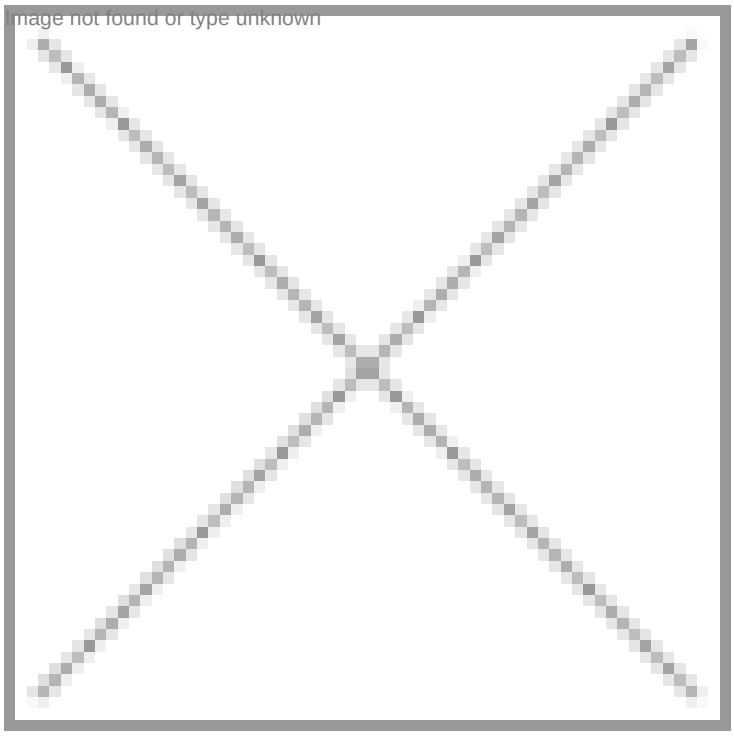
BioSpectrum the business of Bio & Health Sciences

Rising Need for New Age Antibiotics

10 March 2009 | News

Image not found or type unknown



Rising Need for New Age Antibiotics

Resistant strains of bacteria have undermined the effectiveness of current treatment options and creating an urgent need for new class of drugs.

Since the discovery of the first antibiotic penicillin in 1928, millions of patients have been saved by a simple dose of the antibiotic. However as the use and overuse of antibiotics occurred, microrganisms became resistant and the search started to find newer classes to deter the effects of disease.

Virtually all main classes of bacteria have developed resistance to one or more classes of antibiotics thus placing a need for new classes of antibiotics which should be active, not just against the usual suspects, frequently seen disease-causing bacteria, but also against new strains, particularly those with resistance.

Pharmaceutical companies have long been trying to come up with broad-spectrum antibiotics, which work against a wide range of disease-causing bacteria, as against a narrow-spectrum antibiotic, which is effective only against specific families.

Penicillins like benzylpenicillin, used to treat diseases like pneumonia, have a narrow-spectrum of activity. Many companies have thus modified the chemical and came up with semi-synthetic products like amoxycillin and ampicillin that have a broader-spectrum of activity.

The antibiotics have been improved in several stages. The first generation antibiotics had a narrow spectrum, while the second, third and fourth generation antibiotics have been equipped against more. Each generation of cephalosporins, for instance, has greater gram-negative anti-microbial properties. First generation drugs like cephalexin were effective against gram-positive bacteria but second-generation drugs like cefaclor are more effective against gram-negative bacteria. Fourth generation cephalosporin, cefepime, is broad-spectrum and works against both gram-negative and gram-positive, and also against penicillinase producing bacteria. The price difference of drugs in each generation is also huge.

The pharmaceutical industry claims that all diseases can be treated with antibiotics. In India, fixed-dose combinations, like a

mix of an anti-bacterial like ciprofloxacin and an anti-amoebic like tinidazole, have become very popular and are being used for all bacterial, viral or amoebic diarrhoea. However, the increasing antibiotic resistance in hospitals is leading to treatment failure, poor patient outcomes, and increased cost. Most of the disease causing bacteria including pneumococci, staphylococci, enterococci, E coli, enterobacter and acinetobacter have developed resistance to most of the available antimicrobials thus creating an urgent need for new class of antibiotics.

The discovery

Antibiotics are substances derived from a microorganism which are able to inhibit or kill another microorganism. In the late 1920s, Alexander Fleming, a British bacteriologist, found a blue-like mold growing on a grapefruit. Being a scientist, he cultured the mold and found that it had the unique property of killing certain bacteria. He put it aside as a curiosity until in 1940, in the midst of bomb blasts in London many people were dying of wound infections, he decided to resurrect the mold he called penicillin, but found he had no way of making large dosages. He flew to the US in 1940 and talked to the Pfizer & Co. and American Cyanamid, who had large chemical plants. Pfizer at that time made citric acid, a food acidulent, in deep tank fermentation which proved to be an ideal production method for antibiotics. Enough penicillin was made by the year 1944 to save thousands of lives when the Allies landed on the beaches of Normandy. This started the age of antibiotics because soon there came streptomycin, terramycin, bacitracin, neomycin and many others. Unfortunately, as their use spread throughout the world, so too did the bug's ability to counter the effects of the antibiotics as they were severely overused. Since the end of the 20th century the world has awaited for a replacement and the new age has finally come.

Antibiotics of the 21st Century

Antibiotic research led to great strides in knowledge of biochemistry by establishing large differences between the cellular and molecular physiology of the bacterial cell and that of the mammalian cell. This explained the observation that many compounds that are toxic to bacteria are non-toxic to human cells.

Phage Therapy has been used in the past on humans in the US and Europe during the 1920s and 1930s, but these treatments had mixed results. With the discovery of penicillin in the 1940s, Europe and the US changed therapeutic strategies by promoting antibiotics. But antibiotic resistance has led to new interest in phage therapy by several small biotech companies for use as antibiotics. Several types of bacteriophage appear to exist, which are specific for each bacterial taxonomic group or species. Research into bacteriophages for medicinal use is just beginning, but it has led to advances in microscopic imaging. While bacteriophages provide a possible solution to the problem of antibiotic resistance, there is no clinical evidence yet that they can be deployed as therapeutic agents to cure disease. Various companies and foundations in North America and Europe are currently researching phage therapies.

GangaGen Biotechnologies in Bangalore utilizes these nature's antibiotics, bacteriophages, both as a source of therapeutic proteins and as therapeutic entities. By studying the biology of bacteriophages, the company has recognized and developed the components that phages use to kill or otherwise adversely impact bacteria, as therapeutic entities. One example of this approach is StaphTAME, a topical formulation of a therapeutic protein, P128, effective against Staphylococcus aureus strains, including methicillin-resistant strains. StaphTAME is in the final stages of preclinical testing and is expected to enter phase-I trial in the US by the end of the year.

Talking about this product Bharathi Sriram, vice president, R&D, GangaGen Biotechnologies said, "Infection with Staphylococcus aureus that is resistant to currently available antibiotics is a growing problem worldwide. GangaGen's StaphTAME offers a unique therapeutic modality effective against a wide range of Staphylococcus aureus strains without impacting normal commensal flora, many of which provide beneficial effects."

Bacteriocins are also a growing alternative to the classic small molecule antibiotics. Different classes of bacteriocins have different potential as therapeutic agents. Small molecule bacteriocins like microcins and lantibiotics may be similar to the classic antibiotics; colicin-like bacteriocins are more likely to be narrow-spectrum, demanding new molecular diagnostics prior to therapy but also not raising the spectra of resistance to the same degree. One drawback of the large molecule antibiotics is that they will have relative difficulty crossing membranes and traveling systemically throughout the body. For this reason, they are most often proposed for application topically or gastrointestinally. Because bacteriocins are peptides, they are more readily engineered than small molecules. This may permit the generation of cocktails and dynamically improved antibiotics that are modified to overcome resistance.

Probiotics have emerged as a third alternative that goes beyond traditional antibiotics by employing a live culture which may establish itself as a symbiont, competing, inhibiting, or simply interfering with colonization by pathogens. It may produce antibiotics or bacteriocins, essentially providing the drug in vivo and in situ, potentially avoiding the side effects of systemic administration Probiotics brings back again the live microorganisms which, when administered in adequate amounts, confer health benefits. Probiotic bacteria reduce the risk of certain diarrheal diseases, assist lactose intolerant people and enhance the immune function. While the bacteria had built up a resistance, the world has entered an age wherein new products are being developed worldwide at an accelerating rate and resistance may no longer be a problem.

Finding new targets has been another approach. Instead of searching for new antibiotics by modifying existing ones, some researchers are trying to find the most vulnerable targets in a bacterium and then designing something that hits one or more of them hard. While having full genome of many microbes, researchers believe that knockingout genes galore to find out which ones are necessary and going after them is not a sensible strategy. People have been doing that for a while with

absolutely no success.

Market players

There is no shortage of ideas for unearthing new antibiotic candidates but it takes time to enter medical practice. The bottleneck lies in the development process of turning them into effective therapies. Several researchers blame the big pharmaceutical companies for dropping out from the new drug discovery for battling infectious disease.

Though the big companies have the money to develop anti-infectives, but since it is not a billion dollar market they hesitateto invest and rather leave it to small biotech companies. Cubist produced daptomycin, approved in September 2003, by licensing it from Eli Lilly, which shelved the new compound after concluding its potential market was only $250 million.

Thus the size of the market is an important barrier to new antibiotics resulting in a dry pipeline and a serious lag at the basic research level. Moreover antibiotic discoveries are hard. It is a long process to get decent antibiotics. However there are few big players like Wyeth Pharmaceuticals, Pfizer, Cubist, Eli Lilly, Novartis and the mid-sized players like Gangagen operating well in this space. In India the important players include Hindustan Antibiotics Ltd, Indoco Remedies, Micro Labs and few others.

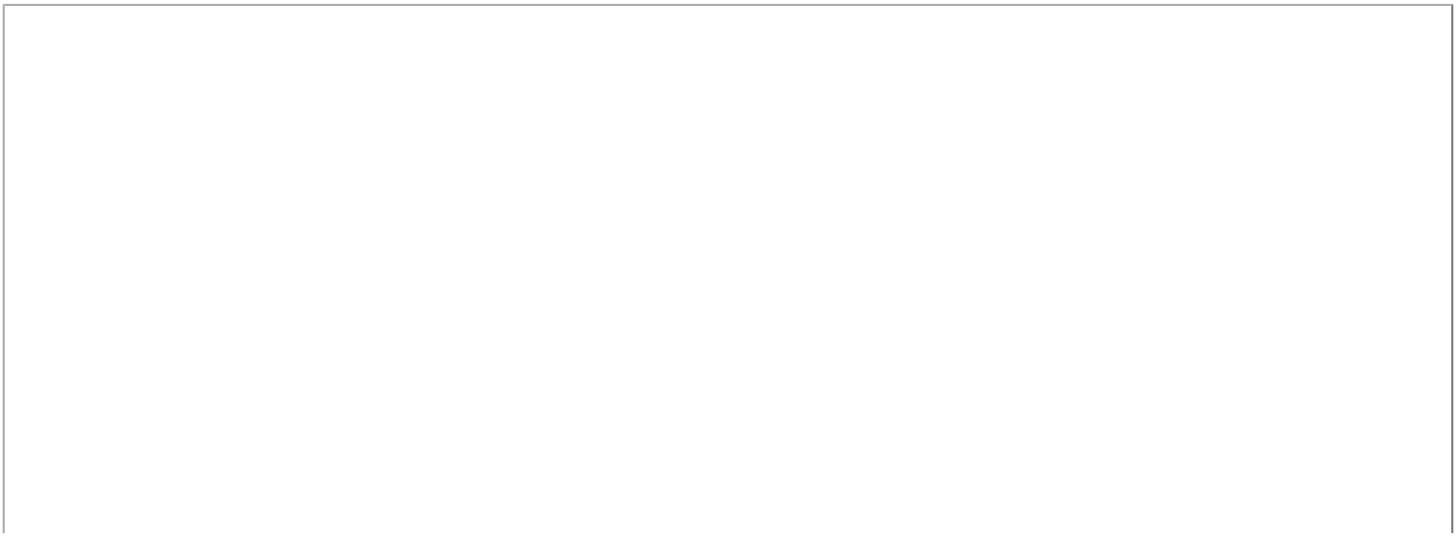
Gangagen Biotechnologies has a portfolio of 11 issued and 31 pending patents in 13 patent families, and is pursuing worldwide protection for its anti-infective technologies and products. The company has additional anti-infectives in preclinical development, including a therapeutic targeting Pseudomonas aeruginosa, a frequent opportunistic pathogen of burns and other wounds.

Wyeth's Tygacil is claimed to be the world's first glycylcycline intravenous antibiotic. It has an expanded broad-spectrum antibiotic activity and is the only such agent effective against resistant gram-negative and gram-positive organisms including the superbug MRSA, which is a national and global concern. As such, it offers a significant improvement in the treatment of patients at risk of difficult-to-treat bacterial infections and gives doctors the confidence to successfully manage these conditions.

Technological development

Eighty years after the discovery of penicillin, a group of researchers at Rutgers University are on the verge of developing a new class of antibiotics. They have described a group of antibiotic compounds, first isolated decades ago from naturally occurring antibacterial substances in soil called myxopyronin that is expected to show great promise. Myxopyronin has been synthesized in the lab and shown to be safe in animal trials, and although the drug hasn't been tested in humans yet, cell-based experiments suggest that it is potent enough to kill a wide range of stubborn microbes, including drug-resistant strains of tuberculosis and the deadly type of staph known as MRSA. It is hoped that myxopyronin will be useful in the battle against drug-resistant tuberculosis, a disease for which clinicians have never had a perfect therapy. The success of TB treatment depends on the destruction of active and dormant bacteria to prevent relapse. One way to kill a dormant cell is to target biochemical processes that continue even in latency. But myxopyronin works by interfering with the enzyme RNA polymerase, which controls gene transcription in cells and is necessary for cell survival.

In another development to study antibiotic action, the team of scientists in London made nano-probes coated with molecules found in bacterial cell walls from normal bacteria and bacteria resistant to antibiotics. They then added doses of the antibiotic, vancomycin, to the system and found that probes from normal bacteria were stressed and changed shape, whereas probes from resistant bacteria were only weakly affected. These bent probes could be detected with a laser, indicating that the antibiotic was applying a force to the surface. This allowed the researchers to quickly assess the effectiveness of an antibiotic and propose new ways in which antibiotics may be acting to cause the bacteria to burst and die. This advance helps to understand the mode of action of drugs targeted against resistant bacteria, and could also lead to rapid diagnostic tools and novel methods for investigating antibiotic action.



India's new mission to develop antibiotic molecules

Department of Biotechnology has recently initiated a network project called 'Screening for biomolecules from microbial diversity collected from different ecological niches'. The project involves nine institutes, with NPIL Research and Development Limited (NRDL) as an industrial partner. The total cost of the project is Rs 24.86 crore with DBT contribution of Rs 17.98 crore and NRDL contribution of Rs 6.88 crore. The participating institutes include National Environmental Engineering Research Institute (NEERI); Nagpur National Center for Cell Science (NCCS), Pune; Institute of Genomics and Integrative Biology (IGIB), Delhi; University of Delhi, South Campus (UDSC), Delhi; Institute of Life Sciences (ILS), Bhubaneswar; M S Swaminathan Research Foundation (MSSRF), Chennai; Guru Nanak Dev University (GNDU), Amritsar; Institute of Bioresources and Sustainable Development (IBSD), Imphal and National Institute of Oceanography (NIO), Panjim.

The project will lead to selection of potential candidate molecules, which will be taken to process scale-up strategies with appropriate partners. The credit sharing in this project amongst the PI and industry has been mutually worked out and an agreement has been signed on February 22, 2008.

A separate microbial repository is being set up at National Center for Cell Science (NCCS), Pune to maintain the 2,00,000 isolates generated under this project. This would be the largest such facility in the country and would adhere to International Depository Authority (IDA) standards.

Jahanara Parveen