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RECENT ADVANCES OF B-BLOCKERS AS DRUG REPURPOSING APPROACH: A SYSTEMATIC REVIEW

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Repurposing pharmaceuticals is a potentially effective method in drug development to find novel therapeutic applications for already FDA-approved medications that deviate from their original intended usage. Compared with conventional methods of de novo drug discovery, it offers numerous benefits because it can drastically cut down on development time and medical expenses. In this review, the potential repurposing of β-blockers that have been previously authorized by the FDA for the management of cardiovascular disorders such as (hypertension, arrhythmias, and aortic dissection) was discussed. β-blockers have been shown to have encouraging anti-cancer, antibacterial, antimigraine, and spermicide properties in many experimental and epidemiological investigations. The outcomes have led to new drug indications or may lead to new drug indications. The objective of this review is to collect medications and their plausible modes of action that support repurposing, address difficulties in repositioning β-blockers for other disorders, and explore the possible therapeutic benefits of incorporating these medicines into nano-system formulations.

Keywords: *Drug repurposing, Anti-hypertensive, B-blockers, Nano-systems*

INTRODUCTION

History of β-blockers

Beta-blockers, also known as β-blockers, are compounds that block β-adrenergic receptors (ARs), which have been shown to perform a major part in the regulation of several metabolic and central nervous system functions as well as physiological activities like blood pressure, and airway strength[1]. Following their discovery in 1965 by Sir Henry H. Dale, ARs emerged as important goals in the treatment of respiratory conditions like asthma, cardiovascular conditions like hypertension and heart failure (HF), and numerous other serious conditions like prostatic hypertrophy, nasal congestion, and pain[2]. However, it wasn't until 1948 that Raymond P. Ahlquist discovered two distinct paths that, depending on the organ in question, induced pharmacological effects. Ahlquist separated ARs into two categories based on these trials: α-ARs, which relate to furthermost "excitatory" Purposes like vasoconstriction, and β-ARs, which are related to "inhibitory" purposes like vasodilation, and one "excitatory" purpose like myocardial stimulation[3]. Later, in 1958, Ahlquist's theory was confirmed by Sir James Black, who created the first β-blocker as a medication to reduce oxygen consumption during angina attacks. This innovation was one of the greatest medical achievements of the 20th century and earned the Black and the AR community a second Nobel award in 1987. Alonzo M. Lands and associates proposed in 1967 to divide β-ARs into two distinct subtypes: β1-ARs, which are mostly found in the heart, and β2-ARs, which are accountable for vascular and airway

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relaxation. Soon after, a third subtype is known as β3-AR was discovered in rat brown adipose tissue cells that shared as many similarities as differences and was resistant to most medications[4]. The most recent milestone was reached in 2007 when Robert J. Lefkowitz and Brian K. Kobilka helped to solve the β2-AR 3-dimensional crystalline structure and reveal how β-ARs cooperate with cell structures, as well as how they are dynamically regulated and desensitized. Lefkowitz and Kobilka received the third Nobel award for their effort on ARs in 2012.

Development of β-blockers

Sir Black accomplished the magnificent suggestion in 1958 by aiming for a decrease in myocardial oxygen requirement during angina attacks rather than improving its availability by vasodilation. Driven by Ahlquist's hypothesis, Black became fixated on finding a medication that could prevent the "excitatory" impact of β-AR on the heart, hence regulating heart rate. In the meantime, Eli Lilly Laboratories published dichloroisoproterenol, which had been believed to be a bronchodilator, but which proved precise antagonistic influences on the heart[4]. Black proposed to create dichloroisoproterenol analogs with more selective and effective β-adrenergic blockade properties after learning about this research. During this search, he developed propranolol, the first β-blocker that was accepted for utilization in clinics[5]. The first class of β-blockers, or medications with similar effects on β1 and β2-ARs, was prototyped by propranolol[6] and for this justification, are ‘‘nonselective β-blockers’’. Propranolol is the medication in this group with the greatest accumulation of clinical experience and indications[6]. Later, in 1966, the Imperial Chemical Industries team fabricated practolol, the first bioactive representative of the second generation of β-blockers, which are drugs showing a higher attraction for β1 than for β2-AR and are known as "β1-selective β-blockers" or "cardioselective β-blockers" because of the main existence of the β1 subtype in the heart. This search was conducted to find derivatives able to elude the bronchoconstriction outcome of propranolol in asthma patients. Practolol was taken off the market in 1975, and subsequent medication had additional cardio-selective β-blocking activity brought to the market. The two highly distinctive medications in this category are metoprolol and atenolol[7]. The third category of β-blockers comprises medications that have additional vasodilating properties; as a result, they are also referred to as "vasodilating β-blockers." This vasodilator action is advantageous since it maintains cardiac output, stroke book, and left ventricular function while reducing peripheral vascular endurance. This class of compounds can be either non-selective or selective for β1-AR, but they display additional mechanisms that describe their vasodilatory action, such as β1 antagonist activity (carvedilol and labetalol) and nitric oxide (NO) release (nebivolol). Moreover, vasodilating β-blockers have beneficial (carvedilol) or neutral (labetalol and nebivolol) effects on lipid and glucose metabolism, while most of the clinical research indicates that non-vasodilating β-blockers typically have a detrimental effect on lipid and glucose parameters[8]. Long-term and extremely short-term planning has been completed in this developing sector, which has helped expand the treatment toolkit. Without a doubt, the establishment of β-blockers over 50 years ago changed the field of human pharmacotherapy and improved the lives of millions of patients with both cardiovascular and non-cardiovascular illnesses **(Fig. 1)**.

Approaches of drug repurposing

Systematic repurposing approaches can be largely divided into those based on experimental screening approaches, and in silico approaches that employ existing data to identify potential new drug-disease associations. Experimental screening approaches: Experimental screening approaches are used as a source of hits for both drug discovery and drug repurposing, with notable differences in their application and outcomes. Repurposing programs focus on advanced known molecules either approved or failed with some knowledge of their safety or mechanism of action available, led by in-depth screening, and with smaller-size compound libraries. Another key difference between drug discovery and repurposing is the fate of the hits. For a repurposing screen, a compelling hit is a drug molecule that is a candidate to be advanced into development. This is quite

distinct from a high-throughput screening hit in drug discovery that becomes a starting point for a newly found medicinal chemistry program which then evolved iteratively. Lastly, for drug discovery screens, an efficient assay must be simple and fast to manage the number of potential compounds for review, whereas, for repurposing screens, the limited scale allows a broader range of complexity of assay types. Three types of screens, commonly used and adaptable for high-throughput screening, are cell-free or cell-based, target-focused screens, and phenotypical screens. The first is based on a specific compound activity to a specific mechanism. The second is based on cell behavior (e.g. growth and death) with or without the compound addition. The third has historically been more successful than target screening in generating new drugs. In silico repurposing approaches: In silico repurposing approaches apply sophisticated analytical methods to existing data identifying new potential associations between drugs and diseases. Approaches can be broadly divided into two categories: (i) molecular approaches, which are based on the understanding of drug activity and disease pathophysiology and are often powered by large-scale molecular data, such as genomic, transcriptomic, or proteomic data, as well as data on drug targets and chemical structure, and (ii) real-world data approaches, focusing on identification of unknown, and at times unexpected, relationships between drugs and diseases or their symptoms[9]

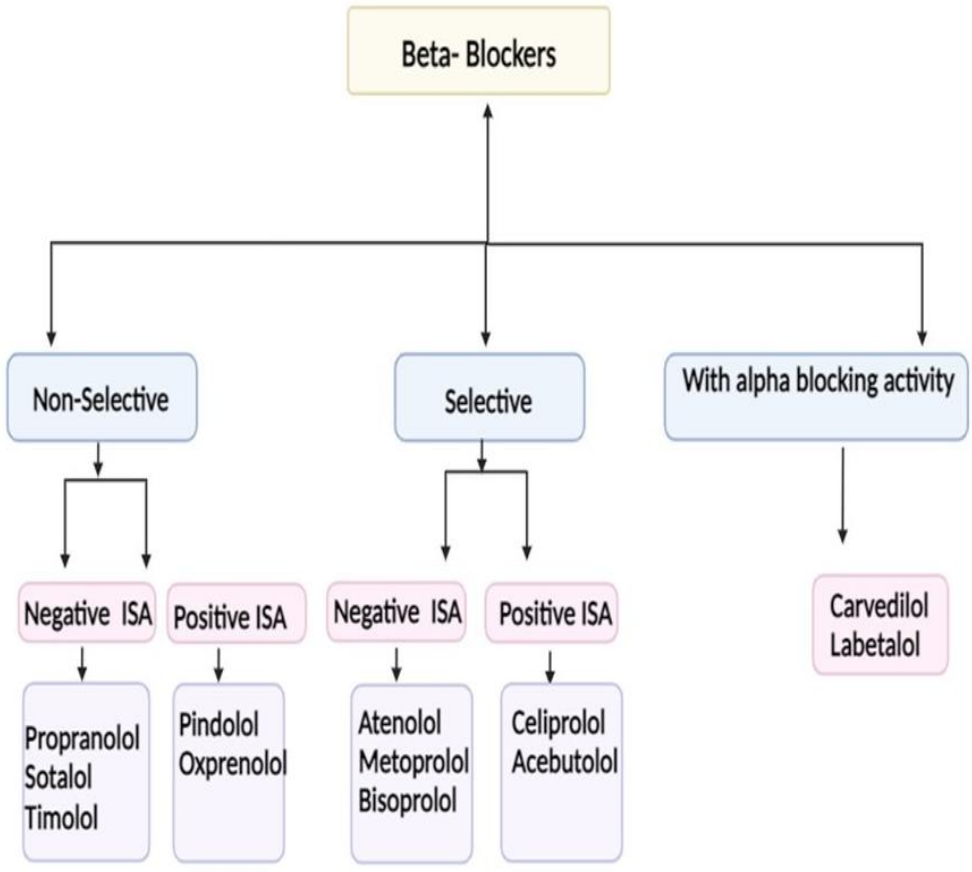

Fig. 1: Classification of β-blockers.

Strategies and methodologies of drug repurposing

Literature mining: Conduct a comprehensive review of scientific literature, clinical trial databases, and patents to identify potential connections between existing drugs and new therapeutic targets. Computational approaches: Utilize computational methods, such as bioinformatics and data mining, to analyze large datasets, including genomic data, protein-protein interaction networks, and gene expression profiles. Systematic screening: Perform high-throughput screening of existing drug libraries against new disease targets. Clinical observation: Analyze clinical data, including electronic health records, to identify potential associations between existing drugs and improved patient outcomes for different diseases. Combination therapies: Investigate the possibility of combining existing drugs with different mechanisms of action to create synergistic effects or enhance therapeutic efficacy. Repositioning based on mechanism of action: Identify drugs that have a similar mechanism of action to drugs already approved for a specific disease. Repurposing based on shared pathways: Identify diseases that share similar pathophysiological pathways or molecular targets with diseases for which drugs are already approved. Collaboration and partnerships: Foster collaborations between academia, pharmaceutical companies, and government agencies to facilitate the sharing of resources, data, and expertise. Clinical trials: Conduct well-designed clinical trials to evaluate the safety and efficacy of repurposed drugs in the new disease context.[10,11]

Opportunities and strengths of drug repurposing

Drug repositioning is a highly promising technique that has attracted growing attention from governments and pharmaceutical companies for its key role in reducing time, cost, and risk in the process of developing drugs for cancers and other incurable illnesses. Also, repositioning drugs can be done regardless of the status of the investigated drug, approved, withdrawn, in clinical trials, or failed in clinical trials. Adopting some computational drug repositioning models within the traditional, costly, failure-prone de novo drug development process can help to push drug steps forward in the development pipeline and eventually improve drug efficiencies in clinical trials. Further, drug repositioning might provide the opportunity for developing urgently needed drugs to treat the current epidemic of coronaviruses.[12]

Translational focus: Translational research in academia offers incentives by fostering novel collaborations and pairing up basic scientists with clinicians across multiple disciplines. Disease focus: Clinical education and clinical research afford in-depth expertise in particular disease areas and enable projects to rapidly advance past the early stages. Conversely, clinical observations can lead to immediate pathway links and studies. In this manner, diseases that lack effective therapies can rapidly be subjected to drug repurposing efforts. Target focus: Those targets, are related to points in general mechanisms such as cell division, autophagy, apoptosis, and metabolism, and can be subjected to therapeutic manipulation for various, sometimes clinically different endpoints.[13]

Limitation of drug repurposing

Dosing and Safety: Because drugs are approved only after intense scrutiny, which observes clear therapeutic benefits within well-defined safety margins, the clinical utility of finding novel drug–target interactions is often hampered by issues related to dosage (i.e. approved dose range) and delivery capability (i.e. the ability to deliver the drug to targets at the disease focal region) where it has been rare to find novel drug–target interactions within the constraints of the approved therapeutic window. Lack of integration: It is unusual to include scientists from pharmaceutical and toxicological sciences in the translational efforts. Appropriate intellectual property coverage: For off-patent drugs, the number of options for intellectual property (IP) protection is more limited. Even if truly novel mechanisms are fully explained, this rarely leads to protected marketing rights from regulatory agencies. Lack of experts: Because drug repurposing is quite a novel field for academia, there are no experts in the legal issues related to this field. Disclosure: The disclosure of novel drug–target–disease associations via PubChem or other online databases, or publications effectively hamper

IP protection efforts, often to the point of not seeking patent protection.[13]

Challenges

There have already been notable successes in drug repurposing. Nevertheless, repurposing does not always succeed. The are many reasons for failure in the repurposing field including failure to begin to pursue a promising candidate beyond initial studies, patent considerations, regulatory considerations, and organizational hurdles. Patent considerations: There are difficulties associated with patenting a new repurposed indication and enforcing patent rights, as they have a great impact on the potential profit expected from the repurposed product. Although many of the potential repurposing uses are already known in the scientific literature or clinical practice, it is difficult to obtain patent protection unless the patentee can somehow differentiate their patent claims over the information that is already available in the public domain. For off-patent drugs, a new method-of-use patent can be obtained for a new repurposed use of an old generic drug. However, enforceability can become a major issue here if the new repurposed indication makes use of available formulations and dosage forms of the generic drug. This is because the generic drug may be widely available from other manufacturers and prescribed by clinicians for other non-patented indications. The generic manufacturer can legitimately label their product only for the non-patented indications and do not encourage its use in the patented indication in some other way. In this scenario, it can be difficult to stop off-label use for the newly patented repurposed indication, thereby reducing the potential profitability of the product. Regulatory considerations: Regulatory considerations are critical determinants for the development of repurposed drugs. It was found that in both the EU and the US, most repurposing cases were approved before the patent expiry of the original product. For repurposed drugs with a designated orphan indication, the market exclusivity provided in the EU/EEA is 10 years of protection from market competition and an additional 2 years if they comply with an agreed Pediatric Investigation Plan. For repurposed drugs without an orphan designation, 10 years of data exclusivity are available for complete dossier applications. In the US, the FDA offers 3 years of data exclusivity for a new use of a previously marketed drug[14]

Future perspectives of drug repurposing

Over the past few years, the industry has become aware that the tools are now available to work systematically towards gaining insight into the complete therapeutic potential of a particular new molecular entity. Multiplexed in vivo assays, cell-based screening, and functional in vitro assays, as well as in silico literature and systems biology-based approaches have been developed that remove serendipity from the process of indications discovery. Some in the industry are now grasping this opportunity on a retrospective basis, exhuming compounds that stalled in development for reasons other than safety. Going forward, it is increasingly likely that these tools will be employed more routinely during preclinical drug development. This will ensure that the full potential of compounds is understood much earlier, enabling the industry to better prioritize drug development programs and increase their return on investment. The pharma industry initially showed some inertia in investing in repurposing their failed or abandoned compounds, taking the view that their research had been thorough and that the compounds were best left on the shelf to free up resources for new research and development projects. However, the pressure on the industry caused by the 'innovation gap' of rising development costs and stagnant product output changed their perspective and is a major reason for the growing interest in drug repurposing that has been observed. In the current economic climate, two factors may continue the flow of compounds into repurposing projects. First, the need to expand product pipelines with new projects, especially those for which an element of the risk has been removed, has become more acute. Second, the pool of potential compounds abandoned for strategic reasons is growing.[15] These factors may continue to provide opportunities for academia as well as a small number of indications discovery companies or those wishing to validate novel discovery platforms. Pharma companies signed deals with companies aiming to systemically identify new targets for stalled compounds. Some of these

repurposing companies have now moved away from indications discovery to focus on clinical development and they must validate their repurposing business models with positive proof-of-concept data in the future. However, it is the demands of the largest pharma companies, reflecting their level of confidence in their current pipelines, that will drive the repurposing field forward over the coming years.[16]

Drug repurposing for β-blockers

Drug repurposing or employing identified medications and chemicals for treating previously unidentified purposes requires less money and less time for approval than creating a de-novo medication as these "old drugs" have been shown the proper safety in human trials. Several experimental investigations have recommended that authorized cardiovascular medications such as β-blockers be repurposed for various uses. There's no doubt that some of the pleiotropic effects and modes of activity of cardiovascular drugs may be valuable in stopping the growth, angiogenesis, and metastasis of tumor cells. Repurposing of β-blockers in pathogenic settings other than cancer is also on the rise[17].

β- blockers for cancer management

Previous experimental investigations on cancer have clarified the correlation between the growth of tumors and long-term stress, depression, and social isolation. Since β-adrenoreceptors mediate the effects of catecholamines like norepinephrine and adrenaline, which are elevated below chronic stress, catecholamine activation of these receptors is stated to show a major part in the growth of tumors **(Table 1)**. The existence of β-adrenoreceptors has been proven in the cell lines of breast cancer[18], pancreatic cancer[19], nasopharyngeal cancer[20], ovarian cancer[21], and catecholamines significantly raised cell proliferation as cell migration in human cancer cell lines. Likewise, in a mouse model of ovarian cancer, β-adrenergic stimulation not only enhanced angiogenesis and tumor attack during the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) pathway[21] but blocked the cancer cells from apoptosis by triggering focal adhesion kinase (FAK**) (Fig. 2)**[22,23] .

Table 1: Summary of ongoing clinical trials using β-blockers, as anti-cancer drugs.

Intervention/treatment	**Condition or disease**	**Clinical Trials**
• Propranolol	• Locally advanced malignant neoplasm	NCT01847001
• Propranolol hydrochloride	• Locally recurrent or metastatic solid tumors	NCT02013492
• Propranolol + Relaxation/Guided	• Advanced, recurrent, incurable cervical cancer	NCT01902966
• Propranolol vs Atenolol	• Infantile Hemangioma	NCT03237637
• Propranolol vs Nadolol	• Infantile Hemangioma	NCT02505971
• Timolol Maleate	• Infantile Hemangioma	NCT01873131
• Timolol Maleate 0.5% gel vs Pulsed Dye	• Infantile Hemangioma	NCT02913612
• Propranolol vs no intervention	• Hepatocellular Carcinoma	NCT01451658
• Carvedilol	• Glioblastoma	NCT03861598

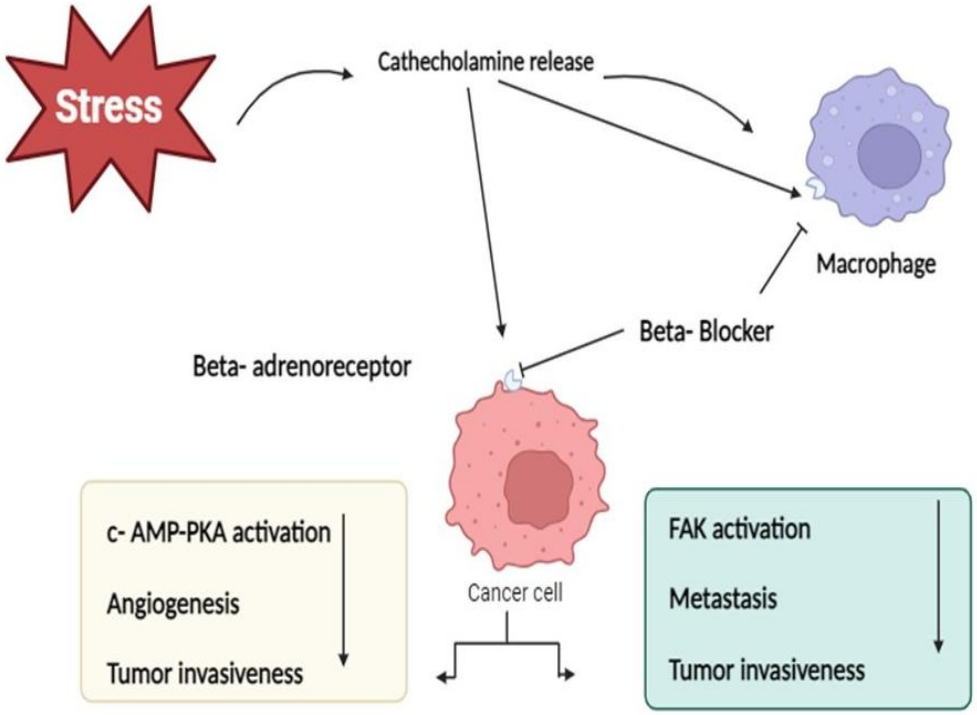

Fig. 2: Mechanisms of action of β-blockers in preventing tumor progression.

β-blockers for breast cancer treatment

Preclinical research suggests that angiogenesis, proliferation, and invasion could be affected by activation of the β2-adrenergic receptor alone. Additionally, a significant interaction between β2-adrenergic receptor and HER2 (Human Epidermal Growth Factor Receptor 2) has been demonstrated in preclinical versions of breast cancer, with β2-adrenergic triggering enabling challenge to HER2-blockade[24]. Thus, non-selective β-blockers that operate on β2-adrenergic receptors, like propranolol, can prevent these effects, slow the progression of cancer, and restore sensitivity to HER2-blockade[25,26].

β- blockers for retinal hemangioblastoma treatment

From Hippel-Lindau disease, retinal hemangioblastomas are the most common and early manifestation. These tumors range in size from less than one to numerous optic discs in diameter. They are multiple and bilateral. These lesions are classified as peripheral and juxtapupillary (when they occur on or near the optic nerve), and they share pathological similarities with hemangioblastomas of the central nervous system. Peripheral and central hemangiomas may cause hemorrhages, cataracts, and exudative retinal detachment, all of which can result in blindness. These lesions are especially tiny and difficult to see when they first appear[27]. Smaller lesions can typically be healed more successfully and with fewer side effects than larger ones. Generally peripheral retinal tumors may be treated with cryotherapy for bigger tumors or laser photocoagulation for smaller tumors; however, these treatments are not currently available for lesions that are close to the optic nerve. With the considerable danger of damaging the optic nerve, observation is the most thorough therapeutic approach in these instances. The application of photodynamic therapy has yielded inconsistent results. While several antiangiogenic medications, such as ranibizumab and bevacizumab, have been used, their effects on tumor growth are not long-lasting. Until yet, no drug has been able to change how the illness progresses, therefore the possibility that these individuals would recover if propranolol was used to treat them is unquestionably an excellent therapeutic need. When propranolol was accidentally discovered in 2008, it was the recommended course of treatment for this type of vascular tumor[28].

Recently, propranolol has been the subject of cancer research due to clinical evidence suggesting that using β-blockers as propranolol could improve overall and relapse-free survival. The information from trials utilizing propranolol to manage angiomas at various levels, such as cerebral cavernous angioma and airway angioma, validate the feasibility of investigating its use in this uncommon condition with little pharmacological activity[29].

β- blockers for osteosarcoma (OSA)

Even though catecholamines like norepinephrine and adrenaline stimulate the sympathetic nervous system and activate signaling routes that are strongly linked to the advancement of cancer[30], little is acknowledged about the exact function of catecholamines or β-AR signaling in OSA. As lately informed, demonstration of β-ARs and various catecholamines, involving norepinephrine, was substantially greater in OSA in relationship to healthy bone. Furthermore, it was noted that all subtypes of β-AR were stated in a variety of human and canine OSA or other bone sarcoma models, making the non-selective β-blocker propranolol an appealing option for further research. Given the unsatisfactory clinical requirements of OSA and the numerous stated profits of propranolol as a broad anticancer drug, the earlier study's goal was to evaluate the drug's antitumoral action *in vitro* and *in vivo* in OSA, either alone or in mixture with metronomic chemotherapy[31].

β-blockers for Marfan's syndrome treatment

Marfan's syndrome is an autosomal prevailing connective tissue disease triggered by mutations in the fibrillin-1 (FBN1) gene and over-activation of TGFβ. It is characterized by several cardiovascular indications, with progressive aortic root dilatation and dissection serving as the general morbidity and mortality issue. Propranolol, a β-blocker, was found to preserve the architecture of the aorta wall while preventing aortic dilatation, root growth, and wall thickness in several animal models used in experiments[32]. Clinically relevant endpoints including death, cardiovascular surgery, and aortic dissection or rupture showed no detectable variance[33].

β-blockers for migraine management

It is thought that migraine is both a central nervous system disorder and a systemic metabolic syndrome, with a significant role in serotonin release from platelets in this condition. In the late 1960s, β-blockers were first used to treat migraine. Many mechanisms of action for β-blockers in migraine prophylaxis have been hypothesized, including platelet-derived serotonin release regulation and suppression of cerebral artery dilatation. The American Academy of Neurology guidelines propose β-blockers as a first-line medication for suppressing migraine specifically propranolol and metoprolol[34]. Metoprolol, and in the same instance both bisoprolol and timolol, were beneficial despite the inferior quality of the evidence. A very small number of randomized controlled trials estimated the efficiency of β-blockers in treating tension-type headaches and chronic migraines. Propranolol performed no better in these studies than either valproic acid or flunarizine, and neither propranolol with topiramate nor propranolol plus flunarizine performed any better than topiramate and flunarizine alone[35]. Ultimately, most trials determined that β-blockers would be effective after 12 weeks, which is a significant constraint given that migraine is a chronic condition. Therefore, it is unknown if therapy benefits continue, rise, or fall, and more research is necessary to determine this. Future studies may potentially clarify why β-blockers are more effective than other pharmaceutical classes in treating episodic, chronic, and tension headaches, as well as migraine prophylaxis.

β-blockers for the management of Alzheimer's disease (AD)

It's still unclear exactly what causes AD. Therefore, without a clear knowledge of why AD poses such a significant risk, enormous resources such as money, time, and effort have been used to create a treatment for the condition. Since there hasn't been a successful treatment for AD that works for everyone, changing the paradigm to provide targeted care for individual AD patients who have different hereditary or pathological links is a workable strategy[36]. It has been determined that midlife hypertension increases the risk of both atherosclerosis and AD. Atherosclerosis causes

the cerebral arteries to remodel and hastens the arterial lumen. Brain hypoperfusion, which regulates blood flow and oxygenation in the central nervous system's white matter, is the ensuing damage to cerebral autoregulation. Myelin-producing oligodendrocytes and myelin-encased axons make up white matter, which is involved in the transmission of signals across different brain areas[37]. Ischemic and hypoxic damage are impacted, respectively, by decreased blood flow and oxygen delivery to the tissues. After the cells in the affected areas demyelinate, ischemic periventricular white matter leads to oligodendrocyte cell death and the formation of white matter lesions (WMLs). In the cerebrospinal fluid of AD patients, WMLs have been demonstrated to manifest together with abnormalities of tau and amyloid[38], indicating that they promote the creation of senile plaques and neurofibrillary tangles (NFTs). Both demyelination and oligodendrocyte cell death are associated with two processes: oxidative stress and inflammation. Prior research has demonstrated that ischemia can induce oxidative stress because of an excess of reactive oxygen species (ROS)[37]. Apart from ischemia, angiotensin II also tends to trigger the fabrication of reactive oxygen species (ROS) by enhancing the NADPH oxidase activation, hence promoting oxidative stress. People with hypertension have high levels of Ang II found in them. As mentioned before, oxidative stress increases the accumulation of Aβ and facilitates the establishment of NFT[39]. It has also been demonstrated to activate NF-κB, a transcription factor that starts the inflammatory cascade and influences the development of AD[40]. Since there is now proof that AD and hypertension are correlated, it was thought that antihypertensives (AHTs) could help prevent AD. The idea of employing AHTs in AD is undoubtedly of great interest, especially considering the necessity and significance of obtaining new AD medications that have experienced multiple unsuccessful assessments in previous years. Propranolol's ability to increase the disruptive behaviors of residents in an assisted living facility with AD was evaluated throughout a six-month trial. Propranolol may help reduce aggressiveness and uncooperativeness, according to this study, suggesting a potential treatment option for noncognitive dysfunction associated with AD. Wang et al. diagnosed various drugs that have been authorized by the Food and Drug Administration, for their capability to adjust the action of amyloid beta (Aβ). It was reported that propranolol decreased the amounts of Aβ in vitro[41]. Results from an in vivo investigation by Dobarro et al. showed that propranolol was able to recover memory deficits and hence reestablish cognitive function, even at levels lower than those recommended for hypertension in patients (5 mg/kg/day). Furthermore, it has been reported that propranolol lowers Aβ42 levels, shows protection against Aβ neurotoxicity, and reduces tau protein hyperphosphorylation[42]. Gelber et al. have noted that the impact of β-blockers on arterial hypertension is not related to the outcomes of this investigation. According to their research, patients with a baseline systolic blood pressure (SBP) of ≥ 150 mmHg did not exhibit mitigation of cognitive impairment. This suggests that propranolol's effects are somewhat dependent on SBP control[43]. Up to 40 mg of propranolol administered three times a day was shown to be well tolerated. It is advised to treat mild-to-moderate hypertension with carvedilol, a non-selective β-adrenergic receptor blocker[44]. Because of its capacity to scavenge free radicals and hence reduce lipid peroxidation, carvedilol has demonstrated its antioxidant properties in several previous studies. Corresponding to Yue et al., carvedilol is a far more powerful antioxidant than other β-blockers like propranolol, atenolol, and pindolol[45]. In vivo investigations on AD mice exhibiting behavioral problems and impairment caused by D-galactose and colchicine[46]. Similar results have also been reported by in vitro research. After being cured with carvedilol, cells demonstrated a dose-dependent increase in sensitivity to hydrogen peroxide-induced cell death. Carveilol showed protection against cell toxicity in an in vitro cell model by inhibiting the production of ROS brought on by hypoxia[47]. Furthermore, because of the three-dimensional pharmacophore shape of carvedilol, structural research has suggested that it is capable of binding Aβ. The inhibition of oligomeric fibril organization is enhanced by Aβ binding. Wang et al.[48] find that with carvedilol management, oligomerization of

$A\beta_1$-42 was not monitored, while oligomerization of $A\beta_1$-40 was affected in a dose-dependent manner. Decreased oligomeric Aβ levels should be improved to enhance synaptic neurotransmission. However, carvedilol treatment does not affect the APP transgene's expression[48]. Moreover, the fact that carvedilol pre-treatment inhibits NF-κB suggests that it may have anti-inflammatory aspects. A modulator of pro-inflammatory cytokine levels, NF-κB is a regulator of the inflammatory cascade. Following carvedilol pretreatment, a reduction in TNF-α, IL-1β, and IL-6 levels was observed, along with an increase in iNOS expression. According to a study by Gao et al., carvedilol may be utilized to manage ischemia or hypoxia, which can ultimately result in Aβ-induced neurotoxicity[47].

β-blockers for infantile hemangioma (IH) management

The 2008 discovery that the β-blocker propranolol might involute hemangiomas began what has been called a "revolution in the management of IH"[49]. The stimulation of endothelial cell death and the reduction of vascular endothelial growth factor-mediated angiogenesis have been identified as the mechanisms of action[50]. Many investigations documented positive clinical outcomes for IH of various kinds in various anatomical locations when treated with β-blockers, either locally or systemically applied. Numerous investigations on topical timolol in babies with hemangiomas have demonstrated its effectiveness and the absence of any significant side effects[51]. No appreciable difference in heart rate or blood pressure was seen across the groups, and neither group reported any adverse events. While this study suggests that preterm children may be more vulnerable than their term counterparts, an evaluation of the risk-benefit ratio and the aggressiveness of IH should still be conducted. Another potential cause of topical timolol side effects could be accidental ingestion, as demonstrated by a case of hypoglycemia and drowsiness that required hospitalization in a 1-year-old child, in which a home video showed the infant ingesting ophthalmic timolol prescribed for topical handling of IH[52].

β-blockers for chronic wounds

Since the earliest case reports of topical timolol's repurposing for chronic wounds, its use in the therapy of non-healing wounds has expanded[53]. There have been numerous case reports for wounds with various etiologies[54]. With no significant side effects other than sporadic itching around the ulcers, a case-controlled prospective study involving 60 patients whose leg ulcers were treated with topical timolol or standard of care found a significantly superior reduction in the ulcer area in the timolol-treated patients[55].

β-blockers acting as spermicide

Various mechanisms have been anticipated to explain the spermicidal activity of propranolol. Propranolol, as previously stated in the literature, exhibits long-lasting, short-latency localized anesthetic or membrane-stabilizing activity[56]. The impact of locally administered anesthetics as spermicides is determined by their lipid solubility, where the lipoprotein-based sperm plasma membrane is found, ability to potentially immobilize the sperm, and the development of vesicles inside the sperm[57].

β-blockers acting as antifungals

In vitro and a mouse model of invasive candidiasis, the effects of fluconazole and β-blockers (nadolol, penbutolol, propranolol, and bunitrolol) were inspected. *In vitro*, nadolol and other β-blockers proved to be ineffective, and they did not considerably impede survival in vivo. Three drugs that showed promise *in vitro* tests bunitrolol, propranolol, and penbutolol also showed promise *in vivo*. In a mouse model, propranolol monotherapy doubled the survival rate, suggesting its effectiveness[58]. In two different investigations, bunitorolol treatment increased survival by 60–100%. The animal's overall disease worsened only after receiving carteolol therapy, which proved poisonous. Histological analysis demonstrated the inhibitory impact of the combination, as the survival rate of infected mice given a low dosage of fluconazole mixed with propranolol quadrupled over that of mice given fluconazole alone[59].

β-blockers acting as antibacterials

One of the most widely prescribed anti-hypertensive drugs is propranolol, which also has anti-quorum sensing properties. Quorum sensing systems show a key function in tracking the pathogenicity of bacteria, and their targeting may reveal substantial declines in the virulence components' assembly and biofilm formation. Propranolol's anti-virulence properties were evaluated using two Gram-negative *P. aeruginosa* or *S. marcescens* models. For every investigated virulence factor and biofilm configuration, propranolol explained the considerable lowering behavior. At sub-MIC, propranolol inhibited biofilm formation, the movement of swarming, and the production of hemolysins, proteases, and virulent pigments. Its anti-quorum sensing behavior may be caused by downregulating the genes that encode for quorum sensing or by binding to the receptors. Similarly, propranolol demonstrated *in vitro* synergetic impacts when mixed with antibiotics and markedly reduced the bacterial capacity to produce pathogenesis in mice. Although a prior study suggested that propranolol might be used as a promising addition to antibiotics in the treatment of serious illnesses, it also called for more pharmacological and pharmaceutical research. Promising outcomes are also seen in the estimation of propranolol's anti-virulence activity against Gram-positive bacteria and other Gram-negative clinically significant pathogens[60]. However, a different investigation confirmed that carvedilol has antibacterial aspects against Gram-positive bacteria. However, Gram-negative bacteria showed great resistance to carvedilol in the corresponding experiment. Carvedilol was found to suppress *S. aureus* and *S. epidermidis* bacterial growth. Changes in the fatty acid makeup of S. aureus's cellular membrane may indicate that carvedilol's antibacterial effect is a prospective target for the membrane of Gram-positive cells. Additionally, measurements of the infiltration of the cell membrane during the carvedilol incubation of bacteria suggested that Gram-positive bacteria underwent more significant changes. However, strains of *P. aeruginosa* and Gram-negative E. coli were also found to exclude carvedilol from the growth medium. The obtained results might suggest that blocking the β-blocker by inactivating carvedilol during its breakdown by Gram-negative bacteria is a promising route of resistance[61].

Advanced techniques utilizing repurposed β- blockers encapsulated inside nanocarriers

Nanocarriers have the potential to significantly increase the therapeutic efficacy of medications that have been repurposed, several examples have been illustrated in **(Table 2)**.

Table 2: Application of β-blockers as repurposed nanocarrier drug delivery systems.

β-blocker	Nanocarrier type	Disease	Reference
Propranolol	Invasomes	Local contraceptive	[46]
Propranolol	Nanoemulsion	Infantile hemangiomas	[52]
Propranolol	Nanostructured lipid carriers	Infantile hemangioma	[53]
Carvedilol	Transferosomes	Skin Cancer	[54]
Carvedilol	Gold nanoparticle	Liver cancer	[58]
Propranolol	Mesoporous Silica Nanoparticles	Infantile Hemangiomas	[59]
Propranolol	Nano-propranolol hydrogel	Infantile hemangiomas	[60]
Carvedilol	PLGA nanoparticles	Anti-inflammatory/ anticancer	[61]
Carvedilol	Pro-niosomal gels	Skin Cancer	[62]
Carvedilol	Transferosomes	Skin Cancer	[63]

Nano-emulsion

For treating IH, researchers developed a nano-emulsion containing 1% propranolol. They subsequently accomplished system characterization and safety assessments using ex-vivo permeability, cytotoxicity, and biodistribution *in-vivo*. To avoid overheating the system, nano-emulsions were created by combining the oil phase with water utilizing the ultrasonic processor beneath the ice bath. Concerning the study's findings, the nano-emulsion showed a particle size (PS) of 26 nm, polydispersity index (PDI) of 0.4, skin-compatible pH, and zeta potential (ZP) of -20 mV. The nano-emulsion generated droplets with a spherical form and nanometric size, as demonstrated by electron microscopy. Furthermore, the propranolol nano-emulsion provided exceptional stability. The nano-emulsion demonstrated a respectable level of propranolol deposition in the dermis, the location of drug activity, in the ex-vivo cutaneous permeation analysis. Additionally, just a little propranolol was able to penetrate the skin because of the nano-emulsion. The radiolabeled formula stayed on the skin and a limited quantity entered the bloodstream, according to in vivo biodistribution. In the quantities estimated in the cytotoxicity check, the nano-emulsion demonstrated minimal cytotoxicity to fibroblasts, macrophages, and keratinocytes[62].

Nanostructured lipid carriers (NLC)

A study used NLC to provide propranolol for the management of IH. The essential oil of Rosa rubiginosa was opted as a liquid lipid and potential medicinal adjunct. The developed NLCs were evaluated in terms of their cell activity, stability, drug release, and skin penetration. The NLC showed 99% entrapment efficiency (EE%), a pH of 5.5, a PDI of 0.5, and a ZP that was almost neutral. The deeper layers of skin showed less drug deposition for the NLC during the intact skin permeation assays. Ultimately, using human brain microvascular endothelial cells, propranolol-NLC demonstrated strong anti-proliferative and anti-migratory effects superior to the unformulated medication. Indeed, after 6 days, propranolol-NLC reduced cell migration to roughly 25% and prevented cell proliferation by ≥50%, in contrast to almost 100% of controls. For the topical treatment of IH, topical propranolol -NLC has therefore been shown to be a potential drug delivery method[63].

Invasomes (INVs)

Propranolol was the subject of a prior study that attempted to entrap it within invasomes to produce a locally affecting contraceptive-gel. Propranolol- INV was designed by the thin-film hydration process and optimized using D-optimal design optimization. It was bestowed to Design Expert® to suggest the ideal formula. The chosen invasomes underwent additional research before being combined into a gel for both *in vivo* and *ex vivo* tests. The optimum INV illustrated a round shape with EE% of 65.01±1.24%, PS of 243.75±8.13 nm, a PDI of 0.203±0.01, ZP of 49.80±0.42 mV, and amount of drug release of 53.16±0.73%. In comparison to propranolol-gel, propranolol-INV-gel, and propranolol solution, permeability experiments validated the intended long-term effect of propranolol-INV-gel. The ability of the propranolol-INV-gel to suppress sperm motility was demonstrated by the sperm motility experiment. Furthermore, the histopathological analysis confirmed that the synthesized propranolol- INV-gel was tolerable. When considered collectively, the data provided evidence for the efficacy of propranolol- INV-gel as a contraceptive[56].

Transferosomes

The most common kind of cancer is skin cancer, which involves melanoma and non-melanoma cancer[64]. Previous studies have indicated that carvedilol, a β-blocker, has a positive effect on UV-induced skin carcinogenesis and chemical carcinogens both *in vitro* and *in vivo*[65]. Carvedilol's anticancer actions are multifunctional, reducing UV-induced oxidative stress, DNA damage, and inflammation[66]. Since topical administration is a common and straightforward self-treatment strategy and increases the likelihood that the drug will reach the sites of harm, it is the primary alternate route for preventing skin cancer. It has been shown that the β-blocker carvedilol inhibits the development of skin cancer both in vivo and in vitro. To focus on skin absorption, the authors created carvedilol-loaded transferosomes. Phospholipids and

surfactants were used in different ratios to create transferosomes, which were then analyzed. The best formula was comprised of phosphatidylcholine, and Tween-80 at 1:3:0.5, which had PS of 115.60 ± 8.70 nm, ZP of 11.34 ± 0.67 mV, and EE% of 93.70 ± 5.10%. Only at high concentrations did the optimal formula cause cytotoxicity in JB6 P+ and human keratinocytes HaCaT, but it prevented EGF-induced neoplastic alteration of mouse epidermal JB6 P+ cells at non-toxic doses. The best formula, related to the drug, leaked via the dialysis membrane, and spread slowly over the skin of the pig's ears, but it accumulated the drug in the skin. Surface application of the optimal transferosomes consistently inhibited UV-induced DNA impairment, inflammatory gene expression, and apoptosis while exhibiting slower drug absorption on rebuilt full-thickness human skin. Based on these findings, transferosomes might be a hopeful strategy for carvedilol administration to inhibit UV-skin damage and carcinogenesis[67].

Gold nanoparticles (GNPs)

A prior investigation details the anticancer and cytoprotective properties of carvedilol applied alone and in conjunction with GNPs. Apoptosis was investigated using flow cytometry with FITC/propidium iodide stain; caspase-3, caspase-8, Bcl-2, and MAPK/ERK activity by immunofluorescence microscope; PCR was used to analyze the expression of genes linked to cell death, such as Akt, mTOR, EGFR, MDR1, survivin, FADD, and Apaf; and western blot analysis was used to look for MAPK/ERK, Akt, and mTOR. Oxidative stress estimation was accomplished by decreased glutathione and malondialdehyde (MDA) levels. Intracellular GNPs targets were identified by transmission electron microscope. Using flow cytometry, mortality induced by apoptosis was found to be increased after exposure to a mixture of GNPs and carvedilol. This was due to the production of pro-apoptotic proteins FADD, caspase-3, and caspase-8, as well as sub-regulation of anti-apoptotic MAPK/ERK, Akt, mTOR, EGFR, and MDR1 resistance. A cytoprotectant for non-tumor cells was found, exhibiting elevated GSH and decreased MDA levels. GNPs were found in the cell close to the core when carvedilol was added. In tumor cells, the mixture of GNP and carvedilol led to the over-expression of pro-apoptotic proteins and the downregulation of anti-apoptotic and drug-resistant genes. Additionally, it kept non-tumor cells from apoptosis[68].

Conclusion

A new field of opportunity has been created by systematic drug repurposing. However, there have been few reported clinical successes with β-blockers so far. The current situation considers the methodical repurposing of drugs, but it also suggests that significant obstacles may need to be surmounted. Some, including the inability to create a suitable benefit-risk ratio in clinical trials, are intrinsic to the development of any new medication; however, toxicity is less likely to constitute a barrier for medications that have been repurposed. Additional barriers include those that are specific to the repurposing of drugs and include intellectual property protection, which lowers the financial goal for repurposing. Consequently, improvements that incentivize drug repositioning programs and establish an acceptable gain on financing that is appropriate to inspire the work might quicken drug repositioning. Definite suggestions have been made to recognize the possibility of drug repurposing. In instantaneous, the junction of computational and experimental tools has accompanied a new era of purposeful medication repurposing enabling the synchronization of an existing drug's mechanisms of action with the molecular dysfunctions causing disease, and if necessary, optimization of the treatment based on its ability to modulate disease.

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التطورات الأخيرة في حاصرات β كنهج لإعادة استخدام الأدوية: مراجعة منهجية

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تعد إعادة استخدام المستحضرات الصيدلانية طريقة فعالة محتملة في تطوير الأدويـــة للعثـــور على تطبيقات علاجية جديدة للأدوية المعتمدة بالفعل من إدارة الغذاء والـــدواء والتـــي تختلـــف عـــن استخدامها الأصلي المقصود. بالمقارنة مع الطرق التقليدية لاكتشاف الأدوية الجديدة ، فإنه يوفر العديد من الفوائد لأنه يمكن أن يقلل بشكل كبير من وقت التطوير والنفقات الطبية. في هذه المراجعة ، تمـــت مناقشة إعادة الاستخدام المحتملة لحاصرات β التي تم التصريح بها مسبقا من قبل إدارة الغذاء والدواء الأمريكية لإدارة اضطرابات القلب والأوعية الدموية مثل (ارتفاع ضغط الدم وعدم انتظـــام ضـــربات القلب وتسلخ الأبهر). ثبت أن حاصرات β لها خصائص مضادة للسرطان ومضادة للبكتيريا ومضـــادة للصداع النصفي ومبيد للحيوانات المنوية في العديد من التحقيقات التجريبية والوبائية. أدت النتائج إلـــى مؤشرات دوائية جديدة أو قد تؤدي إلى مؤشرات دوائية جديدة. الهدف من هذه المراجعـــة هـــو جمـــع الأدوية وطرق عملها التي تدعم إعادة الاستخدام ، ومعالجة الصعوبات في إعادة وضع حاصـــرات β للاضطرابات الأخرى ، واستكشاف الفوائد العلاجية المحتملة لدمج هذه الأدوية في تركيبات نظام النانو.