

# PRODRUG: APPROACH TO BETTER DRUG DELIVERY

## Abstract

Albert was the first to introduce the idea of a prodrug in medicinal chemistry.

"A prodrug is a molecule that lacks intrinsic biological activity but can produce a biologically active drug through the various stages of its metabolism," according to the definition provided. This definition and the one adopted by IUPAC both state that a prodrug is any substance that goes through biotransformation prior to manifesting its pharmacological effects. Prodrugs can be thought of as medications that temporarily alter or remove undesired qualities in the parent molecule by adding specialised non-toxic protecting groups.

In order to be effective, a prodrug must be able to solve a crucial paradox: while it must be hydrophilic enough to satisfy solubility, bioavailability, and transport requirements, it must also be lipophilic enough to cross a membrane or metabolic barrier.

An appealing substitute is a chemical remedy that uses a prodrug strategy. By modifying physico-chemical factors that affect absorption or by focusing on certain enzymes or membrane transporters, the prodrug method has also been frequently employed to enhance drug delivery to its site of action. With this in mind, a prodrug design is a lead modification technique used to fix a flaw in a drug candidate. It may be helpful in avoiding issues with formulation and solubility, absorption and distribution, instability, site specificity of liberation, prolonged release, and toxicity, among other effects.

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## I. INTRODUCTION

Since the late nineteenth century, the prodrug notion has been utilised to enhance medications' unfavourable characteristics. Prodrugs are biodegradable, inactive derivatives of active drug molecules that must be changed in vivo in order to release the active parent drug, which can then provide the desired pharmacological action in the body. The majority of the time, they are straightforward chemical derivatives that come from the active parent drug after just one or two enzymatic or chemical processes.

Prodrugs are widely available on the market with the intention of removing barriers to drug usage.

Though creating a prodrug can be quite challenging, it is a feasible approach to improve the unexpected properties of experimental treatments or pharmaceuticals that are already marketed.[1]

## II. PRODRUGS IN MEDICINAL CHEMISTRY AND ENZYME PRODRUG THERAPIES

Finding the disease and the appropriate drug target, the lead and pharmacophore, and optimising the drug lead molecule's interaction with the target are the conventional steps in developing a successful drug for the market. Despite being successful up until this point, the therapeutic development programme could yet fall short due to the molecule's subpar pharmacokinetics (PK). Each of the four constitutive barriers—absorption, distribution, metabolism, and excretion, or ADME—can contribute to PK deficiencies. Pharmacological lead is heavily optimised to increase its PK and get around these obstacles employing prodrugs in many cases of drugs that have been introduced successfully to the market. Prodrugs are by definition the precursors or derivatives of therapeutically active compounds that are bioconverted into their active state. which, whether by spontaneous mechanisms (such hydrolytic breakdown) or through a biocatalytic mechanism, are bioconverted into their active form inside the body. When a prodrug technique is used in drug delivery, the goal is usually to help the drug get past a barrier—either literal or figurative—in order to increase the amount of the drug that can be delivered. Poor water solubility, which can greatly reduce a drug's usefulness for therapeutic purposes, poor absorption from the gastrointestinal system into blood, low rates of cell penetration, etc. are a few examples of such barriers.[2]

Prodrug degradation with subsequent drug recovery and prodrug activation are the two categories into which prodrug bioconversion processes can be arbitrarily divided (Scheme 1). A prodrug molecule for the prodrug degradation class is a conjugation of the parent drug; a masking group (commonly called a "promoiety") is removed during the bioconversion reaction; and the chemical complexity of the molecule reduces. The prodrug undergoes a point chemical modification (such as the cardamine-to-carbonyl transformation) in the prodrug activation category (also known as the "bio precursor" category), which leaves the molecule's chemical complexity largely unaltered but significantly increases therapeutic activity. Alternately, prodrug activation entails a conjugation step that increases the molecule's chemical complexity (for example, phosphorylation for nucleoside analogues). These two classes are here and below, these two classes of prodrug bioconversion are denoted as "drug recovery" and "prodrug activation", respectively.[2]

The structural characteristics of the parent drug molecule and, more particularly, the availability of suitable chemical functionalities that may be utilised to mask the drug's pharmacodynamic activity by, for example, an attachment of the modifying group, determine the design strategy for a prodrug in the first place. The second, equally crucial factor relates to the bioconversion mechanisms of medication release. Although this process could be spontaneous, the bulk of the time, enzymatic processes are used to create drugs (either by recovery or activation). The primary goal of conventional prodrugs in medicinal chemistry is normally to obtain a quantitative recovery of the drug. The medication distribution throughout the body is often given little to no thought in these applications, and the bioconversion enzyme (such as esterase and phosphoesterases) may be dispersed throughout the body. In some cases, a specific enzyme may be primarily expressed in one organ, such as the liver, and bioconversion of a prodrug may occur primarily there (for example, the first step of capecitabine's bioconversion is carried out by carboxylesterases, and HepDirect prodrugs are intended for activation by cytochromes). The presentation following just briefly discusses the design of these prodrugs for broad therapeutic use in order to provide the right context, both scientifically and historically.[2]

The creation of prodrugs for an advanced drug delivery potential known as Enzyme Prodrug Therapy (EPT) is the major topic of this research. To do this, a clever subclass of prodrugs is created so that bioconversion is carried out by a designated enzyme implanted in a specified site within the body. By doing this, the medicine can only be recovered or activated where the enzyme is. In the case of EPT, quantitative drug recovery is less crucial than it is for general medicinal prodrugs, and achieving a site-specific drug recovery is the main objective. There are several methods for localising the enzyme at the desired spot, with varying degrees of effectiveness and development from the lab to the clinic. The initial widely acknowledged success of EPT in the past was attributed to antibody-directed enzyme-prodrug therapy (ADEPT). With this injection-based method of EPT, the enzyme is coupled to an antibody, which makes it easier for the enzyme to bind to the site of action. Examples of ADEPT frequently rely on drug recovery mechanisms that extracellular prodrug bioconvert via. Encapsulated enzymes that were surgically implanted at the site of a tumour that had been removed for post-operative chemotherapy have also shown some early success. There has been a significant increase in interest in this type of EPT recently. The EPT method with the most active clinical trials right now is that of gene-directed EPT (GDEPT), also known as "suicide gene therapy". In this instance, the cells express the enzyme for prodrug conversion upon transduction of the latter, and viral vectors are the most effective means of achieving this. Examples of GDEPT nearly completely rely on the supplied prodrugs' intracellular activation.[2]

### **III. STRATEGIES FOR ENZYME/PRODRUG CANCER THERAPY**

Enzyme-activating prodrugs are administered in two stages. In cancers, an enzyme that triggers medication activation is first expressed and targeted. In the second phase, a nontoxic prodrug that is a substrate of the foreign enzyme generated in tumors is given systemically. The net benefit is the capacity to transform a systemically given prodrug into a highly concentrated local version of an active anticancer drug in tumors. Enzymes and prodrugs must both fulfill particular requirements in order for this method to be clinically useful. The enzymes should be either from non-human sources or be human proteins that are either completely absent from healthy tissues or only very weakly present.

The protein must have high catalytic activity and sufficiently express itself in the tumors. Additionally, the active medication's half-life should be both long enough to cause a bystander effect and brief enough to prevent drug leakage into the systemic circulation.[3]

Priority should be given to the enzyme when selecting the ideal enzyme/prodrug combination. It is anticipated that acceptable prodrugs can be developed for practically any enzyme substrate specificity based on prior experience (Connors, 1995). The bystander effect necessary (see the Bystander Effect section) would not be accomplished if the cells were killed by the activity of the enzyme alone; expression of the enzyme alone shouldn't result in cytotoxic effects. To prevent harmful activation of the prodrug in healthy tissues, the reaction route should also be distinct from any endogenous enzyme. The fundamental disadvantage of using proteins of human origin is that they may not completely prevent difficulties associated with acquired immunity, particularly after extended dosing or prolonged protein expression. The chosen prodrug should have appropriate pharmacological and pharmacokinetic qualities, be chemically stable under physiological settings, and be easily diffusible throughout the tumour (perhaps a neutral species). The released drug should be at least 100 times more toxic than the prodrug in order to achieve meaningful therapeutic benefit. Additionally, the hazardous substance should have a half-life that permits diffusion to neighbouring transfected cells (bystander effect) while guaranteeing that any drug that escapes and enters the bloodstream would be rendered inactive. Additionally, to kill a variety of cell types, the induced cytotoxicity should not depend on the cell cycle phase or proliferation independent, to kill a wide range of tumour cell populations.[4]

#### **IV. PRODRUG-ACTIVATING ENZYMES DELIVERY TO TUMOR CELLS OR TISSUES**

ADEPT is a technique that targets specific tumor tissues by combining a tumor-associated monoclonal antibody with a systemically administered chemical. After being administered systemically, a pretargeted enzyme on the surface of the tumor converts a harmless prodrug into a hazardous drug that kills tumor cells. The best drugs for ADEPT are small molecules that may permeate inside tumor tissues, including antigen-positive and antigen-negative tumor cells, and cause a bystander effect. It is important to maximize the time between enzyme and prodrug infusions when employing ADEPT clinically to avoid systemic toxicity. By doing this, it will be made sure that the conjugate only builds up in tumors and not in blood or healthy organs. Deliveries have been done often utilizing.[5]

#### **V. BACTERIAL-DIRECTED ENZYME PRODRUG THERAPY**

A tissue phenotype that distinguishes cancer tissue from healthy tissue is related to the selectivity of bacterial proliferation within tumours. Ironically, the tumor's microenvironment, which shields it from the majority of anticancer treatments, also serves as its "Achilles heel," making it susceptible to bacterial anticancer medicines. It is widely known that distinct experimental cancers selectively accumulate different microorganisms. For instance, Salmonella strain VNP20009 has shown cancer to normal tissue ratios of 300–25,000:1. Many explanations have been put out to account for such observations. The principal causes of this characteristic are zones of necrosis, which are either the direct or indirect outcomes of cancer growth processes. Neovascularization, also referred to as the process of creating new blood vessels, is necessary for cancer growth and development. When the tumor's radius reaches a certain size, oxygen can no longer sufficiently reach the tumor's inner layers, and

the cells begin to gradually lose oxygen. Low oxygen partial pressure causes more angiogenesis in the hypoxic zone. The delivery of therapeutic medicines and immune cells encounter physiological hurdles in these newly created arteries because of their aberrant structure and function. The fact that they are made up of pores with different sizes ranging from 200 nm to 2  $\mu$ m (depending on the tumor)[6] is one of its exploitable abnormalities. [6]

This could make it possible for germs to leave the vasculature and settle locally inside the tumour mass. Necrotic zones are pockets of dead cells that are typically, though not always, located in the centre of the tumour mass. Such areas are favourable for bacterial growth because they should offer defence from the immune system and enough nutrients (such as purines) from the dead cancer cells. In fact, some cancers (often large with substantial necrotic sections) have been anecdotally reported by surgeons to produce a decaying aroma upon surgical removal, most likely coming from infected microbes.[7]

Depending on the species, the specific site of bacterial proliferation within the tumour may change. Anaerobic bifidobacterial development was seen as several clusters within non-viable tumour regions, according to a new 3D imaging investigation. According to data by Forbes et al., salmonellae multiplied inside the necrotic regions of model tumours. Such a finding suggests that their application is restricted to big tumours. This, however, conflicts with current evidence and older data published by that show Salmonella proliferation in both normoxic and hypoxic regions. A clinical setting prefers such a capability. A good bacterial anticancer agent should target and spread inside of microscopic metastatic tumours, which by nature don't have necrotic areas. For instance, it has been demonstrated that Escherichia coli K12 MG1655 and HJ1020 with light emitting genes can target both tiny and large tumours, and even anaerobic Bifidobacterium breve has showed a comparable ability.[8]

As vehicles for cancer gene therapy, bacteria have many benefits. For instance, it is simple to alter bacteria to produce exogenous products with therapeutic value, enhance their tumour selectivity, or express prodrug activating enzymes and reporter proteins for visual confirmation of treatment site and therapeutic outcome. Different kinds of bacteria have various ways of becoming tumor-specific. Obligate anaerobes can produce spores that can only germinate in the anoxic areas of tumours, like Gram-positive Clostridium species. As a contrary, facultative anaerobes like Gram-negative Salmonella and Escherichia coli build up inside tumours for a variety of reasons, including immune system protection, positive chemotaxis towards resources within the tumour microenvironment, and trapping in the disordered vasculature of tumours. Over their viral vector cousins, bacteria have one major advantage over them: bacterial infections during cancer treatment are easily managed by antibiotics.[9]

Effective blood flow is necessary for tumour growth. Inhibiting angiogenesis is a potentially effective method of treating cancer patients. Despite the discovery of a large number of endogenous angiogenesis inhibitors, clinical testing was hampered by the necessity for high doses, production restrictions, and the relative instability of the required recombinant proteins. [10] Microvascular endothelial cells produced at the tumour site are the target of antiangiogenic therapy. Specific antiangiogenic therapy does not require the entry of therapeutic molecules into tumour cells, has minimal to no toxicity, and cannot cross the hematoencephalic barrier. Regardless of the tumor's cell type, it regulates tumour growth and prevents the development of acquired drug resistance. [11] A viable method of avoiding problems associated with systemic drug administration is the addition of genes that code for

antiangiogenic proteins. Therapeutic genes that code for antiangiogenic compounds can be delivered to patients using a variety of carrier systems, such as recombinant adenoviruses or liposomes. [12] Antiangiogenic gene therapy can be applied locally or systemically. On the optimum application strategy, scientists are still at odds. Local (intratumor) administration is accompanied by a potent "bystander effect" that amplifies the antagonistic action of inserted genes, and it shouldn't be linked to possible systemic therapeutic adverse effects. [13] On the other hand, a persistent rise of endostatins in blood is made possible by systemic administration of genes coding antiangiogenic agents. [14]

## VI. CONCLUSION

With a focus on enzyme-prodrug therapy, this study aims to describe the enzymes employed to achieve prodrug bioconversion as well as the concerns linked to the manufacturing and utility of prodrugs specific to these enzymes. Given that so many marketed medicines are prodrugs, the state of the art in prodrug design already portrays this field as being highly successful. EPT, on the other hand, has had only little success since its inception a few decades ago. When compared to traditional therapy, ADEPT has some benefits, including: Since each enzyme molecule can cleave a large number of prodrug molecules, there is increased selectivity for malignant cells that takes advantage of the specificity of the Ab; internalisation of the Ab-enzyme conjugate into tumour cells is not required; there is an amplification effect; and in the majority of the examples described here, the released active drug is of low molecular weight, enabling it to.

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