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Review article

Revolutionizing Antibiotics: Breakthroughs in Discovery and Development

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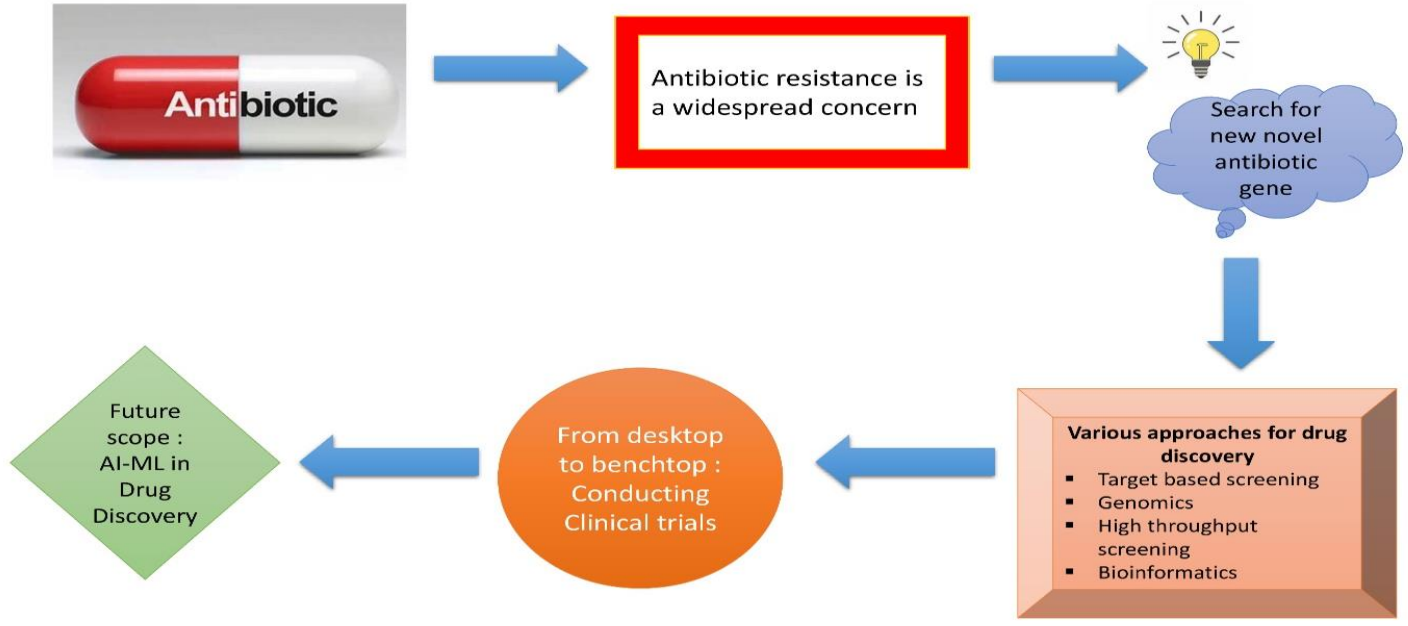
ABSTRACT

Antibiotics are chemical substances that inhibit the growth of bacteria and other microbes. Antibiotics should cause minimal or no toxicity and should be effective against a particular infection. The early era of 1940-1960s is considered as golden age of antibiotics. Most of the antibiotics are becoming resistant to various bacteria, fungi and spores, leading to necessity of new antibiotics to combat resistance. Significant technological advances have provided researchers access to biological events and repositioned their mind set for antibiotic research. Target based screening, cell based adenosine diphosphates, genomics, high throughput screening, whole genome sequencing, bioinformatics based predictions, transcriptions and metabolic profiling are some of the innovative technologies used in antibiotics drug discovery. Research community is working tirelessly to discover newer antibiotic compounds due to its increasing demand. Discovery of newer antibiotics is based on symbiotic relationship between researchers, regulators, antibiotic production, environmental and intracellular signalling. An overview of some of the technologies used in the creation of brand-new, innovative antibiotics is provided by this review.



Keywords: Antibiotics, Drug discovery, Artificial intelligence, Innovation, Clinical trials.

INTRODUCTION

The term 'antibiotic' was introduced by Selman Waksman. Antibiotics are chemical substances, produced by micro-organisms, which can inhibit the growth or destroy bacteria and other micro-organisms. They are formed by a microbe, with opposed properties on the growth of other microbes. An antibiotic interferes with bacterial growth by a specific mechanism at beneficial concentrations. Antibiotics should cause minimal or no toxicity wherein it should have potency to be effective against a particular infection. The golden age of antibiotics was 1940-1960s where most of the antibiotics used currently were discovered. This leads to an illusion that most of the infectious diseases would be under control which will provide better health care to the humanity [1-3]. But the results were otherwise where it led to increase in drug-resistant pathogens. This could be due to the fact of prescribing more antimicrobials, self-medication by patients and interruption of therapy [4].

The discovery and development of new antibiotics face significant challenges, including the scientific difficulty of identifying effective drug targets without causing toxicity, financial and regulatory hurdles that make the process costly and time-consuming, and rapid development of antibiotic resistance. Many pharmaceutical companies have scaled back antibiotic research due to financial constraints, leading to a loss of expertise. The development process is lengthy and complex, involving multiple stages, and stricter regulatory standards for safety and efficacy make it harder and expensive to introduce new antibiotics to the market. This review addresses these issues that is essential for combating antibiotic resistance and fostering innovation in antibiotic development [5-9].

Need for new Antibiotics

The urgent need for new antibiotics is driven by the rising prevalence of antibiotic-resistant infections, particularly in hospitals. Methicillin-resistant *Staphylococcus aureus* (MRSA) and other resistant microbes pose significant threats worldwide, with limited effective treatment options [10-11]. Infections such as tuberculosis, respiratory infections, urinary tract infections, and gonorrhoea require new antibiotics due to the spread of resistance. The global mortality rate has increased since the 1980s, partly due to the rise of resistant bacteria, such as MRSA and multi-drug-resistant tuberculosis [12-14]. The gap in antibiotic innovation is widening, with few new classes introduced since the 1960s. Furthermore, the decline in expertise in antibiotic development, coupled with regulatory, scientific, and financial challenges, makes the creation of novel treatments difficult. Antibiotic resistance remains a global health risk, exacerbated by the lack of consistent global guidelines and increased international travel, which accelerates the spread of resistant bacteria [15-19].

Antibiotics in Clinical Development

The prime reason for antibiotic discovery is to combat resistant pathogens, but unfortunately most of the patients are infected with drug-susceptible pathogens. So newly discovered antibiotics are tested on patients in clinical trials for various acute infections. However, the rules and regulations are changing much more [20]. Approximately 41 new antibiotics with the potential to treat serious bacterial infections were in clinical development and four were approved since June 2019. There are currently 32 antibacterial agents in clinical development Phases 1–3 targeting WHO priority pathogens, of which 20 have activity against at least one of the critical Gram-negative pathogens [21]. The discovery of antibiotics begins with identifying a validated lead from bacterial populations, focusing on minimizing cross-resistance. Antibiotic research and development (R&D) needs to focus on producing new classes, targets, and mechanisms of action to avoid cross-resistance to current antibiotics [22]. However, developing new antibiotics alone won't suffice to combat AMR. It requires guidelines from multiple stakeholders, such as the WHO Global Framework for Development and Stewardship, which aims to promote responsible antibiotic use in human, animal, and agricultural sectors [23]. Despite advances in biotechnological techniques, new antimicrobial discoveries may not always lead to effective treatments. The Innovative Medicines Initiative, launched in 2013 in Europe, seeks to foster collaboration between the biotech, academic, and industrial sectors to overcome the commercial, regulatory, and scientific barriers impeding antibiotic discovery [24-25].

Antibiotics from Soil, Fungi, Microbes

Entophytic fungi, is key in drug discovery, producing antibiotics like β-lactam-based penicillin's. These antibiotics help protect fungi and host plants from pathogens. Streptomyces, a major antibiotic-producing genus, contributes to two-thirds of antibiotics from bacteria and fungi. Co-culturing Streptomyces with fungi or other bacteria has led to the production of novel antibiotics, such as fumicyclines and alchivemycin A. Additionally, adding small molecules like ARC2 induces secondary metabolite production in *Streptomyces*, yielding antibiotics like doxorubicin and baumycin. Screening orphan biosynthetic gene clusters has also identified small molecule elicitors, leading to the discovery of clinically used antibiotics such as piperacillin and trimethoprim. This highlights the potential of microbial interactions for discovering new antibiotics [26-32].

Antibiotics from Medicinal Chemistry

Development of antibiotics over the past ten decades has been a breakthrough success in the area of medicinal chemistry. Despite the fact that medicinal chemistry discovers newer antibiotics, pathogens are fighting back and there exist a situation of big fight with these microbes. Deaths due to bacterial and viral infections are very common in the developing and economically deprived world. The

WHO has stated that tuberculosis was responsible for around 6 million deaths from 2010-2020 and most of them occurring in Africa and Asia. Across the globe multiple-resistant Staphylococcus aureus is a growing problem, with most new infections developed in and from the hospitals. Elderly or immune compromised patients are prone to death from MRSA [33].

Synthetic Biology

The use of synthetic biology techniques opens up new possibilities for the creation of antibiotics. In order to create new antibiotics or improve the effectiveness of already existing ones, scientists might build and engineer new production pathways. This method may be able to circumvent the constraints on the manufacturing of natural antibiotics and produce customized medications [34].

Genomics and Metagenomics

Advances in genomics and metagenomics have revolutionized the field of antibiotics discovery. By sequencing the genomes of bacteria, scientists can identify unique gene clusters responsible for producing antibiotics. Metagenomics allows for the exploration of diverse microbial communities, including unculturable bacteria, to uncover novel antibiotic-producing organisms [35].

New-target Identification Employing Genome Sequencing

High-throughput screening techniques enable the rapid screening of large compound libraries for potential antibiotics. This approach involves testing thousands of compounds against a bacterial target to identify those with antimicrobial activity. Automated robotic systems and improved screening assays have accelerated the screening process. The sequencing of microbial genomes was empowered due to the advancement in high-throughput automated DNA sequencing. By this more than 35 bacterial genome sequencing has been completed. This process is growing at an exponential rate. Revolution in genome sequencing has opened up new strategies for antibiotic drug discovery. Genome sequencing support the determination of protein and RNA coding capacity, to find most probable drug targets [36]. Open reading frames (ORFs) are revealed with the employment of genome sequence of the specific organism under research area [37].

Essential Gene Determination

Gene inactivation technique could be employed along with plasmid integration and allele replacement mutagenesis in which upstream and downstream of the desired gene was amplified by combining with a gene encoding resistance to a relevant antibiotics [37]. Rapid PCR-based method provides DNA cassettes which are taken directly from the organisms under study for mutagenesis and non-essential genes are isolated. Conditional lethal mutants can also be isolated and can be subjected to further in vitro assessment of the reduced gene products activity in cell [38]. Novel antibiotic leads are identified using advances in genomics since it leads to the determination of many molecular targets. Some of the areas under investigation are DNA replication, protein secretion, cell division, peptidoglycan biosynthesis, signal transduction, aromatic amino acid biosynthesis and isoprenoid biosynthesis [39]. Three target areas that have yielded novel leads are: Aminoacyl-tRNA synthetases, polypeptide deformylase, and fatty acid biosynthesis.

Antibiotics using Machine Learning and Artificial Intelligence

Traditional high-throughput screens and lead-optimization are comparatively expensive that computer-aided drug discovery techniques, that are faster, that aids in accelerated novel antibiotics identification [40]. Machine-learning methods emphasizes on results obtained from crystallographic and assay data [41]. Artificial neural networks mimic cognitive function of the brain. Network behaviour is trained by optimizing the network's capability in regard to prediction of the activities in respond to different vectors of molecular, structural, or pharmacophoric descriptors, that helps in identifying potential ligands. ANNs are used along with ligand-based QSAR to identify novel antibiotics. Neural networks in ligand-based QSAR are used in creating generalized receptor-based scoring functions [42]. Artificial intelligence has significantly impacted antibiotic discovery, particularly through deep learning tools. These tools use intuitive algorithms to identify lead molecules by analyzing chemical descriptors. One such AI-driven discovery is halicin, a molecule initially used for diabetes treatment, which has shown promising antibacterial activity, including against *Mycobacterium tuberculosis* and carbapenem-resistant *Enterobacteriaceae*. The AI model screens libraries of compounds, predicting their functions based on structural data [43].

Reduction of Antibiotic Resistance Development

The most effective way of managing the antimicrobial resistance crisis is to modify the antibiotic usage, especially with the third-generation cephalosporins. Antimicrobial resistance varies regionally, with the highest occurrence in Asia-Pacific countries, as revealed by the SMART global surveillance system. To combat AMR, appropriate antibiotic prescribing is crucial, with updated guidelines recommending high-dose, prolonged infusions and early multi-antibiotic therapy to prevent resistance and improve survival rates. Additionally, nanomedicine plays a vital role in overcoming antibiotic resistance by enhancing the effectiveness of current antibiotics. It improves drug stability, allows biofilm penetration, extends release duration, and ensures targeted delivery to infection sites, ultimately reducing side effects and increasing therapeutic efficacy. Key elements that regulate essential activities such intracellular absorption, biodistribution, or clearance are the physicochemical characteristics of nanosystems, specifically particle size, surface charge, and solubility. Better drug loading efficiency for both hydrophilic and lipophilic antibiotics, and consequently an increased antibacterial activity, are made possible by nanometer-sized particles. The reticulo-endothelial

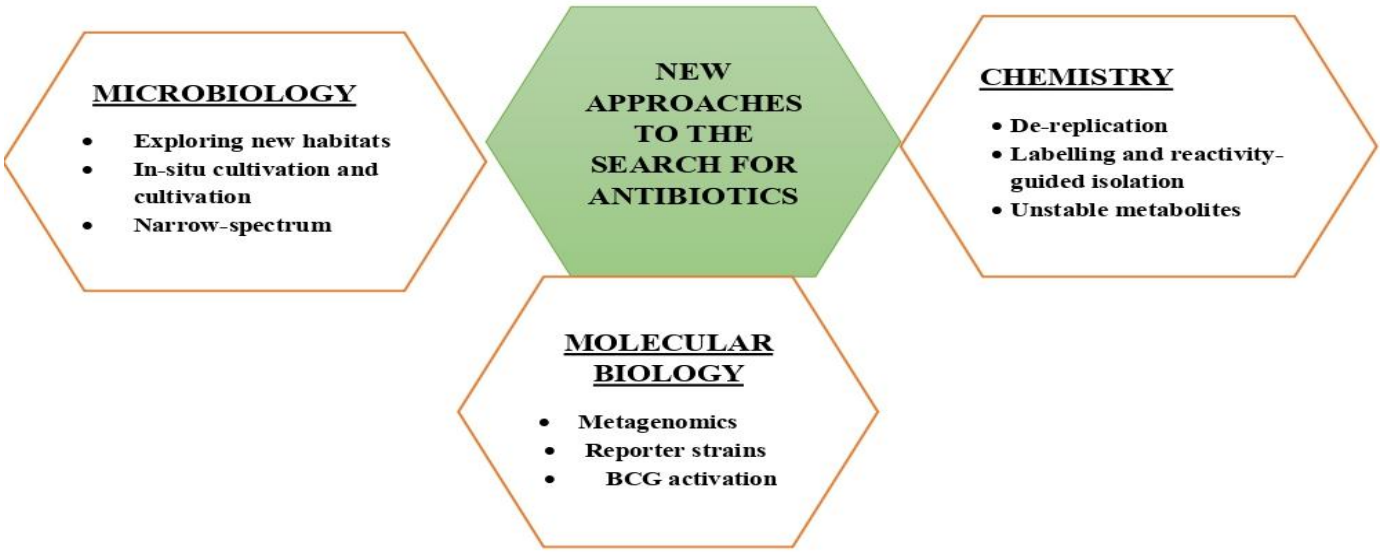
system was passed in order to accomplish the more anticipated cellular internalisation of the antibiotic-loaded nanosystems. The zeta-potential and surface charge of nanosystems influence cellular biodistribution and absorption via influencing interactions with proteins, tissues, or different tissue components. Because of their anionic nature, host cells like macrophages are drawn to positively charged nanosystems as opposed to uncharged and negatively charged on. Therefore, the improved antibacterial drug delivery capabilities of nanosystems stem from a number of mechanisms, such as their capacity to maximise the physicochemical properties of entrapped antibacterial drugs, their preferred accumulation in the vicinity of the cytoplasm, their electrostatic interactions with the bacterial membrane, their high oxidising power and generation of reactive oxygen species, the avoidance of undesired interactions and protection of antibacterials from degradation, and the improved clinical use of antibacterials through more favourable routes for patients.

Platforms for Antibiotic Discovery

The emergence and spread of resistance microorganisms continue to be an issue since there is a deficiency of efficient research methods for antibiotic discovery. In the dearth of a platform capable of producing lead compounds, the odds of finding an antibiotic are extremely slim. The discovery of new antibiotics involves various innovative platforms to address challenges in the field. Together, these platforms offer diverse strategies to combat antibiotic resistance and improve the discovery of novel antimicrobial agents. Antibiotic research and development face several challenges, including the disparity in financial incentives for developing drugs for neglected tropical diseases, which are prevalent in low-income countries. The Target Product Profile approach helps prioritize antibiotic development by aligning R&D with unmet health needs and financial incentives, ensuring that antibiotics meet specific criteria for effectiveness and accessibility. These approaches, along with a global commitment to collaboration and funding, are essential to overcoming the barriers to developing new antibiotics and addressing the growing threat of antimicrobial resistance. Antibiotic resistance genes (ARGs) have become a major environmental pollutant, contributing to the spread of antibiotic resistance across microbial populations in various ecosystems. These genes, can transfer between bacteria, exacerbating the issue. They enter ecosystems through wastewater effluents, agricultural runoff, and improperly discarded pharmaceutical waste. This environmental presence poses a dual threat by disrupting natural microbial communities and creating reservoirs of resistance that can transfer to human and animal pathogens, complicating infection treatment. Combating ARG pollution requires stricter regulations on antibiotic use, improved wastewater treatment technologies, and global surveillance to track and mitigate the spread of these pollutants.

Modern Approaches in the Screening of new Antibiotics from Natural Sources

Figure 1: captures the concise knowledge of modern approaches in the screening of new antibiotics



Metagenomics Screening and Genome Mining

The full biosynthetic potential of microorganisms may be accessed by the identification of biosynthetic gene clusters in metagenomic data and the subsequent heterologous expression of those clusters. Even actively cultivated and researched actinobacteria have great cryptic biotechnological potential, according to genomic analyses. The main interest is in the study of microorganisms from ecological niches that are underutilized. Metagenomic research on the human microbiome as a source of antibiotic chemicals is likewise quite popular. A number of strategies, including nonribosomal peptides, ribosomally produced and post-translationally modified peptides (RiPPs), and polyketides, have been effectively employed in the hunt for novel antibiotics with diverse biochemical origins.

Reporter Strains and Chemistry

Determining an antibiotic's molecular target and mode of action is crucial for research purposes as well as for future logical

modification and potential assessment of the substance. These days, promoting a possible medication to the pharmaceutical industry also need this information. For a new natural substance, more biochemical testing and profiling are usually required to clarify its mechanism of action. Reporter strains are the most appropriate among target determination assays for mechanism-based screening and antibiotic discovery. Under the influence of sublethal antibiotic doses, reporter strains work by selectively increasing a gene's expression. Chemistry continues to be one of the most significant areas of innovation in the quest for novel natural compounds, even though we do not take advancements in the field of synthetic compounds and semi-synthetic modification of natural products into consideration in this analysis. First of all, successful and frequently used techniques for classifying and ranking natural antibiotics are based on chemical techniques. However, it is possible to utilize some reagents for screening and prioritizing specific structural groups directly in extracts and mixtures of natural origin thanks to the knowledge in highly selective transformations developed within the framework of bio-orthogonal chemistry. The final portion focuses on how to work with labile chemicals.

Dereplication

Dereplication provides a solution to the re-discovery issue and enables us to rank the study subjects, concentrating resources exclusively. Most of the efforts in the field are related to MS-based Dereplication, based on early assessments. The hierarchical cluster analysis with principal component analysis, or hcapca, algorithm can find common fragmentation patterns, distinct and common components, and make it easier to find congeners or distinctive chemicals. Few notable case studies includes Synthetic Antibiotics Development, AI-Driven Drug Discovery and Genetic and Molecular Approaches [44].

CONCLUSION

Antibiotic discovery has come a long way from semi-synthesis to fully synthetic molecules. The world now understood the consequences and ever-growing threat of antimicrobial resistance. This necessitates the strengthening of new antibiotic research and development. Many government and non-government organizations across the globe are working on this. The current R&D programmer of various countries in collaboration with pharmaceutical and biotechnology companies are more oriented towards making newer antibiotics more viable and economical to the public. Though the basic research and preclinical trials are carried out smoothly, a hindrance at clinical research stage is encountered where regulators pitch in with legal hurdles. A common policy will resolve this by creating a win-win situation for governments, regulators and companies working with antibiotics. Noteworthy technological advances have provided researchers access to biological events and repositioned their mind-set for antibiotic research. Innovative techniques such as target-based screening, cell-based ADPs, genomics, high throughput screening, whole-genome sequencing, bioinformatics-based predictions, transcription, and metabolite profiling will lead to discover antibiotics. The increasing demand for new antibiotics drives the research community continuously to discover and identify new compounds. A subtle connectivity between antibiotic production, regulatory networks, and environmental and intracellular signals are essential to discover new antibiotics. The main goal today in front of human kind is to develop technologies that could have sufficient benefits and results to overcome one of the major problems of this century- the lack of novel antibiotics.

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REFERENCES

1. Clardy J, Fischbach M, Currie C, 2009. The natural history of antibiotic. Current Biology. 19, Pages R437-R441. Doi: 10.1016/j.cub.2009.04.001

2. D M Livermore, 2011. Discovery research: The scientific challenge of finding new antibiotics. Journal of Antimicrobial Chemotherapy 66(9), Pages 1941–1944. Doi: 10.1093/jac/dkr262.

3. I A Rather, B C Kim, V K Bajpai, 2017. Self-medication and antibiotic resistance: Crisis, current challenges, and prevention. Saudi Journal of Biological Sciences. 24, Pages 808–812. Doi: 10.1016/j.sjbs.2017.01.004.

4. U Theuretzbacher, 2011. Resistance drives antibacterial drug development. Current Opinion in Pharmacology. 11(5), Pages 433–438. 2011. Doi: 10.1016/j.coph.2011.07.010.

5. L L Silver, 2011. Challenges of antibacterial discovery. Clinical Microbiology Reviews. 24(1), Pages 71–109. Doi: 10.1128/CMR.00030-10.

6. A Zorzet, 2014. Overcoming scientific and structural bottlenecks in antibacterial discovery and development. Upsala Journal of Medical Sciences. 119(2), Pages 170–175. Doi: 10.3109/03009734.2014.907670.

7. D M Livermore, 2004. The need for new antibiotics. Clinical Microbiology and Infection. 10(4), Pages 1–9. Doi: 10.1111/j.1469-0691.2004.01035.x.

8. A Zumla, J M Grange, 2001. Multidrug-resistant tuberculosis – Can the tide be turned?. Lancet Infectious Diseases. 1, Pages 199–202. Doi: 10.1016/S1473-3099(01)00064-9.

9. N Woodford, M E Ward, M E Kaufmann, et al, 2004. Community and hospital spread of Escherichia coli producing CTX-M extended-spectrum beta-lactamases in the UK. Journal of Antimicrobial Chemotherapy. 54(4), Pages 735–743. Doi: 10.1093/jac/dkh370.

10. K A Fenton, C Ison, A P Johnson, et al, 200.. Ciprofloxacin resistance in Neisseria gonorrhoeae in England and Wales in 2002. Lancet. 361Pages 1867–1869. DOI: 10.1016/S0140-6736(03)13495-4.

11. G L Armstrong, L A Conn, R W Pinner, 1999. Trends in infectious disease mortality in the United States during the 20th century. Journal of the American Medical Association. 281(1), Pages 61–66. Doi: 10.1001/jama.281.1.61.

12. M L Cohen, 2000. Changing patterns of infectious disease. Nature. 406, Pages 762–767. Doi: 10.1038/35021202.

13. C Walsh, 2003. Where will new antibiotics come from?. Nature Reviews Microbiology. 1, Pages 65–70. Doi: 10.1038/nrmicro732.

14. D M Shlaes, 2003. The abandonment of antibacterials: why and wherefore?. Current Opinion in Pharmacology. 3, Pages 470–473. Doi: 10.1016/S1471-4892(03)00096-X.

15. S J Projan, 2003. Why is big Pharma getting out of antibacterial drug discovery?. Current Opinion in Microbiology. 6, Pages 427–430. Doi: 10.1016/S1369-5274(03)00090-1.

16. R T Cirz, J K Chin, D R Andes, 2005. Inhibition of mutation and combating the evolution of antibiotic resistance. PLoS Biology. 3, Pages e176, Doi: 10.1371/journal.pbio.0030176.

17. E P Abraham, E Chain, 1988. An enzyme from bacteria able to destroy penicillin. 1940. Reviews of Infectious Diseases. 10(4), Pages 677–678, Doi: 10.1093/clinids/10.4.677.

18. C Nathan, 2004. Antibiotics at the crossroads. Nature. 431, Pages 899–902. Doi: 10.1038/431899a.

19. J H Rex, 2013. A comprehensive regulatory framework to address the unmet need for new antibacterial treatments. Lancet Infectious Diseases. 13, Pages 269–275. Doi: 10.1016/S1473-3099(13)70023-5.

20. U Theuretzbacher 2017. Antibiotic innovation for future public health needs. Clinical Microbiology and Infection. 23(10), Pages 713–717. Doi: 10.1016/j.cmi.2017.05.023.

21. D J Payne, M N Gwynn, D J Holmes, 2007. Drugs for bad bugs: confronting the challenges of antibacterial discovery. Nature Reviews Drug Discovery. 6, Pages 29–40. Doi: 10.1038/nrd2245.

22. L Czaplewski, R Bax, M Clokie, et al, 2016. Alternatives to antibiotics – A pipeline portfolio review. Lancet Infectious Diseases. 16, Pages 239–251, Doi: 10.1016/S1473-3099(15)00418-5.

23. U R Abdelmohsen, T Grkovic, S Balasubramanian, 2015. Elicitation of secondary metabolism in actinomycetes. Biotechnology Advances. 33, Pages 798–811. Doi: 10.1016/j.biotechadv.2015.01.009.

24. E Recio, A Colinas, A Rumbero, 2004. PI Factor, a novel type quorum-sensing inducer elicits pimaricin production in Streptomyces natalensis. Journal of Biological Chemistry. 279, Pages 41586–41593. Doi: 10.1074/jbc.M405591200.

25. G L Challis, D A Hopwood, 2003. Synergy and contingency as driving forces for the evolution of multiple secondary metabolite production by Streptomyces species. Proceedings of the National Academy of Sciences of the United States of America. 100, Pages 14555–14561. Doi: 10.1073/pnas.2335992100.

26. A R Ola, D Thomy, D Lai, et al, Inducing secondary metabolite production by the endophytic fungus Fusarium tricinctum through co-culture with Bacillus subtilis. Journal of Natural Products. 76, Pages 2094–2099. Doi: 10.1021/np400708k.

27. J Y Cho, M S Kim, 2012. Induction of antifouling diterpene production by Streptomyces cinnabarinus PK209 in co-culture with marine-derived Alteromonas sp. KNS-16. Bioscience, Biotechnology, and Biochemistry. 76, Pages1849–1854. Doi: 10.1271/bbb.120178.

28. H Onaka, Y Mori, Y Igarashi, 2011. Mycolic acid-containing bacteria induced natural-product biosynthesis in Streptomyces species. Applied and Environmental Microbiology. 77, Pages 400–406. Doi: 10.1128/AEM.01428-10.

29. Y Igarashi, Y Kim, Y In, et al, 2010. Alchivemycin A, a bioactive polycyclic polyketide with an unprecedented skeleton from Streptomyces sp. Organic Letters. 12(15), Pages 3402–3405. Doi: 10.1021/ol101268s.

30. S M Pimentel-Elardo, D Sørensen, L Ho, et al, 2015. Activity-independent discovery of secondary metabolites using chemical elicitation and cheminformatic inference. ACS Chemical Biology. 10(12), Pages 2616–2623. Doi: 10.1021/cb5009538.

31. Y Imai, S Sato, Y Tanaka, 2015. Lincomycin at subinhibitory concentrations potentiates secondary metabolite production by Streptomyces spp. Applied and Environmental Microbiology. 81(11), Pages 3869–3879. Doi: 10.1128/AEM.00189-15.

32. S I Amano, T Morota, Y K Kano, et al., Promomycin, a polyether promoting antibiotic production in Streptomyces spp. Journal of Antibiotics. 63(9), Pages 486–491. Doi: 10.1038/ja.2010.82.

33. K Yamanaka, 2005. Desferrioxamine E produced by Streptomyces griseus stimulates growth and development of Streptomyces tanashiensis. Microbiology. 151(9), Pages 2899–2905. Doi: 10.1099/mic.0.27882-0.

34. S I Amano, T Sakurai, K Endo, H Takano, et al, A cryptic antibiotic triggered by monensin. Journal of Antibiotics. 64, Pages 703. Doi: 10.1038/ja.2011.81.

35. M R Seyedsayamdost, 2014. High-throughput platform for the discovery of elicitors of silent bacterial gene clusters. Proceedings of the National Academy of Sciences of the United States of America. 111, Pages 7266–7271. Doi: 10.1073/pnas.1405917111.

36. D McDevitt, M Rosenberg, 2001. Exploiting genomics to discover new antibiotics. Trends in Microbiology. 9(12), Pages 611–617. Doi: 10.1016/S0966-842X(01)02269-2.

37. K K Koretke, 2000. Evolution of two-component signal transduction. Molecular Biology and Evolution. 17(12), Pages 1956–1970. Doi: 10.1093/oxfordjournals.molbev.a026373.

38. L Aravind, E V Koonin, 2000. The α/β fold uracil DNA glycosylase: a common origin with diverse fates. Genome Biology. 1(4), Pages 1–7. Doi: 10.1186/gb-2000-1-4-research0007.

39. L Alksne, 2000. Identification and analysis of bacterial secretion inhibitors utilizing a SecA–LacZ reporter fusion system. Antimicrobial Agents and Chemotherapy. 44(6), Pages 1418–1427. Doi: 10.1128/AAC.44.6.1418-1427.2000.

40. J D Durrant, R E Amaro, Machine-learning techniques applied to antibacterial drug discovery. Chemical Biology & Drug Design. 85(1), Pages 14–21. Doi: 10.1111/cbdd.12425.

41. A Tropsha, 2010. Best practices for QSAR model development, validation, and exploitation. Molecular Informatics. 29, Pages 476–488. Doi: 10.1002/minf.201000061.

42. J D Durrant, A J Friedman, K E Rogers, 2013. Comparing neural-network scoring functions and the state of the art: Applications to common library screening. Journal of Chemical Information and Modeling. 53(7), Pages 1726–1735. Doi: 10.1021/ci400070n.

43. J D Durrant, J A McCammon, 2010. NNScore: A neural-network-based scoring function for the characterization of protein-ligand complexes. Journal of Chemical Information and Modeling. 50(10), Pages 1865–1871. Doi: 10.1021/ci1002116.

44. M Murcia-Soler, F Perez-Gimenez, F J Garcia-March, et al, 2004. Artificial neural networks and linear discriminant analysis: A valuable combination in the selection of new antibacterial compounds. Journal of Chemical Information and Computer Sciences. 44(3), Pages 1031–104. Doi: 10.1021/ci049883k.