719*, 109165. [CrossRef]
98. Zhang, H.; Cao, Z.; Zhang, Q.; Xu, J.; Yun, S.L.J.; Liang, K.; Gu, Z. Chemotaxis-Driven 2D Nanosheet for Directional Drug Delivery toward the Tumor Microenvironment. *Small* **2020**, *16*, e2002732. [CrossRef] [PubMed]
99. Philpott, H.K.; Thomas, P.J.; Tew, D.; Fuerst, D.E.; Lovelock, S.L. A versatile biosynthetic approach to amide bond formation. *Green Chem.* **2018**, *20*, 3426–3431. [CrossRef]
100. Nishimura, Y. Losmapimod: A Novel Clinical Drug to Overcome Gefitinib-Resistance. *Ebiomedicine* **2018**, *28*, 2–3. [CrossRef]
101. Petchey, M.; Cuetos, A.; Rowlinson, B.; Dannevald, S.; Frese, A.; Sutton, P.W.; Lovelock, S.; Lloyd, R.C.; Fairlamb, I.J.S.; Grogan, G. The Broad Aryl Acid Specificity of the Amide Bond Synthetase McbA Suggests Potential for the Biocatalytic Synthesis of Amides. *Angew. Chem. Int. Ed.* **2018**, *57*, 11584–11588. [CrossRef]
102. Petchey, M.R.; Rowlinson, B.; Lloyd, R.C.; Fairlamb, I.J.S.; Grogan, G. Biocatalytic Synthesis of Moclobemide Using the Amide Bond Synthetase McbA Coupled with an ATP Recycling System. *ACS Catal.* **2020**, *10*, 4659–4663. [CrossRef]
103. Meenu, M.; Verma, V.K.; Seth, A.; Sahoo, R.K.; Gupta, P.; Arya, D.S. Association of Monoamine Oxidase A with Tumor Burden and Castration Resistance in Prostate Cancer. *Curr. Ther. Res.* **2020**, *93*, 100610. [CrossRef] [PubMed]
104. Lubberink, M.; Schnepel, C.; Citoler, J.; Derrington, S.R.; Finnigan, W.; Hayes, M.A.; Turner, N.J.; Flitsch, S.L. Biocatalytic Monoacylation of Symmetrical Diamines and Its Application to the Synthesis of Pharmaceutically Relevant Amides. *ACS Catal.* **2020**, *10*, 10005–10009. [CrossRef]
105. Wood, A.; Weise, N.J.; Frampton, J.D.; Dunstan, M.S.; Hollas, M.A.; Derrington, S.R.; Lloyd, R.C.; Quaglia, D.; Parmeggiani, F.; Leys, D.; et al. Adenylation Activity of Carboxylic Acid Reductases Enables the Synthesis of Amides. *Angew. Chem.* **2017**, *129*, 14690–14693. [CrossRef]
106. Zhang, Y.; Feng, Y.; Qu, Z.; Qi, Y.; Zhan, S. Current situation and challenge of registry in China. *Front. Med.* **2014**, *8*, 294–299. [CrossRef] [PubMed]
107. Baud, D.; Saaidi, P.-L.; Monfleur, A.; Harari, M.; Cuccaro, J.; Fossey, A.; Besnard, M.; Debard, A.; Mariage, A.; Pellouin, V.; et al. Synthesis of Mono- and Dihydroxylated Amino Acids with New α-Ketoglutarate-Dependent Dioxygenases: Biocatalytic Oxidation of C-H Bonds. *Chemcatchem* **2014**, *6*, 3012–3017. [CrossRef]
108. Hara, R.; Yamagata, K.; Miyake, R.; Kawabata, H.; Uehara, H.; Kino, K. Discovery of Lysine Hydroxylases in the Clavaminic Acid Synthase-Like Superfamily for Efficient Hydroxylysine Bioproduction. *Appl. Environ. Microbiol.* **2017**, *83*, e00693-17. [CrossRef]
109. Amatuni, A.; Renata, H. Identification of a lysine 4-hydroxylase from the glidobactin biosynthesis and evaluation of its biocatalytic potential. *Org. Biomol. Chem.* **2018**, *17*, 1736–1739. [CrossRef]
110. Zhang, X.; King-Smith, E.; Renata, H. Total Synthesis of Tambromycin by Combining Chemocatalytic and Biocatalytic C−H Functionalization. *Angew. Chem. Int. Ed.* **2018**, *57*, 5037–5041. [CrossRef]
111. Amatuni, A.; Shuster, A.; Adibekian, A.; Renata, H. Concise Chemoenzymatic Total Synthesis and Identification of Cellular Targets of Cepafungin I. *Cell Chem. Biol.* **2020**, *27*, 1318–1326.e18. [CrossRef]
112. Schober, M.; MacDermaid, C.; Ollis, A.A.; Chang, S.; Khan, D.; Hosford, J.; Latham, J.; Ihnken, L.A.F.; Brown, M.J.B.; Fuerst, D.; et al. Chiral synthesis of LSD1 inhibitor GSK2879552 enabled by directed evolution of an imine reductase. *Nat. Catal.* **2019**, *2*, 909–915. [CrossRef]
113. Bauer, T.M.; Besse, B.; Martinez-Marti, A.; Trigo, J.M.; Moreno, V.; Garrido, P.; Ferron-Brady, G.; Wu, Y.; Park, J.; Collingwood, T.; et al. Phase I, Open-Label, Dose-Escalation Study of the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of GSK2879552 in Relapsed/Refractory SCLC. *J. Thorac. Oncol.* **2019**, *14*, 1828–1838. [CrossRef] [PubMed]
114. Roboz, G.J.; Yee, K.; Verma, A.; Borthakur, G.; Burguera, A.D.L.F.; Sanz, G.; Mohammad, H.P.; Kruger, R.G.; Karpinich, N.O.; Ferron-Brady, G.; et al. Phase I trials of the lysine-specific demethylase 1 inhibitor, GSK2879552, as mono- and combination-therapy in relapsed/refractory acute myeloid leukemia or high-risk myelodysplastic syndromes. *Leuk. Lymphoma* **2021**, *63*, 463–467. [CrossRef] [PubMed]
115. Altmann, K.-H.; Memmert, K. Epothilones as lead structures for new anticancer drugs—Pharmacology, fermentation, and structure-activity-relationships. *Nat. Compd. Drugs* **2008**, *66*, 273–334. [CrossRef]
116. Nayeem, A.; Chiang, S.-J.; Liu, S.-W.; Sun, Y.; You, L.; Basch, J. Engineering enzymes for improved catalytic efficiency: A computational study of site mutagenesis in epothilone-B hydroxylase. *Protein Eng. Des. Sel.* **2009**, *22*, 257–266. [CrossRef] [PubMed]
117. Tse, M.L.; Watts, R.E.; Khosla, C. Substrate Tolerance of Module 6 of the Epothilone Synthetase. *Biochemistry* **2007**, *46*, 3385–3393. [CrossRef] [PubMed]
118. Patel, R.N. Biocatalysis: Synthesis of Key Intermediates for Development of Pharmaceuticals. *ACS Catal.* **2011**, *1*, 1056–1074. [CrossRef]
119. Meyer, F.; Frey, R.; Ligibel, M.; Sager, E.; Schroer, K.; Snajdrova, R.; Buller, R. Modulating Chemoselectivity in a Fe(II)/α-Ketoglutarate-Dependent Dioxygenase for the Oxidative Modification of a Nonproteinogenic Amino Acid. *ACS Catal.* **2021**, *11*, 6261–6269. [CrossRef]

120. Seide, S.; Arnold, L.; Wetzels, S.; Bregu, M.; Gätgens, J.; Pohl, M. From Enzyme to Preparative Cascade Reactions with Immobilized Enzymes: Tuning Fe(II)/α-Ketoglutarate-Dependent Lysine Hydroxylases for Application in Biotransformations. *Catalysts* **2022**, *12*, 354. [CrossRef]
121. Felnagle, E.A.; Jackson, E.E.; Chan, Y.A.; Podevels, A.M.; Berti, A.D.; McMahon, M.D.; Thomas, M.G. Nonribosomal Peptide Synthetases Involved in the Production of Medically Relevant Natural Products. *Mol. Pharm.* **2008**, *5*, 191–211. [CrossRef]