February 15th, 2023

Dear Regina,

Welcome to BioMarketing Insight's monthly newsletter.

Happy Valentine's Day! Hope everyone had a memorable day.

In this month's newsletter I will cover "Antibiotic Resistance Crisis: What Can Be Done and Two Different Approaches" You can find my article under the Table of Content and click on the link.

If you missed the last month's newsletter "Are Non-Competes Harmful or Beneficial in Promoting Greater Economic Opportunity and Competition?", click on this link to read the article.

If you need a little inspiration or something to make us laugh to get us through this

Needs Now," other inspirations and ending with Celine Dion and Josh Groban with "The Prayer".

Please read on for other current news in the Table of Content below. The next newsletter will be March 15, 2023.

We encourage you to share this newsletter with your colleagues by using the social media icons below, or by simply forwarding this newsletter or use the link below. Should you or your colleagues want to join my mailing list, click on "join my email list" link below.

Please email me, Regina Au, if you have any questions, comments, or suggestions.

Sincerely,
Regina Au
CEO, New Product Planning/Strategic Planning
BioMarketing Insight

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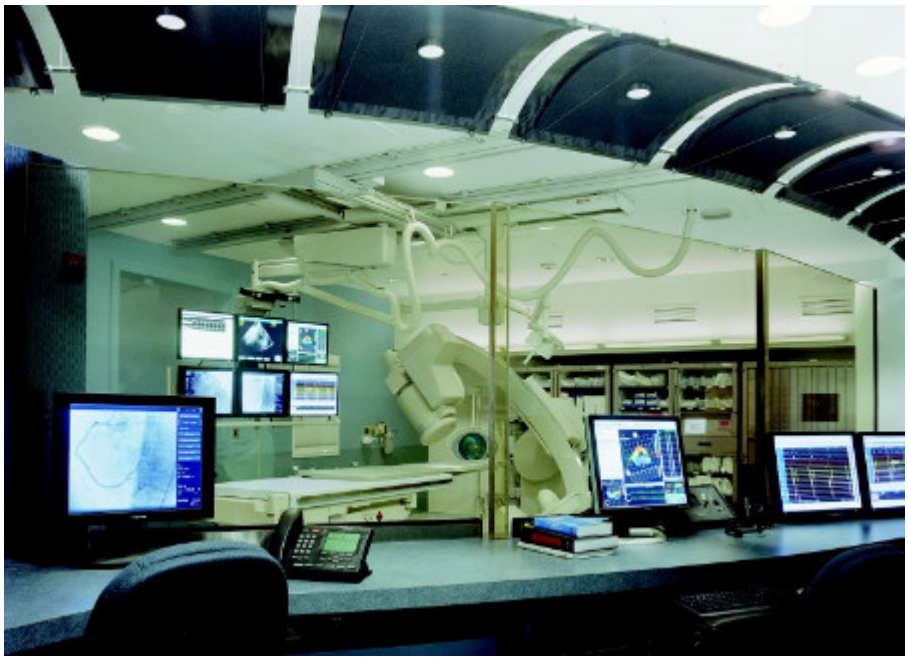
Join my mailing list



Developing a Product? Commercializing a Product?

If you are developing a product and have not conducted the business due diligence to determine commercial viability or success, contact me for an appointment. For successful commercial adoption of your product or looking to grow your business, contact me for an appointment.

For more information on our services, click on the links below:

Product Development
Market Development

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See Photos of the AAPI Heritage Festival - Saturday, May 7th, 2022

Asian American Pacific Islander (AAPI) Heritage month is a celebration of a diverse group of ethnic heritage within the Asian community who bring a wealth of enriched culture to our society. This celebration will endeavor to build awareness and educate our community on the various cultures and contributions these different Asian ethnic groups have brought to enrich our American Story.

History you may not know:

1. 20,000 Chinese men served in the military during WWII where 40% of the men served without American citizenship due to the "Chinese Exclusion Act".They were later honored in September 2021 with the Congressional Gold Medal for their acts of patriotism, loyalty, and courage for the US.
2. 110,000 Japanese American and Japanese were relocated to prison camps during the bombing of Pearl Harbor in 1941.In 1943, Japanese Americans were finally allowed to volunteer for the all-Japanese American 442nd Regiment that fought against the Japanese.These men were awarded the Congressional Gold Medal in 2010.

was on display.

The Festival was a huge success with a full agenda of speakers, including State Senator Cindy Friedman and fireside chats with Shirley Leung from The Boston Globe. We also had a full agenda of performers throughout the festival. We had Tibetan dancers, Cambodian dancer, Japanese dancers, Lion dance, Kung Fu demonstration and many solo performers playing traditional ethnic instruments. Click here for the full agenda.

In addition, we had exhibitors from the various ethnic groups displaying items representing their history and culture that complemented the contributions that AAPI have made to American History.

This is AAPI Heritage month, be sure to enjoy all the activities in your area celebrating the diverse group of ethnic heritage within the AAPI community who bring a wealth of enriched culture to our society and American History. It may surprise you the tremendous amount of people who have contributed to our society and American History.

I would like to leave you with this **one thought** "while everyone is unique in their own way, it is important to celebrate our differences and our commonalities. Every person has a vital contribution to make to society - all races, all ethnicities, all religions and all genders together form one human race.

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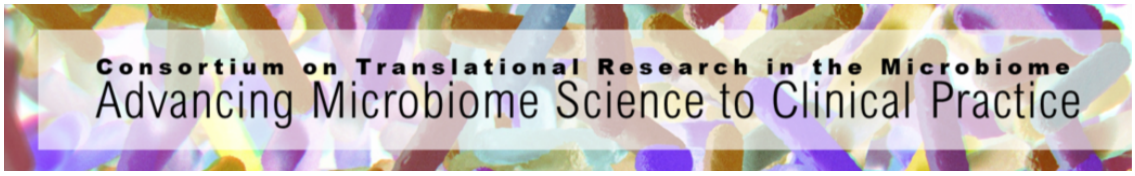

General Guidelines to Launch and Build a Clinical Trial Using Microbiome Products in an Era of Personalized Medicine.

I am pleased to announce that I was a speaker at the Westchester Biotech Project for Consortium on Translational Research in the Microbiome on November 11th, 2021. The Topic: General Guidelines to launch and build a clinical trial using microbiome products in an era of personalized medicine. My presentation was on " How to Launch and Market a Successful Microbiome Product: Five Major Considerations". For more information on this event, click here. This webinar it will be available next month, so check back here.

For more information on Westchester Biotech Project and future webinars, click here.

Fresh Thinking in the Next Normal

I am pleased to announce that I was a speaker at the Institute of Management Consultants event on "What Will the “Next Normal“ Be for Productivity, Motivation and Retention of Employees? Four Things Employers Need to Consider." on July 20th, 2021 at 2 pm. For more information and to register click here.

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Inspirations

Enjoy the song "What the World Needs Now" virtually with the students from the Berklee School of Music.

We Will Get Through It Together

Let's End with Celine Dion & Josh Groban Singing "The Prayer"

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Lioness
FOR THE FEMALE ENTREPRENEUR

One Biotech Executive's View on the COVID-19 Vaccine

I am pleased to announce that my article on the COVID-19 Vaccine was published in Lioness Magazine. To read my article click on the link here.

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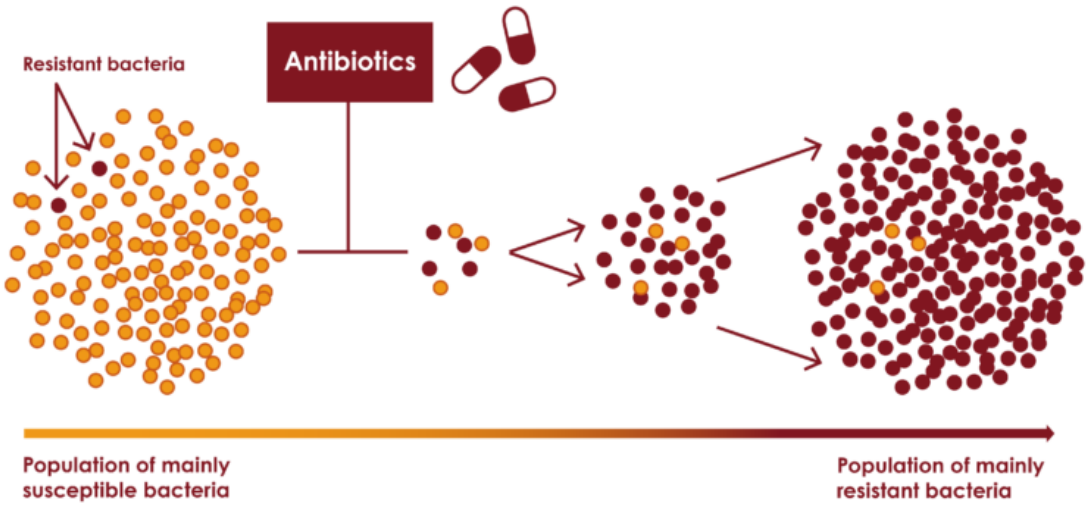

Antibiotic Resistance Crisis: What Can Be Done and Two Different Approaches

The subject about antibiotic resistance is not new but now, it's a crisis. We've run out of alternatives to killing bacteria which turns into an infection and eventually resistant to antibiotics.

Bacteria have been around long before mankind, before the dinosaurs and even before earth was created. Bacteria will still exist long after mankind is gone. The reason bacteria will survive all of us is because they adapt to their environment. Bacteria can thrive in a range of harsh environments, from bubbling hot springs to Arctic ice to the human body, where certain bacteria cause infection.

1) Understanding How Bacteria Grow and Mutate

Bacteria will undergo mutations that allow them to resist the effects of antibiotic drugs. “Antibiotic resistance is a matter of evolution,” said Rolf Müller, a chemical microbiologist at the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS). “It's not a matter of if; it's just a matter of when.”

Bacteria are among the fastest reproducing organisms in the world, doubling every 4 to 20 minutes. For example, a single *Staph. aureus* cell that makes its way into your wound, would take only 10 generations (one generation is 20 minutes) for that single cell to grow into a colony of more than 1,000 (2^{10} = 1,024), and just 10 more generations for it to erupt into a colony of more than 1 million (2^{20} = 1,048,576). With each generation of growth, the bacteria is adapting or mutating.

hours. *S. aureus* has about 2.8 million nucleotide base pairs in its genome. At a rate of about 10^{-10} mutations per nucleotide base, that amounts to nearly 300 mutations in that population of bacteria within 10 hours!

Harvard University and Technion -Israel Institute of Technology researchers used a metre-long petri dish to show the frightening speed at which bacteria can evolve and develop resistance to modern antibiotics.

They found it took bacteria just 11 days to spread from a section of the petri dish with very little antibiotic to a section with 1000 times the amount of antibiotic. The petri dish was set up in 9 panels with zero antibiotic on the two ends and increasing amounts moving inwards (0, 1, 10, 100, 1000) until the middle of 1000x concentration. Watch the YouTube video to see how the bacteria grows.

Harvard University and Technion researchers used a metre-long petri dish to show the frightening speed at which bacteria can evolve and develop resistance to modern antibiotics.

New mutations arise at each barrier where the concentration of antibiotic increases 10-fold. "The experiment shows just how easy it is for bacteria to evolve resistance – how quickly evolution can occur. In just 11 days, resistance levels increased by over 1000-fold," said Professor Kishony from Technion.

"This shows that resistance does not evolve through any one big step but though a series of mutations, each one contributing just a bit and together accumulating to a very large increase in resistance."

the "moderately challenging" pressure of intermediate concentrations was actually essential to allow for resistance to develop. This is the reason why bacteria develop antibiotic resistance every time one uses an antibiotic.

Bacteria also readily swap bits of DNA among both related and unrelated species. Thus, antibiotic-resistant genes from one type of bacteria may be incorporated into other bacteria. As a result, using any one antibiotic to treat a bacterial infection may result in other kinds of bacteria developing resistance to that specific antibiotic, as well as to other types of antibiotics.

Below is a chart on the mechanisms bacteria use to become resistant.

Resistance Mechanisms (Defense Strategies)	Description
Restrict access of the antibiotic	Germs restrict access by changing the entryways or limiting the number of entryways. **Example:** Gram-negative bacteria have an outer layer (membrane) that protects them from their environment. These bacteria can use this membrane to selectively keep antibiotic drugs from entering.
Get rid of the antibiotic or antifungal	Germs get rid of antibiotics using pumps in their cell walls to remove antibiotic drugs that enter the cell. **Example:** Some *Pseudomonas aeruginosa* bacteria can produce pumps to get rid of several different important antibiotic drugs, including fluoroquinolones, beta-lactams, chloramphenicol, and trimethoprim. **Example:** Some *Candida* species produce pumps that get rid of azoles such as fluconazole.
Change or destroy the antibiotic	Germs change or destroy the antibiotics with enzymes, proteins that break down the drug. **Example:** *Klebsiella pneumoniae* bacteria produce enzymes called carbapenemases, which break down carbapenem drugs and most other beta-lactam drugs.
Change the targets for the antibiotic or antifungal	Many antibiotic drugs are designed to single out and destroy specific parts (or targets) of a bacterium. Germs change the antibiotic's target so the drug can no longer fit and do its job. **Example:** *Escherichia coli* bacteria with the *mcr*-1 gene can add a compound to the outside of the cell wall so that the drug colistin cannot latch onto it. **Example:** *Aspergillus fumigatus* changes the *cyp1A* gene so that triazoles cannot bind to the protein.

(Defense Strategies)	
Bypass the effects of the antibiotic	Germs develop new cell processes that avoid using the antibiotic's target. **Example:** Some *Staphylococcus aureus* bacteria can bypass the drug effects of trimethoprim.

2) Antibiotic Resistance Growing with Antibiotics

To date, all antibiotics have over time lost effectiveness against their targeted bacteria. The earliest antibiotics were developed in the 1940s.

Staph Aureus

Nearly all strains of *Staphylococcus aureus* in the United States are resistant to penicillin, and many are resistant to newer methicillin-related drugs or MRSA. MRSA is difficult to treat because bacteria is resistant to several antibiotics. MRSA can be found in both the hospital and community setting.

Since 1997, strains of *S. aureus* have been reported to have a decreased susceptibility to vancomycin, which has been the last remaining uniformly effective treatment. Fewer antibiotic are available to treat more serious infections are trimethoprim-sulfamethoxazole (Bactrim, Bactrim DS, Septra, Septra DS) and linezolid (Zyvox).

Antibiotic resistance is not limited to a particular antibiotic, resistance can be to a class of antibiotics which means the bacteria will be resistant to all the antibiotics in that class. For example, S. aureus is resistant to any penicillin derived antibiotic (penicillin G, amoxicillin, nafcillin, oxacillin, dicloxacillin, flucloxacillin, ampicillin, carbenicillin, ticarcillin, and piperacillin).

***Campylobacter* Infections**

Today, one out of six cases of *Campylobacter* infections, the most common cause of food borne illness, is resistant to fluoroquinolones (the drug of choice for treating food-borne illness). As recently as ten years ago, such resistance was negligible.

Each year, an estimated 2.8 million people in the U.S. develop infections that are resistant to antibiotics, resulting in deaths of more than 35,000 people.

3) Developing Antibiotics

Developing antibiotics by a pharmaceutical or biotech company can be a challenge because of how fast a bacteria can develop antibiotic resistance. The patent life of a new drug is 20 years from its filing but the company may lose up to 10 years developing the

Because antibiotic resistance is developed so rapidly, the bacteria will be resistant to the new antibiotic even before the drug loses its patent protection. This has led many companies to focus on developing other drugs besides antibiotics.

Governments have tried to encourage pharma/biotech companies to developed antibiotics with a number of incentives. This has work for a few companies but majority of pharma/biotech companies would rather focus on a cancer drug than antibiotics.

In 2020, the White House created a 5-year National Action Plan for Combating Antibiotic Resistance Bacteria (CARB). Its recommendations include:

- Slowing the emergency of drug-resistant bacteria and prevent the spread of resistant infections
- Advancing the use of rapid diagnostic tests to identify resistant bacteria
- Accelerating research and development of new antibiotics, vaccines, and other treatments
- Improving worldwide collaboration and capacity for preventing, surveillance, and controlling antibiotic resistant bacteria

4) Two New Approaches to Developing Antibiotics

A) Finding a new classes of chemical compounds that kill bacteria in unforeseen ways in overcoming current resistance mechanisms is difficult. Less than 25 percent of antibiotics under development meet this criterion said Rolf Müller, a chemical microbiologist at the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS).

Instead, the majority represent a descendant of an existing antibiotic with a structure tweaked by scientists to side step an emergent resistance mechanism. The process repeats, wringing every last drop of activity out of the same basic scaffold. For example, the four-ringed tetracycline core has been modified with various side chains to produce oxytetracycline, doxycycline, and tigecycline. “After so many years of first, second, third, fourth, fifth line changes, there's little you can do about these structures anymore because almost all of the positions on these molecules where changes are allowed have been addressed,” Müller said. “That's why it's so important to find novel basic structures where the cycle can be reiterated.”

For years, researchers scoured extracts from common soil bacteria for new antibiotics, but they eventually started to rediscover the same molecules again and again. However, “more than 99 percent of bacteria and fungi on the globe have never been analyzed,” Müller said. With so much microbial biodiversity unexplored and up to a billion bacteria in one gram of soil, even familiar ground can yield unexpected chemistry.

bacteria used cystobactamids to prey on a wide range of fellow microorganisms, they evolved to penetrate and inhibit the growth of even double membraned Gram negative bacteria, which feature an extra layer of protection against antibiotics.

B) “Anything you throw at [bacteria] provides a selection for a mutation that's likely to make them able to grow in the presence of that new antibiotic,” said Bob Hancock, a microbiologist and immunologist at the University of British Columbia. “Bacteria become resistant to virtually everything.”

Hancock attributes the void in effective antibiotics to “trying to do things the same way over and over again,” he said. “Regardless of what compounds we develop, that's really not going to change the equation. It may help to delay it; it may provide more tools to treat with; but it's not going to change the equation.”

Hancock has found another nontraditional approach in cationic antimicrobial peptides, which host organisms produce to defend themselves against bacteria.
Rather than forming precise chemical bonds that inhibit specific enzymes, these peptides act as sand in the bacterial gearbox, affecting many of their biological functions. The positively charged peptides can interact with negatively charged lipids in the cell membrane, disrupting membrane structure and biosynthesis. They can also cross both membranes in Gram negative bacteria to access polyanionic DNA and RNA, inhibiting protein synthesis and other processes that require nucleic acids.

While bacteria can develop resistance to cationic peptides over time, but very slowly, producing no more than a four-fold decrease in activity after reproducing itself 100 times. “It's not this ‘one antibiotic, one mechanism’ kind of thing like how penicillin hits cell wall biosynthesis, but rather it's multiple different mechanisms,” Hancock said. “The reason we don't tend to see resistance is that you can get resistance for one mechanism, but then if you peel off that mechanism, there's a whole bunch of other mechanisms underneath that can still result in susceptibility.”

In 65 percent of human infections, free-swimming bacteria clump together on surfaces in the body to form biofilms, allowing them to become 10- to 1,000-fold more resistant to antibiotics. This adaptive growth state is responsible for antibiotic failure in surface-associated infections such as sinus, wound, and lung infections, and yet not a single approved antibiotic targets biofilms. Hancock’s team has designed cationic peptides that block biofilm formation, likely by deactivating a key signaling nucleotide in the bacterial cell. Similarly, the team demonstrated that cationic peptides with modest direct antimicrobial activity can regulate the expression of cytokines in host cells, suppressing inflammation while boosting infection fighting immune responses. To read the full article, click here.

Closing Thoughts

As Dr. Rolf Müller indicated, “Antibiotic resistance is a matter of evolution. It's not a matter of if; it's just a matter of when.” Since we can't stop evolution, man needs to change in order to slow antibiotic resistance.

There are two things that need to be done. Until we adapt these two things, we will see more and more superbugs to the point where antibiotics won't work.

1. Scientist need to think out of the box and develop new classes (never been developed before) of antibiotics such as the focus of Drs. Müller and Hancock.
    - In addition, our governments still need to provide incentives for researchers to develop these new class of antibiotic since it will take on average 10-15 years and a lot of money.
2. We, healthcare professionals and patients need to change our mindset on how we use antibiotics
    - To help fight antibiotic resistance and protect yourself against infection:
        - **Don't take antibiotics unless you're certain you need them.** An estimated 30% of the millions of prescriptions written each year are not needed. Always ask your doctor if antibiotics will really help. For illnesses caused by viruses -- common colds, bronchitis, and many ear and sinus infections -- they won't.
        - **Finish your pills**. Take your entire prescription exactly as directed. Do it even if you start feeling better. If you stop before the infection is completely wiped out, those bacteria are more likely to become drug-resistant.

cough.

- **Stay safe in the hospital.** Antibiotic-resistant bacteria are commonly found in hospitals. Make sure your caregivers wash their hands properly. Also, ask how to keep surgical wounds free of infection.

To sum things up; 1) use less antibiotic unless medically necessary and 2) think outside the box and develop new classes of antibiotics that have never been developed.

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Should you have any questions or need of assistance with your business due diligence, determining your product's value proposition, target product profile and economic value of your product for reimbursement, feel free to contact me at 781-935-1462 or regina@biomarketinginsight.com.
