THE SILVERINSTITUTE

February 2018

Silver News

Overcoming The Threat Of Antimicrobial Resistance To Silver

By Trevor Keel, PhD., Technical Consultant to The Silver Institute

Extracts from pomegranates may offer a way to prevent antimicrobial resistance to silver.

"It is well known that silver nanoparticles lose their antimicrobial activity if they come together to form larger particles known as aggregates."

Antimicrobial resistance (AMR) represents one of the most significant challenges in healthcare. According to the World Health Organization (WHO), "AMR is everywhere and has the potential to affect anyone, of any age, in any country." A study recently published in the journal *Nature Nanotechnology* suggests that microorganisms can become resistant to the antimicrobial effects of silver nanoparticles, but there is a new way to tackle this.

AMR is the ability of a microorganism to prevent an antimicrobial (such as antibiotics, antivirals and antimalarials) from acting against it. This is a natural evolutionary phenomenon but can be accelerated by a variety of factors including the inappropriate use of medicines (primarily through disease misdiagnoses), weak surveillance and poor infection control systems in typical high-risk locations such as hospitals and clinics. Possibly most critical of all is an alarming lack of new drugs in development. The so-called 'pipeline' is almost dry, with large pharmaceutical companies increasingly moving away from antimicrobial development because of the scientific complexity involved.

Silver has been associated with human medicine and healthcare for over two millennia (See *Silver in Medicine – Past, Present and Future*). We now understand that silver nanoparticles are capable of targeting microorganisms at multiple sites on or within bacterial cells, hence making the metal a potent antimicrobial. However, as with any new drug or treatment, there is always a concern that resistance will develop.

Indeed, this is precisely what Professor Radek Zbořil and his colleagues at Palacký University in the Czech Republic have reported in their recently published article *Bacterial resistance to silver nanoparticles and how to overcome it*.

Their studies have shown that a specific strain of *Escherichia coli* (E-coli) can become resistant to silver nanoparticles after repeated exposure. (E-coli is found in the environment, food and in intestines of humans and many animals. Most strains of E. coli are harmless; others can make you sick.)

continued on page 2

continued from page 1

This is clearly unwelcome albeit unsurprising news. However, the team has also identified a way to remedy this through a previously unreported mechanism of action, as explained by Aleš Panáek, lead author of the work:

"It is well known that silver nanoparticles lose their antimicrobial activity if they come together to form larger particles known as aggregates. We have discovered that flagellar bacteria can exploit this Achilles' heel: upon repeated exposure to nanosilver, they start producing the protein flagellin from their flagella. This protein first reduces the repulsive forces between the nanoparticles and then acts like glue, causing the nanoparticles to stick to one another and lose their antibacterial properties." (Flagella are lash-like appendages that protrude from the cell body of certain bacteria. These structures serve a number of functions, including permitting locomotion.)

Nanosilver loses its ability to fight germs because the aggregation reduces the surface area of silver available to come in contact with the microorganisms. Other researchers have noticed this phenomenon and have offered their remedies, such as coating silver nanoparticles with a thin layer of gold and irradiating these hybrid particles with a laser. (See *Getting Silver to Fight Germs on Cue*, Dec. 2017, *Silver News*).

Here, the Czech team seems to have identified a simpler method to avoid aggregation; they successfully added chemicals that suppress the formation and release of flagellin. Suitable substances are found in pomegranate extracts, among other things. When such extracts are applied together with silver nanoparticles, the bacteria do not produce flagellin and therefore lose their ability to develop resistance to the silver nanoparticles.

Identifying that resistance to silver nanoparticles in *Escherichia coli* is not genetic in nature, and can be handled by the addition of simple, non-toxic chemicals, is a critical step forward in understanding, and further places silver at the heart of the fight against AMR.

Silver Market Trends for 2018

Silver demand from industrial applications, about 60% of total demand in 2017, is expected to continue to grow this year, according to the Silver Institute. Because of silver's excellent electrical conductivity, demand is forecast from the automotive segment as vehicles become more electrified and computerized. Strong demand also is expected from photovoltaic applications; in 2017 demand reached 92 Moz (million ounces). Continued consumption is expected in 2018, driven by large-scale solar capacity additions and uptake from individual households, particularly in China.

Jewelry demand is predicted to continue its steady increase in 2018, expanding consumption by another 4%, following a rise of 1% in 2017. Silver demand from the jewelry sector accounts for approximately one-fifth of total silver demand.

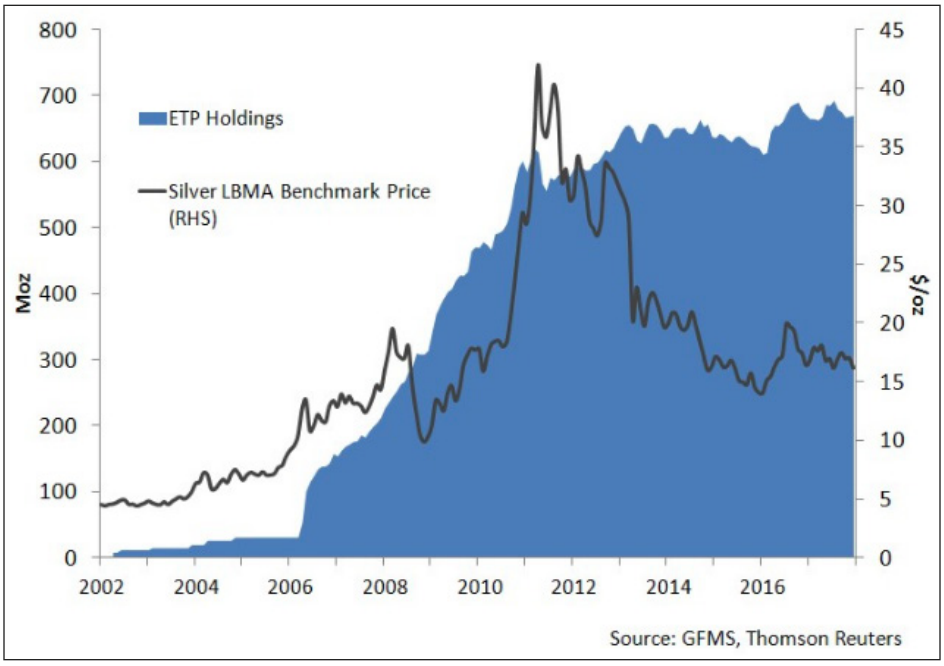
Coin demand almost halved to 73 Moz in 2017. Much of the weakness was concentrated in the United States where the rising stock market diverted some capital away from physical precious metals. Investment is forecast to flow back into precious metals, benefiting silver bar and coin demand this year.

Silver exchange-traded-products (ETP) are estimated to increase about 3% this year after reaching a record high of 670 Moz at the end of 2017.

On the supply side, global mine supply fell 1% in 2016, the first annual decline following 14 years of consecutive growth. In 2017 that trend continued with mine output expected to contract by a further 2% to 870 Moz. Production disruptions out of South America, along with a decline in capital expenditure among the primary producers in the past five years, is expected to constrain output again this year. However, the strong recovery in base metal prices will provide some support to output in 2018, particularly from by-product producers capitalizing on the trend.

The price of silver fell a half percent in 2017 to an average of $17.05/oz. This year the Silver Institute expects the silver price to experience a volatile ride. Short covering in the beginning of this year has already propelled the price above last year's average. On a ratio with gold, currently at around 72, silver has plenty of room for improvement and to migrate towards its long-term average of around 64.

For further details, click here.



Silver ETP Holdings and LBMA Benchmark Price (RHS)

Silver's Role in 'E-Skin' Development Continues

The development of 'electronic' skin's ability to sense and feel has taken great strides recently and silver is playing a continuing role. (See *Silver-Silicone 'Fingertips' Allow Greater Touch*, June 2017 *Silver News*.)

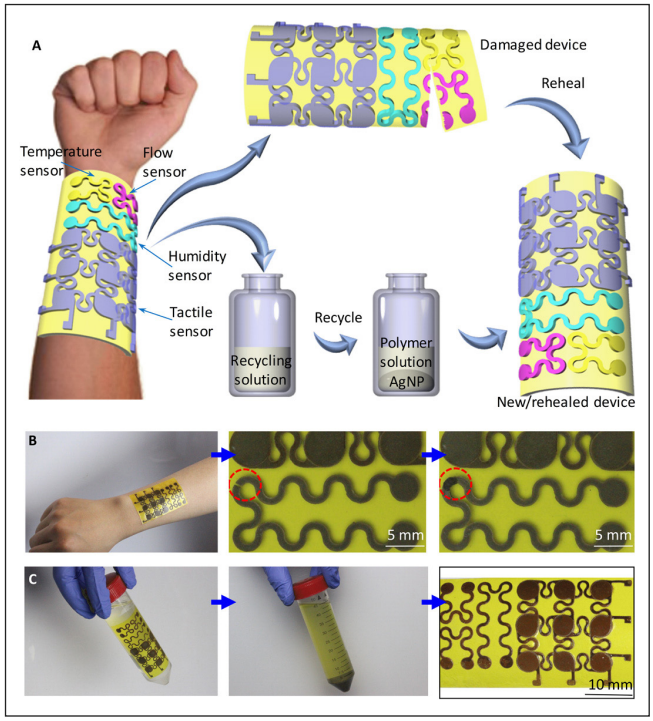
Most recently, University of Colorado Boulder (UCB) researchers have been working on 'e-skin' that they claim is self-healing, recyclable and flexible. Unlike artificial skin applied to patients injured by fire or other maladies, e-skin will find uses in robots and prosthetics.

UCB research team leaders Assistant Professor Jianliang Xiao and Associate Professor Wei Zhang imbedded silver nanoparticles in a polymer known as polyimine. In their paper published in the journal *Science Advances*, the authors note:

"The e-skin can be rehealed when it is damaged and can be fully recycled at room temperature, which has rarely, if at all, been demonstrated for e-skin. After rehealing or recycling, the e-skin regains mechanical and electrical properties comparable to the original e-skin. In addition, malleability enables the e-skin to permanently conform to complex, curved surfaces without introducing excessive interfacial stresses. These properties of the e-skin yield an economical and eco-friendly technology that can find broad applications in robotics, prosthetics, health care, and human-computer interface."

The role of silver nanoparticles in this instance is to provide mechanical strength, chemical stability and, most importantly, electrical conductivity for the sensors that are on the surface.

Because of the chemical bonding structure of polyimine, small holes or tears close on their own at room temperature when chemicals including ethanol are applied. To recycle the e-skin, the device is soaked in a solution that breaks down the polyimine into eco-friendly compounds. The silver nanoparticles sink to the bottom and can be reused in new e-skin.



(A) Schematic illustration of rehealability and full recyclability of the e-skin. (B) The malleable e-skin can be conformally mounted onto a human arm (left). When mechanically cut or broken (middle), the e-skin can be rehealed by applying a small amount of rehealing agent and heat pressing (right). (C) The e-skin can be fully recycled (left), yielding the solution with dissolved oligomers/monomers and AgNPs (silver nanoparticles) at the bottom (middle). The solution and AgNPs can be reused to make a new e-skin (right).

Silver Diamine Fluoride Gets OK From Pediatric Dentistry Group

The American Academy of Pediatric Dentistry (AAPD) has issued an *evidence-based guideline* that recommends use of 38% Silver Diamine Fluoride (SDF) to treat active dental caries, or cavities, in primary teeth in pediatric and special-needs patients.

Silver Diamine Fluoride was approved for tooth hypersensitivity by the U.S. Food and Drug Administration for adults in August 2014, and the first products were available in April 2015. However, SDF has been used in other countries for decades including an 80-year clinical history in Japan. (See *News California Hygienists Association Supports Silver Diamine Fluoride Use*, Feb. 2016, *Silver News*.)

Dentists have been using SDF 'off label' for treatment of cavities in children and adults.

The guideline states that "Prevention of new caries lesion development and outcomes in permanent teeth, such as root caries lesion arrest, were not the focus of this guideline; however, because they are of interest and relevant to caries management within the scope of pediatric dentistry, they are mentioned and will be included in future iterations of the guideline as the supporting evidence base increases."

The main drawback of SDF is possible black staining of enamel and potential staining of skin, clothing and surfaces with which it comes in contact. However, considering the low cost of the treatment and the health dangers of cavities beyond those for teeth, panel members were "confident that the benefits of SDF application in the target populations outweigh its possible undesirable effects."

Two Scientists Receive Awards for Work With Nanosilver

Tran Ngoc Dung Receives L'Oreal-UNESCO Award

Tran Ngoc Dung, head of the Institute for Environment Friendly Technology, an arm of the Vietnam Academy of Science and Technology, has received the 2017 L'Oreal-UNESCO Award for women in science for her work on the bacteria-killing properties of nanosilver.

She said that the deaths of four infants at Bac Ninh Hospital of Obstetrics and Paediatrics in the northern province of Bac Ninh Province in November, 2017 was due to septic shock and that a nanosilver-covered air filter membrane might have prevented microorganisms from entering treatment rooms, according to *Vietnamnet Bridge*, an online newspaper.

While working on methods to produce nanosilver which can be sprayed on surfaces she found that traditional methods were not suited to producing large amounts in facilities in Vietnam. With the help of a U.S. professor, Dung dissolved silver salts in an aqueous solution along with a dispersant that produced particles small enough to be considered nanosilver – less than 100 nanometers.

Dung was one of five women who were given the 2017 L'Oreal-UNESCO award at a ceremony in Hanoi in early January.

VIETNAMNET BRIDGE

Tran Ngoc Dung Receives L'Oreal-UNESCO Award

The L'Oréal-UNESCO Award for Women in Science aims to improve the position of women in science by recognizing outstanding researchers who have contributed to scientific progress. The awards are a partnership between the French cosmetics company L'Oréal and the United Nations Educational, Scientific and Cultural Organization (UNESCO). Each laureate receives a grant of US$100,000.

Carla Meledandri Wins 2017 N.Z. Prime Minister's MacDiarmid Emerging Scientist Prize

Carla Meledandri, Phd., an academic from the University of Otago, in Dunedin, New Zealand, has won the 2017 Prime Minister's MacDiarmid Emerging Scientist Prize, recognizing her innovative nanotechnology research, including using silver nanoparticles to treat and prevent dental disease, and finding ways to store and use clean energy.

The prize is administered by the Royal Society of New Zealand. Meledandri received the AUS$200,000 prize from Prime Minister Jacinda Ardern at the New Zealand Parliament in Wellington this month.

Meledandri has established a start-up company, Silventum Limited, and has secured a technology licensing agreement with a multinational dental company. "In all cases with dental decay, the source of the problems is bacteria," she says.

She notes that tooth decay is one of the "most prevalent chronic diseases" in the world, and that her work may make dental care more affordable and reliable without requiring frequent visits to the dentist. One approach under consideration is to place a silver nanoparticle liquid in a tooth before the dental filling is added. (See *Silver Diamine Fluoride Gets OK From Pediatric Dentistry Group* in this issue.)

Click the image to watch Carla Meledandri explain her work.

U.S. Tariff on Imported Solar Cells Imposed

Worldwide Demand Will Not be Affected by Minimal Decrease in U.S. Output

The January 23, 2018, decision by U.S. President Donald Trump to impose tariffs on solar-energy components imported to the United States is expected to have a slightly negative effect on demand for photovoltaic (PV) units in the United States in the short term, because a large majority of PV modules are imported. This is in contrast to booming demand in China, a major solar cell producer. However, China's demand coupled with strong growth in other regions should spur substantial global growth in this sector in 2018 regardless of the tariff, according to a Silver Institute/GFMS, Thomson Reuters analysis.

The price of solar panels in the United States has already increased in anticipation of the enactment of the tariff. According to Wood Mackenzie, a market analysis and advisory firm on the transformation of the global electricity industry, small scale procurement pricing for Chinese modules in the United States increased from $0.37/Watt in Q1 2017 to over $0.45/Watt in Q4 2017 due to importers looking to stock up before prices jump.

Industry estimations on the potential effects of the tariff vary widely. Bloomberg New Energy Finance estimates that residential units will see an increased cost of about 3%, while utility units including solar farms will see 10% cost increases, taking into account the tax-exempt threshold and the share of domestically produced modules. Research and investment firm Clearview Energy Partners LLC estimates a similar price increase: 6% for commercial, 4% for residential and 10% for utility units. The non-profit Solar Energy Industries Association forecasts a potential price increase of over 100% and a job loss of 23,000.

The tariffs, which took effect on February 7, gradually reduce from 30% this year to 15% in 2021. New U.S. installation is estimated to reach between 9 Gigawatts (GW) and 10 GW in 2018 compared to over 12 GW in 2017. Imports and demand in 2018 will work to mitigate the effects of the tariff, as much of the demand will be met with supply acquired in 2017 in anticipation of the tariff's enactment. Moreover, at this lower level of demand for installation, well over 30% will fall under the 2.5 GW exemption. Installations in the United States are expected to gradually increase once tariff rates decline. This decrease in PV demand in the United States in the coming years caused by the tariff will reduce demand for silver in these applications by approximately 14 million ounces in total over the four-year period.

	Year 1	Year 2	Year 3	Year 4
Safeguard Tariff on Modules and Cells	30%	25%	20%	15%
Cells Exempted from Tariff	2.5 GW	2.5 GW	2.5 GW	2.5 GW

SILVER INSTITUTE/GFMS, THOMSON REUTERS

The new tariffs on imported solar modules and cells are set at an annually decreasing rate schedule over the next four years.

New Medical Electrodes Use Silicone and Silver; Fixes Drawbacks of Conventional Devices

Researchers at ETH Zurich have developed a new type of adhesive electrode – like the kind used for Electrocardiograms (EKGs check the electrical activity of the heart) and Electroencephalograms (EEGs check the electrical activity of the brain) and other monitors – composed of silicone rubber and conductive silver particles that eliminates the drawbacks of conventional electrodes without sacrificing quality.

The scientists hope to bring the electrodes to market this year.

Two types of electrodes are commonly used. The first is a hard-metallic model that is uncomfortable and doesn't adhere over long measurement periods. The second, and most used, is a gel electrode that works well but can irritate skin and even cause allergic reactions in some patients.

The electrode developed by ETH's Janos Vörös, Professor of Bioelectronics, and Christopher Hierold, Professor of Micro and Nanosystems, is as elastic as skin and allows signals from the brain and heart to be recorded with high quality.

The silicone/silver particle combination allows the electrodes to be non-irritating, and the silver particles offer the metal's ability to send signals to wires with almost no electrical resistance.

The duo was inspired by grasshoppers. The insects have feet covered with many tiny pads featuring geometric shapes that adhere to surfaces, an effect known to scientists as the Van der Waals interaction. Applying the same geometric shapes to silicone/silver pads allowed electrodes to stick well to skin. In addition, the shape maximizes the skin/electrode contact area, which allows signals to be recorded with high quality and amplitude.

ETH ZURICH

ETH researchers have developed an adhesive electrode for health monitoring. A new spin-off plans to bring it to market this year.

‘Yam Cake’ and Silver Help Promote Wound Healing

Researchers in China have developed a novel wound dressing that mixes silver nanoparticles with an extract from *konjac*, a plant that grows in subtropical to tropical eastern Asia, whose underground tuber is cooked and eaten mainly in Japan. Known by its Japanese name *konnyaku*, it is sometimes called “yam cake.”

The dressing was tested on rabbits and shown to accelerate healing while killing bacteria that can cause infections.

The combination of silver nanoparticles appears to work on two fronts. First, the silver acts as an antibacterial preventing the wound from getting infected or killing germs that have already entered the site.

Second, the *konjac* acts like a sponge keeping the wound moist by absorbing “exudates.” An exudate is a fluid composed of serum, fibrin and white blood cells that ooze from a cut or wound. Wounds heal faster when the area is kept moist as it helps regeneration of new tissue by attracting healing cells, called fibroblasts, to the site. At the same time, moistness increases the ability of cells to heal. In addition, moist bandages are less likely to damage new tissue when they are removed.

The researchers say that their tests on rabbits were extremely successful. Their study can be found in the Journal *Carbohydrate Polymers,* which stated: “Animal models showed that the KGM/AgNP [*Konjac glucomannan*/silver nanoparticle] composite sponges effectively accelerated wound healing, and histological findings showed that they promoted fibroblast growth and accelerated epithelialization [growth of new tissue over a wound that help protect it from the environment]. The experimental results showed that KGM/AgNP composite sponges have great potential in promoting wound healing.”

If future clinical studies show additional promise, the researchers hope to test their product on humans.

Konjac, also known as “yam cake” in Japan, may hold promise for wound treatment when combined with silver nanoparticles.

Larry Kahaner
Editor

www.silverinstitute.org
@SilverInstitute on Twitter

THE SILVERINSTITUTE
1400 I Street, NW, Suite 550
Washington, DC 20005
T 202.835 0185
F 202.835 0155