microBYTES™

A Hardy Diagnostics eNewsletter

HARDY DIAGNOSTICS

a culture of service...

May 2019

Incidence of Foodborne Illness

Recent surveillance shows the following incidence of disease per 100,000 of the U.S. population last year:

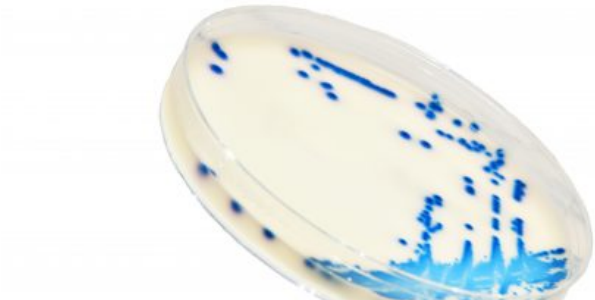
- *Campylobacter* - 19.5
- *Salmonella* - 18.3
- STEC (*E.coli*) - 5.9
- *Shigella* - 4.9
- *Vibrio* - 1.1
- *Yersinia* - 0.9
- *Cyclospora* - 0.3
- *Listeria* - 0.3

Cyclospora, *Vibrio*, and *Yersinia* had the largest increase incidence since 2015. The forgoing data from 2018 is from The Foodborne Diseases Active Surveillance Network (FoodNet) of CDC's Emerging Infections Program, which monitors cases of laboratory-diagnosed infection caused by eight pathogens transmitted commonly found in food in ten U.S. sites. During 2018, FoodNet identified 25,606 infections, 5,893 hospitalizations, and 120 deaths. FoodNet conducts

Micro Musings...

Screen for Carbapenem Resistance

HardyCHROM CRE



active, population-based surveillance for laboratory diagnosed infections caused by *Campylobacter, Cyclospora, Listeria, Salmonella*, Shiga toxin-producing *Escherichia coli* (STEC), *Shigella, Vibrio, and Yersinia* in ten sites covering 15% of the U.S. population (approximately 49 million persons in 2017).

Reference

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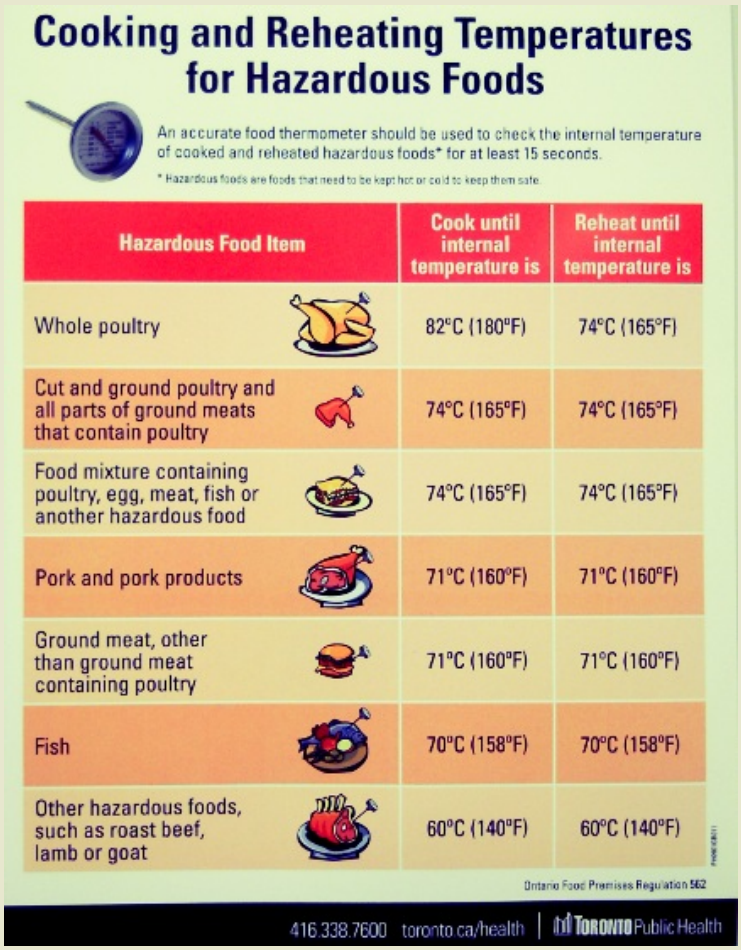
How to prevent foodborne illness...



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* * * * *

Genetically Modified Organisms to Treat Phenylketonuria?

Genetically modified organisms (GMOs) in agriculture have remained a controversy for over 20 years. However, genetically engineered microbes may soon treat phenylketonuria (PKU), as well as a range of other diseases. This form of treatment is called Live Biotherapeutic Product, or LBP. While phage therapy delivers viruses to the site of bacterial infections, this novel approach uses bacteria to express genes to alleviate symptoms or prevent certain conditions. The bacteria are administered via capsules, oral rinses, or topical solutions, simplifying a targeted therapy that remains active in the body for no longer than a few hours, and do not enter the systemic circulation.

Phenylketonuria is a recessive genetic disorder that results in the inability to metabolize the amino acid phenylalanine (Phe). Without the enzyme phenylalanine hydroxylase, the amino acid accumulates in the brain and causes nervous system damage. This results in microcephaly, mental disability, delayed development, hyperactivity, seizures, and eczema. The buildup of phenylalanine results in a "musty" odor, while the patient will have lighter hair, skin, and eyes since the amino acid is responsible for production of melanin. Infants are tested for the condition, and if diagnosed, must adhere to a strict lifetime diet. PKU occurs in about every 12,000 births in the U.S. Foods high in phenylalanine such as dairy, nuts, or bread must be avoided as they cause high blood Phe levels, resulting in difficulty concentrating and remembering. Even the artificial sweetener aspartame contains Phe, so a patient with PKU cannot have diet soda!

All newborns are screened for PKU with a heel stick blood test.

The biotech company Synlogic has engineered a strain of *Escherichia coli* that expresses the enzyme phenylalanine ammonia lyase, called SYNB1618. The enzyme breaks down Phe into trans-cinnamic acid, and further metabolites are excreted in urine, so patients do not experience toxic accumulation of Phe in the brain (think of it as similar to a living lactase supplement). In ongoing trials, the suspension is ingested after the patient eats a dangerous amount of protein, while being closely monitored in a clinic. Participant Jonah Reeder reports feeling more energized and having higher cognitive abilities after ingesting the organism in a protein shake. It sounds odd to be eating *E. coli* to treat illness, since pathogenic strains so often makes headlines when contaminating leafy greens, but this strain has been modified to be non-pathogenic and non-colonizing.

Synlogic is not the only company to manipulate microbes to patients' advantage. Oragenics is developing a treatment for oral mucositis in chemotherapy patients, which uses an oral rinse containing *Lactobacillus lactis*. This organism secretes human Trefoil Factor 1 to heal the sores. Osel has engineered a topical gel containing commensal *Lactobacillus* to reduce infection in women who experience recurrent bacterial vaginosis and urinary tract infections, while secreting HIV entry inhibitors. Additionally, Actobio had modified *L. lactis* to express human proinsulin to reverse type I diabetes.

All in all, purposefully ingesting bacteria to cure disease sounds counterintuitive, but LBPs represent a promising future for previously untreatable gastrointestinal, immunological, and metabolic diseases. While these LBPs are still undergoing development, this approach has the potential to benefit millions of patients. "Genetically Modified

- Plazomicin, "Zemdri" (Z9331)
- Ceftazidime/Avibactam, "Avycaz" (Z9351, Z9355)
- Ceftolozane/Tazobactam, "Zerbaxa" (Z9341, Z9345)
- Delafloxacin, "Baxdela" (Z9301, Z9305)
- Meropenem/Vaborbactam, "Vabomere" (Z9321, Z9325)
- Omadacycline, "Nuzyra" (Z9411)

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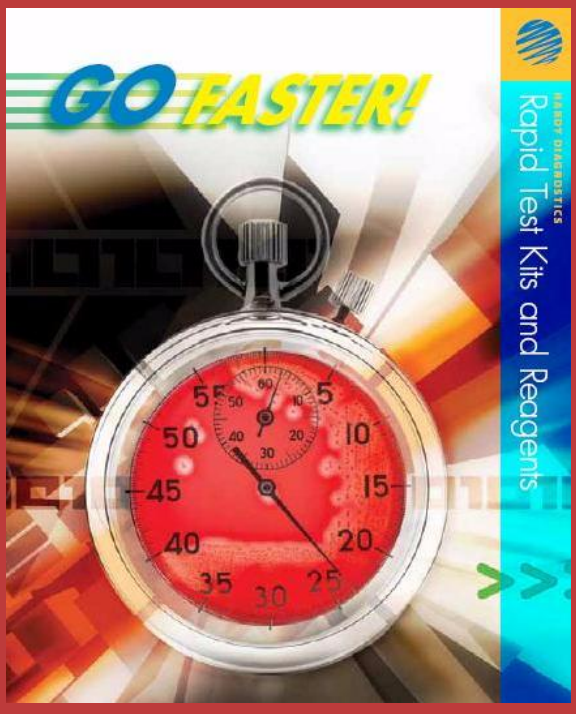
Then look to our Rapid Test Booklet for good ideas. It describes hundreds of "hard to find" rapid test kits and reagents.



View the booklet online

Organisms" have progressed from a subject of controversy in agriculture to offering patients new hope in the treatment of their diseases.

References: 1, 2, 3, 4, 5, 6, 7, 8, 9

By Sara Hepler
R&D Microbiologist
HARDY DIAGNOSTICS

* * *

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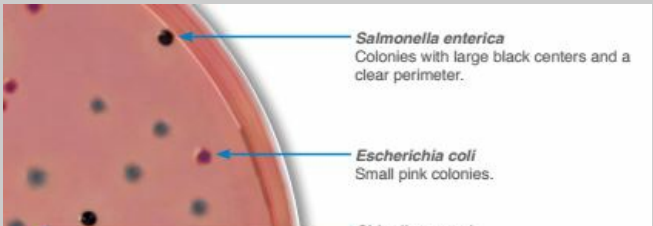
HARDY DIAGNOSTICS

* * *

Stool cultures with no interference from Proteus*!*

HardyCHROM SS NoPRO



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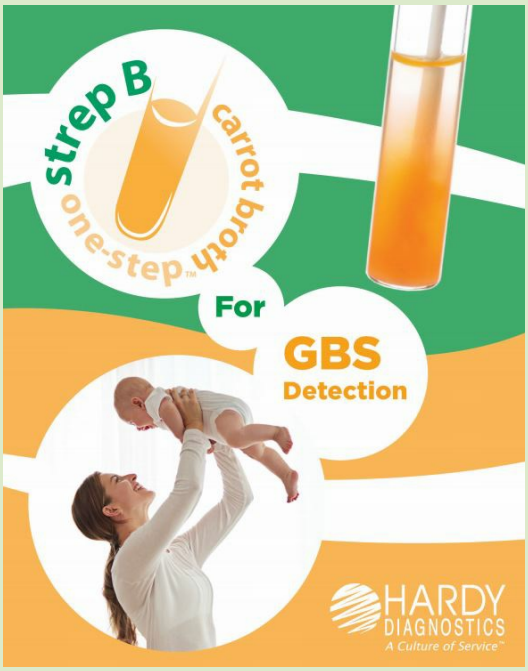
For the detection of Group B Strep...

Carrot Broth One-Step



- Improved...No tile addition needed!
- Detects hemolytic Group B Strep from the initial broth culture
- Provides results in as little as sixteen hours
- Found to be 100% sensitive and up to 100% specific in a recent study

Watch a short video.

Learn more...

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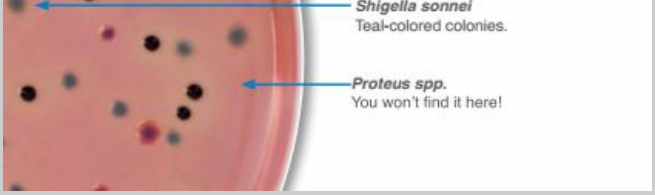
* * *

Strange ads from the past...



NOTE: New study shows **50% less in colony work-ups**, for an overall **cost savings of 80%**!
Find out how you can save also...

- Reduces costly false-positive work-ups, due to *Proteus* spp.!
- Less colony picking, subculturing, and identifications
- No need for TSI, LIA, or KIA tubes
- Reduces use of expensive ID cards
- Reduces the number of plates for primary stool setup
- Increased specificity
- Easy Identification by patented chromogenic reaction
- The only chromogenic media that will detect both *Salmonella* and *Shigella*

Learn more about HardyCHROM SS NoPRO.

Place your order now.

Try out some free samples.

* * * * *

Trio Bas Air Samplers

Two heads are better than one!

Now with Bluetooth capability!

Trio Bas from Orum International has a robust impact air sampler for every type of use. Single, double, or triple heads are available from Hardy Diagnostics.

- Watch a short video that will explain why the Trio Bas is the best choice for your clean room.
- See the complete Trio Bas catalog.

* * * * *

Gram Staining made easy...

No Mess!
No Stress!
No Inconsistencies!

- Please have a sales rep contact me about air samplers.

Testimonial from a Pharmaceutical Lab worker...

"The two heads of TRIO BAS DUO air sampler was one of the best investments during the last two years. The laboratory staff responsible of the bacteriological sampling is able to double the number of environmental microbial cycles per day. This means more efficiency and lower cost, together with the possibility to increase in the future the number of sampling in other areas of the premises."

* * *

Do you perform colony counts?

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- Self diffusing of sample - no spreader needed
- Room temperature storage
- Rigid plate with removable lid
- Stackable plates to conserve space

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Request Samples

* * * * *

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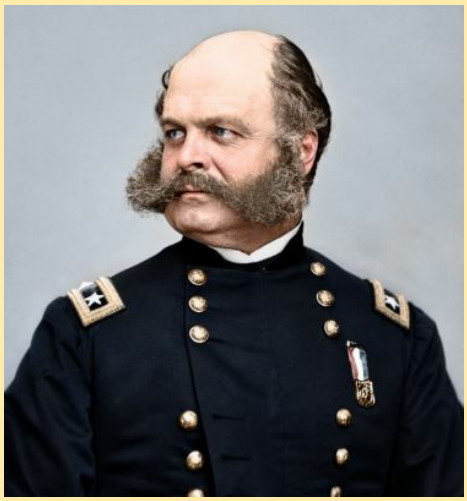
Watch a brief video about how easy it is to set up the GramPRO in your lab.

Learn more about the GramPRO 1.

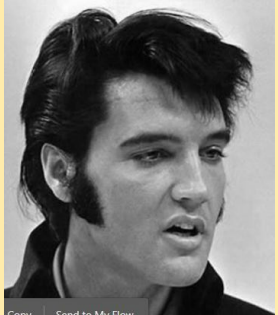
Please contact me to discuss automated slide stainers.

Phraseology...

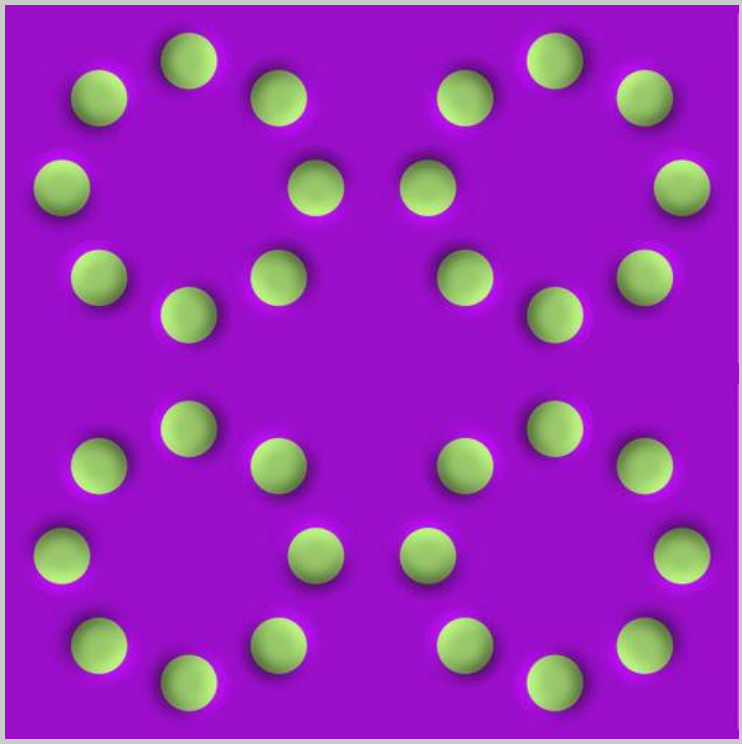


"Sideburns"

The term, "sideburns," became well known after the US Civil War of the 1860s. It is a corruption of the name **Ambrose Burnside**, a Union Army general shown above, who popularized this unusual display of facial hair. Many others adopted this style, not the least of which was Elvis Presley in the 1950s.



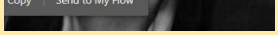
Optical oddities...



Look away from the beans and they move.
Focus on the beans and they stop!

"Believe half of what you see and none of what you hear."
~ Benjamin Franklin ~

RUBES



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What is Hardy all about?

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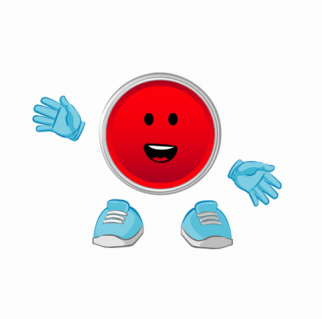

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Brainteasers

Ready for a cranial workout?

Enter the brain gym here ...

CryoSavers

"Yes, Johnny, it's true. Some misguided individuals actually believe the Earth is flat, but as you can see for yourself, the Earth is in fact hollow. ... Why else would globe companies make them that way?"

Find more

Want to book Leigh as a speaker at your next event?

Warning:

PUN ZONE AHEAD

~ Why was Dumbo always so sad? He felt irrelephant.

~ Astronomers got tired of watching the moon rotate around the earth for 24 hours, so they called it day.

~ I really don't like stairs. They are always up to something!

~ What did the grape say when he got crushed...Nothing, he just let out a little whine.

~ Looks like I lost another electron...I should keep a better ion them.

# # #

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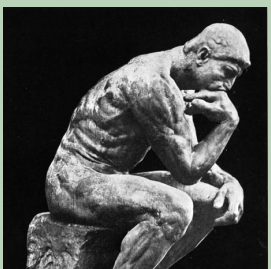
Think about it...



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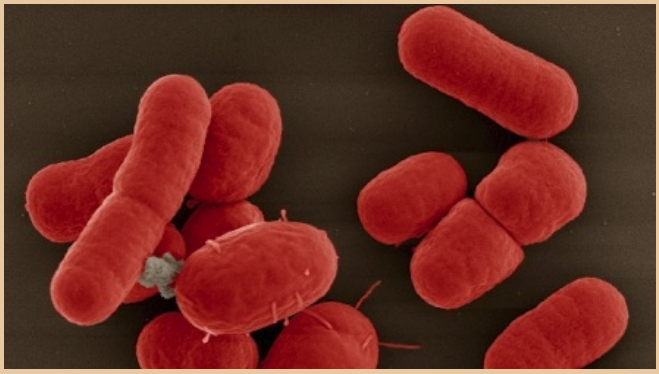
New Mechanisms in the Fight Against Superbugs

Two-component regulatory systems: The next target for novel antibiotics for the multidrug resistant bacteria Acinetobacter baumannii*?*

Acinetobacter baumannii is an opportunistic pathogen that causes Hospital Acquired Infections (HAI) and is listed by the WHO as a Priority 1: Critical pathogen in need of new antibiotics due to it becoming multidrug resistant (MDR)(1).



A. baumannii has become increasingly more resistant to "last resort" antibiotics, such as tigecycline and colistin. Due to this WHO classification, novel approaches for treating MDR *A. baumannii* are being pursue, one of which is targeting the bacteria's two-component systems.

Bacteria are able to quickly respond to stimuli, either physical or chemical, in their environment and through a series of signal transduction pathways and by altering gene expression to adapt to their environment. The pathways responsible are two-component regulatory systems (TCRS). Two component systems contain a membrane-bound sensor histidine kinase that senses a stimulus and a DNA binding response regulator that alters gene expression. In pathogenic bacteria, the TCRS are often implicated in virulence factors such as motility,

* Why is it that people say they 'slept like a baby' when babies wake up like every two hours?

* If a deaf person has to go to court, is it still called a hearing?

* Why are you IN a movie, but you're ON TV?

* Why do people pay to go up tall buildings and then put money in binoculars to look at things on the ground?

* Why do doctors leave the room while you change? They're going to see you naked anyway.

* Why do toasters always have a setting that burns the toast to a horrible crisp that no one would ever eat?

* * *

Wisdom to Ponder...

Coco Chanel

1883 ~ 1971

A French fashion designer and businesswoman. Listed by TIME magazine as one of the 100 most influential people of the 20th Century.

"Gentleness doesn't get work done unless you happen to be a hen laying eggs."

"A girl should be two things: classy and fabulous."

"Success is often achieved by those who don't know that failure is inevitable."

"Nature gives you the face you have at twenty; it is up to you to merit

biofilm, capsule formation, antibiotic resistance, as well as quorum sensing (2,3).

Genomic analysis has identified over 25,000 different TCRS, and over 99% of them are uncharacterized (4). One of the difficulties in characterizing TCRSs is that there are thousands of possible stimuli (pH, chemicals, peptides, etc.), but the histidine kinase sensor is specific for just one stimuli, which can influence hundreds of genes. Further adding to the complexity is that, in some cases, one histidine kinase can activate a number of response regulators; similarly, one response regulator can be activated by a number of histidine kinases (3). Currently, there are six characterized TCRSs in *A. baumannii* related to virulence factors, two of which an environmental stimulus has been identified.

The first characterized and most studied TCRS in *A. baumannii* is AdeRS. This TCRS is responsible for regulating the expression of the efflux pump AdeABC, which has been shown to be involved in antibiotic resistance. Overexpression of the AdeABC pump caused by

mutations in adeRS leads to an increase in tigecycline resistance, which has been observed in some clinical isolates. Moreover, clinical isolates have shown high levels of sequence variation in adeRS, potentially explaining the variability in tigecycline resistance. While the exact environmental stimuli is still unknown, there is evidence that AdeS (the histidine kinase) is responding to NaCl concentrations, which activates AdeR (response regulator) effecting the expression of close to 600 genes, including genes responsible for biofilm formation and surface-associated motility (9). Unfortunately, it is not uncommon for clinical isolates to have a disrupted AdeRS while still maintaining their multidrug resistant phenotype. While the AdeRS TCRS is the most characterized TCRS in *A. baumannii*, the PmrAB TCRS has gained a lot of attention as a target for antibiotic treatment.

The PmrAB (named for polymixin resistance) TCRS is believed to play a significant role in *A. baumannii* colistin resistance. Colistin is a cationic lipopeptide that is a type of polymixin that interacts with lipid A of the LPS (lipopolysaccharide) moiety and increases the permeability of the outer membrane, allowing colistin to pass through the membrane, further disrupting the cellular membrane and causing leakage of cytoplasmic contents (6, 8).

Clinical isolates that show colistin resistance have a mutation in both pmrA which encodes the response regulator, and pmrB, which encodes the histidine kinase, or a mutation in pmrC, which encodes a protein that can modify lipid A of LPS. This modification results in a positively charged phosphate group that prevents colistin from binding to lipid A. Furthermore, mutations in pmrA and pmrB may lead to the pmrCAB operon to be constituently overexpressed, resulting in the bacterial membrane being remodeled to decrease membrane permeability (5, 7). The environmental stimuli that PmrS responds to is still unknown but it is believed to be related to sensing cations and/or pH changes since PmrAB in other pathogens directly influences the expression of pmrA. However, preliminary work has not demonstrated that connection in *A. baumannii*.

PmrAB has been described in other pathogens such as *E. coli, Salmonella enterica, P. aeruginosa, and Klebsiella pneumoniae,* where PmrAB lends colistin resistance via a similar

the face you have at fifty."

"As long as you know men are like children, you know everything!"

"The most courageous act is still to think for yourself. Aloud."

"Don't spend time beating on a wall, hoping to transform it into a door."

"In order to be irreplaceable one must always be different."

"I don't care what you think about me. I don't think about you at all!"

"A woman who doesn't wear perfume has no future."

* * *

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* * *

Did you know?

mechanism of lipid A modification (3). Fortunately, preliminary work

has demonstrated PmrAB-mediated colistin resistance can be reversed. The small molecule 2-aminoimidazole is able to inhibit PmrAB, resulting in colistin susceptibility. This same small molecule is also able to disrupt the BfmRS TCRS, which has been shown to be responsible for biofilm formation and exopolysaccharide production. Furthermore, PmrAB-mediated colistin resistance has been correlated with impaired fitness and virulence and a lower infectivity rate (8). This lower fitness may explain why the prevalence of colistin resistance in *A. baumannii* is still relatively low.

A recent publication in *Nature Chemical Biology* (May 20, 2019), Tabor, et. al described a method for determining the stimuli of TCRS by re-engineering the DNA binding domain to recognize synthetic promoters. They were able to show that the DNA binding domains function similarly to interchangeable modules. The group was able to identify the stimuli for an uncharacterized TCRS, which is present in a number of other bacteria, including *Y. pestis* (10).

This breakthrough mechanism for identifying environmental stimuli could help us better understand TCRS and hopefully lead to methods of exploiting them for treating MDR organisms such as *A. baumannii.*

By Michael Wade
Technical Support Specialist
HARDY DIAGNOSTICS

References: 1, 2, 3, 4, 5, 6

* * *

Why the English language is so difficult to learn...

- The bandage was wound around the wound.
- He could lead if he would get the lead out.

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- Manufactures over 2,700 microbiology products for you to choose from.
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- The soldier decided to desert his dessert in the desert.
- When shot at, the dove dove into the bushes.
- The insurance was invalid for the invalid.
- They were too close to the door to close it.

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President
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