REPURPOSING OF STATIN AS AN ROBUSTING APPROACH TO TREAT MICROBIAL INFECTION

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Drug repurposing is a cutting-edge method that can save time and money in drug development by finding novel therapeutic applications for previously accepted medications. Recently, statins, which are generally used lipid-lowering medications, have drawn interest due to their possible antibacterial potentials. The pleiotropic effects of statins, which were first created to block HMG-CoA reductase in cholesterol production, include immunomodulation and antibacterial action.

According to studies, statins have antibacterial, antiviral, and antifungal potentials. They work against a variety of infections, including Candida albicans, Mycobacterium tuberculosis, and Staphylococcus aureus. It is thought that their antimicrobial effect is achieved by a variety of mechanisms, including as host immune response regulation, bacterial biofilm suppression, and membrane disruption. Additionally, statins have been demonstrated to improve the effectiveness of traditional antibiotics, indicating that combined treatment may have a synergistic impact.

As antibiotic resistance are on peak, statins' potential application in antimicrobial treatment is profoundly imperative. Statins are widely accessible and have a well-established safety profile, making them a potential safer substitute for conventional antibacterial drugs. However, more clinical research is needed to identify the best dosage, effectiveness, and potential side effects while treating infectious diseases. Conclusively, using statins as antimicrobial agents is an intriguing approach to medication development. Developing new treatment approaches to treat drug-resistant illnesses might result from an understanding of their mechanisms of action and clinical application, which would eventually support international efforts to prevent antimicrobial resistance.

Keyword: - *Drug repurposing, Simvastatin, Microbial infection, Medication, HMGCoA reductase inhibitors, drug development, repurposing approaches, gram positive bacteria, gram negative bacteria, antibacterial action, clinical trials.*

1. Introduction of Drug discovery

The process of employing a current medication or drug candidate for a new medical disease or treatment for which it was previously not recommended is known as drug repurposing. Initially, it was developed to treat a specific medical problem[1]. People have described it as an unexpected, fortuitous process. In this procedure, a drug's undesirable side effects may also serve as a clue to investigate if it might be useful for treating a completely unrelated medical issue[2]. Typically, medications with proven human safety that have been tested and developed for efficacy in a different condition than the one for which they were created. By avoiding the drug development process and sending the medications straight to preclinical and clinical trials, this method lowers risk and expenses[3].

Without specifically identifying the mechanism of action, repurposing can find novel drugs based on phenotypic benefits. These findings are more relevant to therapeutic applications and research, and they may be directly tested in

preclinical animal models. Direct advancement to Phase II clinical trials is a possibility. With repurposed medications, the chance of failure is minimal.[4]
Examples of some repurposed drugs

1) Thalidomide: This medication was taken off the market because of its serious teratogenic consequences after being created as a sedative and morning sickness remedy. Later on, though, it was used to treat multiple myeloma and leprosy.[5]
2) Viagra (Sildenafil): Originally created to treat hypertension and angina, Viagra was repurposed and became extremely successful in that market after it was discovered to have a major impact on erectile dysfunction[6].
3) Azidothymidine (AZT): Initially studied as a chemotherapeutic medication, AZT was repurposed as a powerful anti-HIV substance during the HIV/AIDS pandemic. It was the first HIV medication approved by the FDA[7].
4) Everolimus: Tuberous sclerosis is a hereditary condition that causes tumors to grow in many different organs. Everolimus was first used to prevent organ transplant rejection.[8]

Originally created as an immunosuppressant for organ transplant recipients, sirolimus has been repurposed to treat autoimmune lymph proliferative syndrome (ALPS), greatly enhancing the health and quality of life of those who get it[9].

Drug repurposing approaches

Drug repositioning strategies can concentrate on a disease condition with insufficient therapy options or on finding promising medications for repurposing[10]. Through off-label use, examination of discontinued medications, review of medications removed from the market because of safety or efficacy concerns, or recycling of medications that have reached the end of their patent exclusivity, drug-focused repurposing may broaden the use of an existing medication to new indications[11]. Compound screening is one popular method, though there are other approaches that can be taken. These can be broadly divided into two groups: activity-based screening and in silico screening. [12]Activity-based screening and in silico screening frequently work in tandem, with the in silico method offering a way to prioritize candidate compounds for activity-based screening through down-selection. The activity-based screens, on the other hand, can validate predictions and offer more training data for the in silico methods, which might help future development initiatives[13].

In silico screening

Depending on the development objectives and available data, in silico drug screening might take many different shapes. In general, in silico screening converts high-dimensional, large-format datasets (such as transcriptomic, proteomic, or metabolomics profiles) into useful information by examining patterns and relationships between biological entities (such as genes, proteins, and metabolites) at the systems level, frequently across several scales[14]. Conventional in silico methods have concentrated on assessing drug-target interactions by using low-throughput docking simulations that require known 3D chemical structures or by comparing the chemical structures of candidate compounds with those that are known to bind to a target protein. 18 AI techniques have been applied more recently to combine diverse data from several sources and uncover hitherto undiscovered connections between current medications and possible protein targets, disease conditions, and phenotypes. [15]To extract data from drug-centric, disease-centric, and gene or protein-centric databases, these [16]drug repositioning techniques employ a variety of computational models, such as deep learning, network propagation, and classical machine learning[17].
Fundamentally, a lot of computational techniques search for similarities or differences between entities of the same kind (drug-drug comparisons, for example) in order to find new associations on a big scale[18]. For instance, let's say we have compound A under investigation and would like to discover if any FDA-approved medications will act similarly in vivo. It makes sense that medications with comparable properties could have reliable in vivo effects[19]. This presumption allows for the calculation of a similarity score between drug A and all FDA-approved medications based on the information that is currently available, including structures, shapes, protein targets, side effects, molecular activities, previous clinical usage, and a variety of additional data (e.g., bioavailability, PK, etc.).[20]The distribution of similarity scores within a model with possibly millions of elements can then be used to convert the similarity scores into predictions (Figure 1). 19. More complicated models might include other ideas, such as the illness state, along with defining traits, such phenotypic keywords, omics signatures, and current therapies[21]. Creating or compiling pertinent, high-dimensional transcriptional, proteomic, or metabolic information in order to develop a

disease signature might be helpful when there is a lack of established understanding regarding the processes and pathways of a medical state or phenotype[22]. By comparing the input illness signatures to pre-existing signatures in drug perturbation databases, these data can be utilized to forecast medications. 20, 21 section on "Drug repurposing methodologies" goes into further information about these strategies. [23]

Screening using activity

Activity-based screening is crucial to ascertain a compound's biological activity in pertinent assays and disease models, regardless of the in silico screening technique used.[24] Ideally, testing is done on a variety of scales to capture how a compound affects a disease phenotype, how it affects cell viability (as a preliminary measure of toxicity), how well the drug binds to the putative target (if known), and whether it works in functionally relevant tissue, organ, or whole organism disease models. [25]When choosing the main test, important factors to take into account include the kind of in silico prediction (e.g., drug-target binding vs. phenotypic modification), the assay's time and/or cost, and how well it mimics the illness of interest[26].

A relevant model system can be used to track changes in the phenotype during and after treatment in order to evaluate potential drugs for repurposing when knowledge of the disease's mechanism and targets is limited[27]. It is crucial to strike a balance between the model system's accuracy and time and cost constraints because this kind of screening is usually the most difficult and time-consuming. Human micro physiological systems, such as organoids and microfluidic organ-on-a-chip (organ chip) technology, that more closely mimic human physiology and disease states, or small whole-organism models (such as zebra fish or Xenopus laevis (Xenopus)) that capture multi-organ drug responses, can provide a balance between biological relevance and program limitations[28]. In a recent research, for instance, it was demonstrated that a human liver chip model could detect drug toxicities with a sensitivity of 87% and a specificity of 100% in comparison to using animal models. 26 Radio ligand binding assays and other activity-based screens that assess drug–target binding can also be used as an initial assessment of drug activity on the target of interest when carrying out a drug repurposing initiative with well-defined targets and mechanisms, frequently at a significantly lower cost and effort. [29]Once drug-target binding has been proven, phonotypical screening methods may be used to a smaller list of potential drugs[30].

Drug repurposing methodology

To find existing medications for repurposing and to select drug libraries for additional in vitro and in vivo testing, a variety of techniques have been employed. One strategy employs a disease-oriented technique, which matches medications with superior therapeutic effects with illnesses that have no treatment or inadequate treatments[31]. Computational models that identify similarities between illness state features and forecast the use of comparable medications can be utilized to achieve this.[32] A different strategy is therapeutic target-oriented, which seeks for new targets for a particular indication and then matches the novel target with currently available medications. This can be achieved using computational methods that identify drug able targets associated with those mechanisms and experimental identification of novel disease mechanisms[33].

While in silico drug repositioning can offer better speed, lower cost, and the possibility to find novel pharmacological mechanisms, blinded search or experimental screening approaches were previously primarily utilized to serendipitously identify successful medications without prior information[34]. Potential therapeutic candidates can be found and narrowed down using the following computational techniques [35]

1) Based on targets [36]
2) Structure-oriented [37]
3) Based on signatures [38]
4) Network-based or pathway-based [39]
5) Based on knowledge [40]
6) Based on clinical data[41]

Prior to conducting additional animal or human research, these initiatives can also integrate retrospective screening in patient databases with artificial silico drug prediction to assess medications in particular patient populations[42]. 27 Drug repurposing techniques have proliferated in recent years, although many of these strategies have not yet been validated by FDA approval of the medications they found. Therefore, more research is needed to assess the most effective strategies for identifying medications that are clinically helpful. [43]

Why is drug repurposing?

The medication repurposing approach is advantageous in both preclinical and clinical settings for a number of reasons. [44]In target-directed preclinical drug discovery, one common approach is to optimize binding affinity for the principal target first, frequently while simultaneously decreasing affinity for "secondary targets" (i.e., selectivity[45]). Drug pharmacokinetics and safety profiling, as well as target profiling of stated drug candidates for other, unrelated target classes, are frequently neglected in such endeavors. For instance, it was shown that cyclooxygenase 2 (COX-2) was less active than its related enzyme, cyclooxygenase 1 (COX-1), in inflammation and discomfort[46]. Celecoxib, which is an order of magnitude more effective against COX-2 than COX-1, was developed on the basis of this. Osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, pain, ankylosing spondylitis, and dysmenorrhea are among its medicinal applications[47].For a given medicine, a broad body of literature is generally considered advantageous because, despite certain drawbacks, the clinical observation and monitoring needed (especially in high-risk scenarios) is manageable of[48]. When an older medicine is repurposed, it is typically assumed that the expenses of its manufacture, including any potentially hazardous waste, have already been covered. This makes the therapeutic management the new indications more financially appealing[49]. Finally, repurposing has been investigated by a number of significant pharmaceutical corporations as a strategy to prolong the patent life for profitable medication franchises. Overall, there are many potential for drug repurposing due to the incompleteness of the preclinical data and the collection of safety and efficacy data during the various clinical phases[50].

2. STATINS AN OVERVIEW

The development of the statin class of medications was one of the 20th century's most significant and undeniable clinical advances. Around 40 million people with excessive cholesterol levels are treated with these substances, which are well known for their capacity to reduce cholesterol[51]. In the meantime mevastatin was acknowledged in 1976 as a byproduct of Penicillium citrinum metabolism, a total of nine statins have been characterized, seven of which are

approved by the FDA to treat patients with high cholesterol. [52]Statins are renowned structurally by the preserved lactone ring they contain. With the exception of mevastatin, lovastatin, and simvastatin, which have a lactone ring that is hydrolyzed in the liver, all statins include this structure in a hydrolyzed state[53].

There are two major classes of statins:

1. Type 1 statins are thought to structurally resemble mevastatin since they are lipophilic and have a butyryl side chain. Type 1 statins include simvastatin, pravastatin, and lovastatin[54].
2. Traditionally lipophobic, type 2 statins differ from type 1 statins in that they usually have bigger side chains and substitute a fluorophenol group for the butyryl side chain. Type 2 statins include rosuvastatin, pitavastatin, and fluvastatin[55]. .

By attaching itself to the active site of 3-hydroxy-3methylglutaryl-coenzyme A (HMG-CoA) reductase (HMGR), a rate-limiting enzyme convoluted in cholesterol manufacture, atorvastatin lowers cholesterol[56]. HMGR plays a crucial role in the mevalonate pathway, which is necessary for the biosynthesis of cholesterol as well as the manufacture of isoprenoids, which are lipid molecules vital to cell structure and signaling. [57]Statins have been shown to have a variety of "pleiotropic," or cholesterol-independent, effects in addition to their ability to suppress cholesterol[58].

Statins have been reported to confer anti-inflammatory, immune-modulatory and anticancer effects on host cells, and these effects are well characterized. Furthermore, several studies have explored the pleiotropic effects of statins in combating multisystem microbial infections, such as sepsis and pneumonia, and studies also demonstrating that statins can directly influence the growth and virulence of bacterial pathogens[59]. With the global increase in antibiotic resistance to existing antibiotics and the search for new antimicrobial strategies reaching a critical stage, there is increasing interest in the possibility of repurposing existing drugs that have already been approved to treat different clinical conditions but that also possess antimicrobial activity[60]. The repurposing of these drugs would ominously reduce the lead time from bench to bedside. Assumed their pleiotropic activities, statins are stout potential candidates to be repurposed as novel antimicrobial agents.[61]

CLINICAL EVIDENCE THAT STATINS INFLUENCE MORBIDITY AND MORTALITY OF PATIENTS WITH MICROBIAL INFECTIONS

The clinical potential of statins as antimicrobial agents has been the subject of several studies and reviews. These reviews included studies on infections such as bacteremia, pneumonia, sepsis, and some acute infections, and the patient populations received several different statins[62]. Data from the Argument for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, which was originally conducted to determine how well rosuvastatin could reduce the risk of cardiac disease in people without hyperlipidemia, were retrospectively analyzed in 2012[63]. The analysis revealed that rosuvastatin treatment may decrease the occurrence of pneumonia before or after a cardiac event. Likewise a retrospective study of patients in the United Kingdom found that current statin treatment reduced pneumonia-associated mortality, while prior statin treatment also reduced mortality rates in patients in the United States with community-acquired pneumonia (CAP).[64]

The findings also demonstrated that the advantages of statin pretreatment rose noticeably with larger dosages. As a result, a number of studies have demonstrated the encouraging potential of statin usage in the past to lower the incidence or spread of infections[65]. However, it is challenging to determine if the benefits of these statins were pleiotropic effects on comorbidities linked to the infections or directly antibacterial/anti-inflammatory.[66] One may argue that earlier statin usage could improve cardiovascular health and hence reduce mortality rather than having any direct effect on the infection, since cardiovascular events are thought to be responsible for up to 30% of fatalities in patients with CAP.[67]

An interesting study of the effect of prior statin use on mortality in patients with bloodstream infections found a significant reduction in 90-day mortality in statin users with Gram-negative infections (adjusted OR, 0.38; 95% CI, 0.20 to 0.72; P 0.003) but no significant difference in statin users with Gram-positive infections (adjusted OR, 1.22; 95% CI, 0.69 to 2.17; P 0.49), suggesting that the type of bacterial infection may be a significant factor. [68]

In vitro antibacterial assays performed on statins

1. **Screening statins for antibacterial activity**: The antibacterial activity of eight statin drugs including simvastatin, atorvastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin and rosuvastatin were evaluated against two representative Gram-positive and Gram-negative bacterial pathogens (methicillin-resistant Staphylococcus aureus (MRSA) ATCC 43300 and Pseudomonas aeruginosa ATCC 15442 respectively). [69]Simvastatin was the only drug capable of inhibiting MRSA ATCC 43300 growth with a minimum inhibitory

concentration (MIC) value of 32μg/ml. Interestingly, none of the statin drugs examined possessed antibacterial activity against P. aeruginosa ATCC 15442 (MIC> 1024μg/ml), indicating simvastatin's effectiveness as an antibacterial activity may be restricted to Gram-positive pathogens[70].

2. **Gram-positive bacterial activity of simvastatin**: Verification of simvastatin's antibacterial efficacy against MRSA We investigated the potential of simvastatin to suppress the growth of significant strains of Gram-positive bacteria that are resistant to many drugs, as directed by ATCC 43300. Simvastatin demonstrated bacteriostatic activity against all strains of Listeria monocytogenes, methicillin-sensitive S. aureus (MSSA), MRSA, vancomycin-intermediate S. aureus (VISA), vancomycin-resistant S. aureus (VRSA), vancomycin-sensitive Enterococcus, and vancomycin-resistant Enterococcus (VRE). [71]At a concentration of 32μg/ml, it inhibited 90% of the strains tested. Simvastatin also reduced the growth of Bacillus anthracis and Streptococcus pneumonia strains, with MIC90s of 16μg/ml and 64μg/ml, respectively[72].

3. **Simvastatin's antimicrobial activity against Gram-negative bacteria**: Simvastatin's antimicrobial activity was then evaluated against a variety of Gram-negative pathogens. Initially, it was found to have no antibacterial activity against Gram-negative bacteria; however, when the bacteria's outer membrane (OM) permeability was compromised using a sub-inhibitory concentration of colistin, simvastatin demonstrated antimicrobial activity against all tested strains of Gram-negative pathogens, including Acinetobacter baumannii, Escherichia coli, Salmonella Typhimurium, Klebsiella pneumonia, and P. aeruginosa, with MICs ranging from 8 to 32 μg/m[73]. The antibacterial mechanism of action of simvastatin was examined using a standard macromolecular synthesis inhibition assay in S. aureus ATCC 29213. The concentrations below the drug's minimum inhibitory concentration (MIC) (0.25×) significantly inhibited DNA, protein, and lipid synthesis, while simvastatin also significantly inhibited RNA synthesis at 0.5× MIC. Cell wall synthesis was only inhibited at the MIC[74].

Mechanism of actions of statins

The exact mechanism of action behind statins' antibacterial properties is yet unknown. When it comes to Gram-positive bacteria, SMV's antibacterial activity was shown to be bacteriostatic at medication doses equivalent to MIC and bactericidal at concentrations four times higher than MIC. Additionally, it was proposed that statins might cause bacterial cell toxicity by decreasing the formation of a protective membrane-stabilizing metabolite in the mevalonate pathway, which would lower host cholesterol levels[75]. When the chemical structures of statins with and without known antibacterial activity were compared, two methyl groups organized in a tetrahedral molecular geometry were found to be significant components that contribute to the antibacterial activity of statins.[76]

We hypothesize that statins may disrupt the regulatory functions of bacterial cells by causing non-polar interactions between the methyl groups of statins and alanine residues found in Gram-positive bacterial surface structures like wall teichoic acids and lipoteichoic acids; breaking hydrogen bonds in Gram-negative bacterial surface lipopolysaccharide structures; and/or by causing van der Waals forces and hydrogen bonds with other Gram-positive and Gram-negative bacterial surface proteins to produce bacteriostatic effects (or bactericidal effects at higher statin concentrations[77]. Repeating alanine residues are present in wall teichoic acids and lipoteichoic acids, which are significant anionic polymers that help bacteria colonize, infect, and evade the immune system while shielding them from harmful environmental stress[78].

The tetrahedral geometry of statins' two methyl groups may allow them to directly bind with the alanine residues of wall teichoic acids and lipoteichoic acids that protrude from Gram-positive bacteria's peptidoglycan cell wall, resulting in structural distortions that could impede cell division[79].

Surface proteins and lipopolysaccharides are two examples of exposed structures found in gram-negative bacterial cells that protrude from the outside cell membrane[80]. Lipopolysaccharide structures act as both a solute regulator and a barrier of defense. A potential breach in the barrier function occurs when the stable hydrogen bond connections inside lateral lipopolysaccharide structures are disrupted[81]. Statins can attach to immobilized artificial membranes by hydrogen bonding and van der Waals forces, which resemble the fluid phospholipid bilayer of cell membranes. "Because statins' hydrogen bonding forces can break the structure of lipopolysaccharides and/or attach to proteins on the surface of cell membranes, they may have some antibacterial effects on Gram-negative bacteria[82]. Since resistance grows more quickly if the antibacterial action of statins directly jeopardizes bacterial viability, additional research is needed to precisely identify this process.[83]

Current scenario of statins in drug repurposing:

1) By examining their combined effects on progression-free survival (PFS) in patients with ovarian cancer, this study explores the possible therapeutic synergy between concurrent statins and the PARP inhibitor niraparib (Zejula).[84] To find out if niraparib and statins may interact, we looked back at niraparib registration clinical studies in ovarian cancer. Patients on niraparib in the PRIMA trial showed better PFS than those on placebo (HR = 0.62; P < 0.001; median PFS 13.8 vs. 8.2 months)[85]. According to the post hoc analysis, patients on maintenance niraparib who also reported using statins had a substantially better PFS than those on placebo who also used statins (HR = 34; P < 0.001; median PFS 18.2 vs. 6.0 months) [86]. It is noteworthy that the niraparib–statin interaction (P = 0.005) showed that the concurrent statin patients' enhanced effectiveness was significantly better than that of the statin-naive patients' two-arm comparison. These results underline the need for more research and point to new oncological prospects for the use of statins in combination therapy with PARP.[87]
2) New treatments are required for children with high-risk neuroblastoma because relapse and treatment resistance are frequent. Traditional drug development is long, costly, and sometimes ineffective in practice; as a result, it is not particularly effective in treating uncommon and pediatric illnesses[88]. Repurposing drugs is a promising approach in certain situations. In order to find licensed medications for repurposing against neuroblastoma, we employed two separate in silico prediction technologies, using machine learning[89]. In human neuroblastoma organoids, statins and phenothiazine had potent synergistic effects. In xenografts produced from MYCN-amplified neuroblastoma patients, the combination reduced tumor development and extended life, a combination of safe and licensed drugs combine[90]. The medication combination affected cholesterol metabolism by a dual-hit mechanism and promoted a phenotypic flip towards an adrenergic cell state accompanied by greater sensitivity to chemotherapy. 1. The incorporation of the medication combination into regular chemotherapy caused tumors to retreat and extended the lifespan of xenografts obtained from chemo resistant patients[91]. In chemo resistant neuroblastoma, therefore ed to standard-of-care chemotherapy works better than chemotherapy alone.[92]
3) A major contributor to low back pain, intervertebral disc degeneration (IVDD) has a big financial impact and a major negative impact on the quality of life for the aged. Due to the lack of medications that can reverse or cure IVDD, therapeutic treatments now mostly target symptom management[93]. Statins, a family of medications that have historically been used to treat cardiovascular illnesses, have been demonstrated in recent years to have positive benefits on IVDD through a number of pathways. An increasing amount of data points to statins' potential as potent treatment agents for IVDD as research into their pleiotropic effects advances[94]. In addition to summarizing statins' pleiotropic effects, this review investigates their possible mechanisms and activities in IVDD, paying special attention to alterations in the expression of pertinent molecular markers. The potential of mixing statins with other medications as part of multi-target therapy approaches is also covered, as well as current developments in the use of statins for the treatment of IVDD. A scientific reference for future research on statin usage in IVDD therapy is what this study seeks to offer.[95]
4) Inhibiting the rate-limiting enzyme HMG-CoA reductase (HMGCR) in the mevalonate pathway lowers cholesterol levels. Statins are commonly prescribed drugs. Because of their many advantages, statins are being modified to be safe, effective, and affordable anti-cancer medications[96]. Numerous studies have demonstrated that because many cancers depend on the mevalonate pathway for development and survival, they respond to statin drugs. Statins are a family of medications that are commonly recommended to treat high cholesterol because of their strong suppression of cholesterol synthesis[97]. However, there is increasing interest in using statins for other purposes, sometimes in combination with chemotherapy and radiation therapy, to treat malignant neoplastic illnesses. The BCL2 signaling pathway targets apoptosis, the p53-YAP axis controls the cell cycle, and epigenetic modifications are imparted by deregulating DNMTs and HDACs, respectively, and changing the methylation patterns on CpG islands and histone acetylation[98]. Some studies have indicated a higher survival rate and a lower incidence of tumor recurrence in individuals on long-term statin treatment, which has raised the possibility of a chemo preventive impact. [99]However, population-based clinical trials with bigger patient populations and longer follow-up periods are necessary before statin use in cancer treatment is definitively approved. The anti-cancer potential of statins appears to extend beyond their impact on cholesterol production. Their effects on signaling pathways that promote cancer will require more research[100]. Since statins seem to improve the effectiveness and solve the drawbacks of traditional cancer therapies, they may become a viable option in the battle against carcinogenesis due to their unique characteristics.[101]

5) Statins, being competitive inhibitors of HMG-CoA reductase (HMGCR), have pleiotropic effects outside of their lipid-lowering effects, in addition to lowering cholesterol and improving cardiovascular risk. Of these, the anti-cancer characteristics of statins have garnered significant interest and suggested that they could be repurposed medications for the treatment of cancer[102]. Statins' anticancer properties have been documented in numerous clinical and epidemiological studies; however, there is conflicting evidence regarding their anticancer efficacy. It's possible that some cancer molecular subtypes are more susceptible to statin therapy than others.[103]
6) There is ongoing research to determine whether statins have clinical anticancer effects. In the context of combined cancer therapies, statins should be taken into consideration because they seem to improve the effectiveness and address the drawbacks of traditional cancer treatments[104]. We offer a thorough analysis of statins' potential in anti-cancer therapies here. We go over our present knowledge of the processes that underlie statins' anti-cancer benefits and how they affect various cancers. We also provide suggestions for the planning of upcoming carefully thought-out clinical studies examining the effectiveness of statins in preventing cancer[105].
7) It is now well acknowledged that alterations in lipid metabolism are a characteristic of tumor cells; in particular, increased lipogenesis has been linked to a number of cancer forms. Several malignancies have shown significant or dysregulated mevalonate pathway activity, and numerous studies have indicated that tumor cells rely more on the constant supply of mevalonate pathway metabolites than their non-malignant [106]counterparts. The current status of statin therapy for human cancer is summarized in this paper. Statins have recently been suggested to have a variety of effects in a range of physiological and pathological states in addition to their anti-inflammatory and neuroprotective properties. [107]

In this review article, we give an overview of the current preclinical and clinical status of statins as antitumor agents, and we evaluate various patents that describe the role of mevalonate pathway inhibitors and methods to determine whether cancer cells are sensitive to statins treatment. Statins have been shown to act through mevalonate-dependent and -independent mechanisms that can affect several tissue functions and modulate specific signal transduction pathways that could account for statin pleiotropic effect.

4. Conclusion:

In the final analysis, the most effective approach to the increasing problem of antibiotic resistance is the repurposing of statins as antimicrobial agents. Statins possess a variety of pleiotropic effects, such as anti-inflammatory, immunomodulatory, and most importantly, antibacterial qualities, while being best known for its ability to decrease cholesterol. The many facets of statin repurposing have been extensively investigated in this study, including its theoretical foundations, empirical data, and modern research trends.

Drug repurposing gives researchers a tactical edge in accelerating the translational asphalt from bench to bedside, as demonstrated by the success stories of azidothymidine, sildenafil, and thalidomide. To avoid the complicated and costly procedure of de novo drug creation, we can use current medications with proven safety profiles. Given statins' substantial clinical expertise and broad usage, this method has great potential in this setting.

Several Gram-positive bacteria, including drug-resistant species, have been shown to be susceptible to the antimicrobial effects of statins, especially simvastatin, in vitro. A believable explanation for their antibacterial properties is offered by the suggested mechanisms of action, which include interference with vital metabolic processes and breakdown of the integrity of the bacterial cell wall. But the effectiveness against Gram-negative bacteria seems to depend on the permeabilization of their outer membrane, underscoring the intricacy of their antibacterial action.

Despite being mainly retrospective, clinical research has indicated a possible link between statin usage and lower rates of morbidity and death in patients with infections, specifically pneumonia. However, the confounding effect of the cardiovascular advantages of statins means that these results should be interpreted with care. The establishment of statins' therapeutic significance depends on future retrospective clinical trials that are explicitly intended to assess their antibacterial activity.

Statins, specifically in cancer, have demonstrated synergistic potential in combination therapy beyond their direct antibacterial properties. The synergistic effects of phenothiazine against neuroblastoma and the reported increase in niraparib efficacy in ovarian cancer highlight the effectiveness of statins as a variety of therapeutic agents. Additionally, the growing body of research demonstrating statins' protective benefits against intervertebral disc degeneration and their potential as anticancer drugs expands their treatment options.

Several important factors need to be taken into account despite the encouraging results. The pharmacokinetics and pharmacodynamics of statins in the setting of infection, the long-term safety of high-dose statin treatment, and the

possibility of bacterial resistance development are all issues that need more research. Furthermore, the specific mechanisms by which statins exert their antimicrobial effects—especially against Gram-negative bacteria—remain unclear.

The economic ramifications of repurposing statins as antimicrobials are substantial, providing a financially viable substitute for the creation of new antibiotics. However, thorough scientific confirmation and cautious clinical application are necessary for this method to succeed. In summary, although statins have clear antibacterial properties, further study is necessary to convert these properties into real therapeutic advantages. It will be possible to judiciously repurpose statins in the battle against microbial infections if in vitro, in vivo, and clinical investigations are integrated and their mechanisms of action and safety profiles are thoroughly understood.

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