ELSEVIER

editorial

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# Drug resistance: a growing problem

*Numerous legends of the quest for the Holy Grail, which would bring healing and eternal life, have been recounted in various ancient treatises.*
*Christian Mythology*

''**What if** . . .''

A high school classmate of mine, who was a dreamer, used the term ''*what if* . . .'' so frequently that the teacher said she would write it on the chalkboard 100 times if she said it again. She countered with ''But *what if* I forget?''

*What if* drug resistance was not an issue? For sure, we would have many more antibiotics on the market. Perhaps we would not have as many classes of antibiotics, had we not needed to keep searching for new targets that were not so resistance prone, and maybe we would not have found the more complex scaffolds, such as the tetracyclines, vancomycin and daptomycin. Perhaps we also would not have investigated so many bacteriostatic and bactericidal drug mechanisms. However, we surely would have many more useful workhorse drugs; the penicillins and the fluoroquinolones would be more widely used, β-lactamase inhibitors would not be needed, and we would certainly have more than one marketed oxazolidinone. Bacterial infections would not be so life-threatening; antibiotics would comprise a 'met' medical need. Would we still be using sulfa drugs as a primary line of defense?

These are nice dreams, but the reality is that *drug resistance is a huge problem*. The Holy Grail of antibiotic research is to discover the drug target and associated drug scaffold that are not prone to drug resistance. Alas, this Holy Grail has not yet been found, and fewer people are now looking.

Drug resistance is defined as the *reduction in effectiveness of a drug* to cure a disease or improve patient symptoms. Commonly, the term is used in the context of diseases caused by pathogens, for example, bacteria, fungi, parasites and viruses, where it is an enormous challenge. However, as we will see, drug resistance is not restricted to infectious disease, and has emerged in other disease states as well.

## Drug resistance in infectious disease

Antimicrobial agents are those medicines used to combat infections caused by bacteria, fungi, parasites and viruses. Resistance is problematic in the treatment of all four types of infections. However, as an example, in the case of antibiotics, which are used to combat bacterial infections, resistance evolves by way of natural selection acting upon random mutation, which is effective because of the rapid division of bacterial cells. This resistance can also be engineered by applying an evolutionary stress on a population. And bacteria can transfer genetic information thus generated in a horizontal fashion by plasmid exchange. If a bacterium carries several resistance genes, then it is termed multi-resistant or a 'superbug.' An example of a multidrug-resistant pathogen is methicillin-resistant *Staphylococcus aureus* (MRSA), whose progression is shown in the graphic when an ineffective drug, for example, a β-lactam antibiotic with low affinity for the specific penicillin-binding protein (PBP2a) found in MRSA, is administered. Prognosis is poor, and serious illness or death can occur. For comparison, when the same antibiotic, which has good affinity for wild-type PBPs, is administered to methicillin-sensitive *S. aureus* (MSSA), then progression of the infection is halted. This discussion is depicted in the graphic. Colonization of superbugs is particularly dangerous to humans and occurs with certain antibiotic classes. Risk of colonization increases with (1) lack of sensitivity, or resistance, of the superbugs to the antibiotic used; (2) high tissue penetration of the antibiotic; and (3) broad spectrum activity of the antibiotic used, such that normal flora is reduced or eliminated. For methicillin-resistant *S. aureus*, increased rates of

1359-6446/06/$ - see front matter  doi:10.1016/j.drudis.2010.04.002

infection are also seen with antibiotics other than β-lactams, for example, glycopeptides, such as vancomycin and especially quinolones [1,2]. Daptomycin is a clinically useful antibiotic for both MRSA and MSSA [3]. MRSA is now referred to as 'hospital-acquired' and 'community-acquired', and the clinical strains differ in these two types of MRSA infections.

## Why many pharmaceutical companies have abandoned infectious disease research

Twenty years ago, virtually all big pharma companies had active antibiotic programs in anti-infective research departments. Today, only Pfizer, AstraZeneca, GlaxoSmithKline and Novartis are engaged with internal antibiotic programs [4]. However, all big pharma companies are still very interested in the license or purchase of new antibiotics that show promise. Novartis recently purchased the rights for PTK0796 from Paratek Pharmaceuticals and AstraZeneca recently purchased the French biotech company Novexel (a spin-off from Sanofi-Aventis when they ended anti-infective research in 2004) to capture their experimental antibiotic CAZ104.

Why have pharmaceutical companies almost uniformly exited from anti-infective research? The reason is economics and is twofold: with the cost of drug development in the range of US$1.3 billion to US$1.7 billion [5], companies do not want to invest these sums in a new anti-infective agent over a 10-plus year timeframe, only (1) to have the new drug succumb to resistance within a few years, which may not allow the company to even recoup its investment; or (2) to see the new drug perform very well and not produce resistant mutations, and have it 'shelved' for use only as the 'the drug of last resort'. It is instructive to look at two recent and different classes of antibiotics that have been developed. Zyvox (linezolid) was approved in 2003; resistance was reported in 2007. Cubicin (daptomycin) was approved in 2003; resistance was reported in 2006. With these scenarios, many companies are not incentivized to maintain internal anti-infective research departments.

## Drug resistance in cancer

Drug resistance has more recently been noted in cancer, and is now problematic with a variety of drugs. This section will briefly describe resistance challenges with three anti-cancer drugs.

*Gleevec* (*imatinib*): Imatinib is a small molecule inhibitor of Bcr-Abl kinase and is used to treat chronic myeloid leukemia (CML) [6]. The Bcr-Abl tyrosine kinase, which develops due to a fusion of *ABL* and *BCR* genes, is a constitutively active enzyme that is the drug target for imatinib. The Bcr-Abl mutations that confer resistance to imatinib are well-mapped, and current drug discovery efforts center on the design of inhibitors that will bind to the conformations of the mutant kinases. This is a rational approach to the identification of new drug targets and the design of new drugs that will be effective against the resistant mutations.

*Velcade* (*bortezomib*): Bortezomib is a proteasome inhibitor that is used clinically for the treatment of refractory multiple myeloma. A mechanism for resistance has been defined. Selective overexpression of a mutant (Ala49Thr mutation) in the PSMB5 protein has been demonstrated in JurkatB cells, and is thought to constitute an important mechanism of bortezomib resistance [7,8].

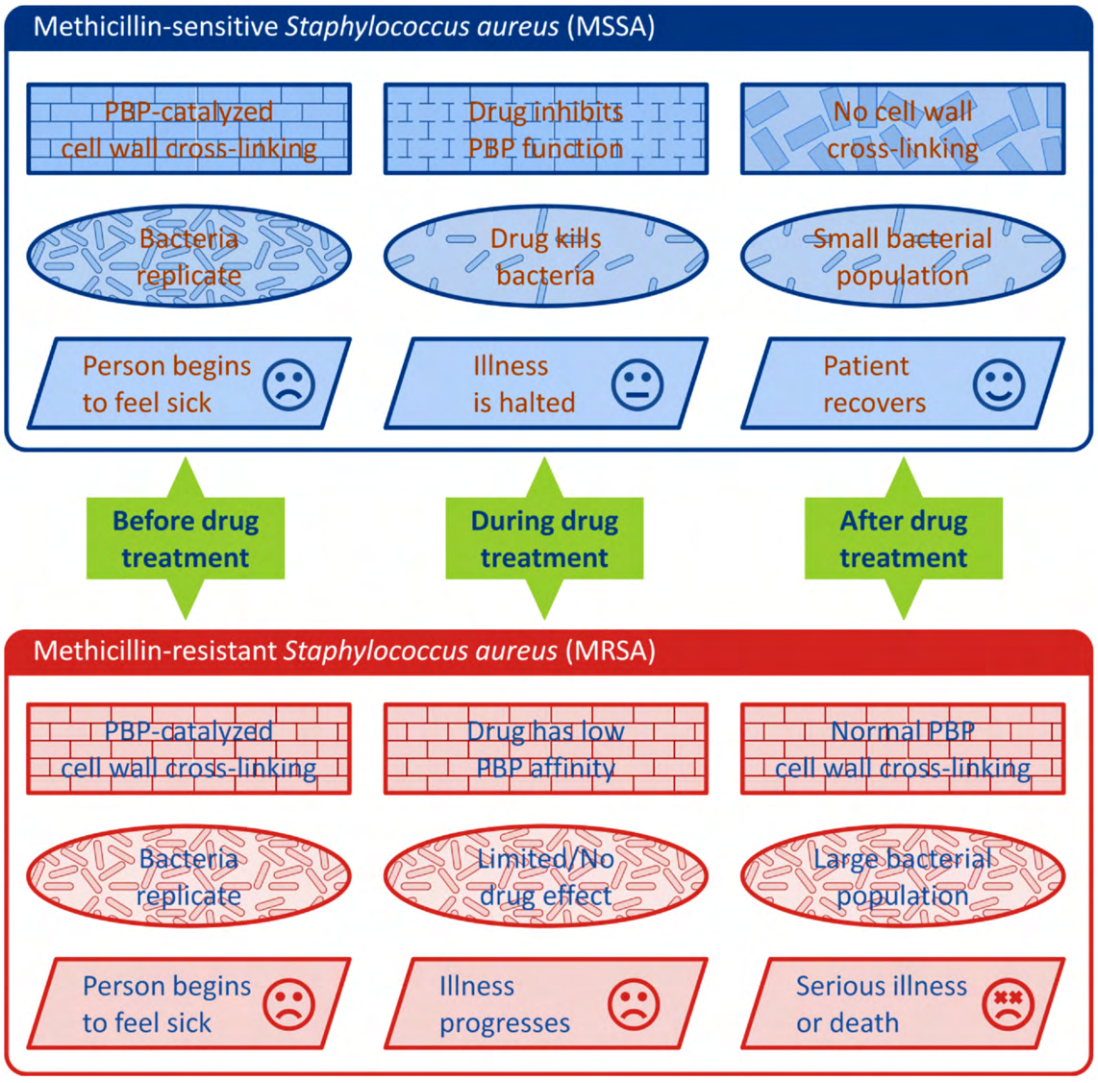
*Herceptin* (*trastuzumab*): The HER receptors are imbedded in the cell membrane and regulate cell growth and other functions through a signal transduction mechanism. Trastuzumab is a monoclonal antibody that interferes with the HER/neu receptor and is useful for the treatment of breast cancer. Resistance develops rapidly after treatment by virtually all patients, and it is thought to be connected to a lack of p27Kip1 translocation to the nucleus (in some strains), which enables cdk2 to induce cell proliferation [9].

## Who is interested in drug resistance?

Several organizations are actively involved with monitoring, containing and preventing drug resistance, and specifically antimicrobial drug resistance. These include the Food and Drug Administration (FDA) [10], the Centers for Disease Control and Prevention (CDC) [11] and the World Health Organization (WHO) [12]. The FDA (in conjunction with eight other agencies) has established the National Antimicrobial Resistance Monitoring System (NARMS) to surveil antimicrobial resistance in foodborne pathogens and to track changes in antimicrobial drug susceptibilities. The United States Department of Agriculture (USDA) and the Department of Health and Human Services (DHHS), which participates in NARMS, are also concerned with the potential for new animal antimicrobial drugs to confer resistance to related drugs in humans, since antibiotics are routinely added to livestock feed to prevent disease and promote growth. The CDC has launched a 'Campaign to Prevent Antimicrobial Resistance' that targets healthcare systems, including long-term care facilities where infectious disease and associated resistance is particularly problematic. WHO is approaching drug resistance from a public health perspective with goals of improving antimicrobial use, for example, discouraging misuse and over-prescription; and blocking transmission (containment) of resistant organisms, for example, by the proper use of antiseptic agents and isolation of infected individuals and groups. A new organization, whose charter is specifically to address drug resistance by defining existing and new 'resilient' drug targets [13] and to design inhibitor scaffolds that will not provide strong selection for resistance mutations, is the *Institute for Drug Resistance* (IDR) [14]. The IDR was founded in 2009 at the UMass Medical School by Celia A. Schiffer, Professor of Biochemistry and Molecular Pharmacology; her colleague Peg Riley, Professor of Biology (UMass Amherst); and Tien Bui (Principal of Biozen Consulting).

## Publications

The *Journal of Infection and Drug Resistance* [15] highlights the epidemiology of antibiotic resistance and the mechanisms of resistance development and spread, both in hospital and community settings. *Microbial Drug Resistance* [16] deals with the molecular biology of resistance mechanisms, virulence genes and disease through molecular epidemiology and covering the broad areas of drug design, infection control and medical practice. *The Open Drug Resistance Journal* [17] is an online journal that publishes reviews on basic and clinical research in both cancer and infectious disease. *Drug Resistance Updates* [18] publishes reviews and commentaries on drug resistance developments for both infectious disease and cancer.





## Summary

What approaches should we use to combat the growing problem of resistance? Here are three specific ideas for the way forward: (1) define 'resilient' drug targets [19], both existing and new; (2) design 'robust' drugs [20] for these selected resilient targets; and (3) develop new 'sensitive' assays that will distinguish drugs, at an early stage, that are effective in restricting the accumulation of resistant mutations in a drug target protein [21]. In addition, as the federally funded Human Microbiome Project progresses and the billions of microbial inhabitants, that are present in our bodies and outnumber our own cells by 10-fold are cataloged, perhaps we can learn how to cultivate communities of bacteria that aid our health and deter resistant bacterial strains from gaining a foothold. These approaches can help us to proceed in a rational manner to produce a next generation of drugs that will be useful in replacing those overworked present drugs whose clinical utility is waning.



## Acknowledgements

The author thanks John D. Williams, PhD, of Microbiotix, Inc., for designing the graphic and Donald T. Moir, PhD, also of Microbiotix, Inc., for critically reviewing this editorial.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