Drug & Poison Information Center—Faculty of Pharmacy—Tanta University

Drug & Poison Information Bulletin

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Malacidins: a newly discovered class of antibiotics from soil microbiome

In a letter to *Nature Microbiology,* scientists reported the discovery of a new class of antibiotics that was termed malacidin. The new class was discovered while screening soil microbiome.

The screening method developed by the research team encompasses a culture-independent Natural Products (NPs) discovery platform that involves sequencing, bioinformatic analysis and heterologous expression of biosynthetic gene clusters captured on DNA extracted from environmental samples.

Malacidins belong to calcium-dependent antibiotics, which are a small family of *N*-acylated cyclic peptides that require calcium for antibacterial activity.

Calcium-dependent antibiotics include antibiotic daptomycin that was approved for commercial use by the FDA in 2003. The name "malacidin" is derived from the abbreviation of metagenomic acidic lipopeptide antibiotic and the suffix -cidin.

Inside this issue:

Structurally, malacidins are ten membered cyclic lipopeptides that differ only by a methylene on the branch at the terminus of their lipid tails. Calcium-dependent antibiotics have been shown to have discrete modes of action, targeting either cell wall biosynthesis or cell membrane integrity.

Malacidins' mechanism of action appears to be by binding to Lipid II in a calcium-dependent manner; lipid II is a precursor to cell wall molecules, leading to destruction of the bacterial cell wall and eventually the bacteria.

Fortuitously, despite the fact that vancomycin also binds lipid II; the malacidins are active against both vancomycin-intermediate- and vancomycin -resistant pathogens.

The malacidins are active against multidrug-resistant pathogens, sterilize *methicillin-resistant Staphylococcus aureus (MRSA)* skin infections in an animal wound model and did not select for resistance under the laboratory conditions.

Moreover, unlike daptomycin, which is unable to treat severe community-acquired pneumonia due to loss of activity in the presence of pulmonary surfactants, malacidin does not share this liability.

Finally, malacidins may provide a potentially powerful approach for combating antibiotic resistance.

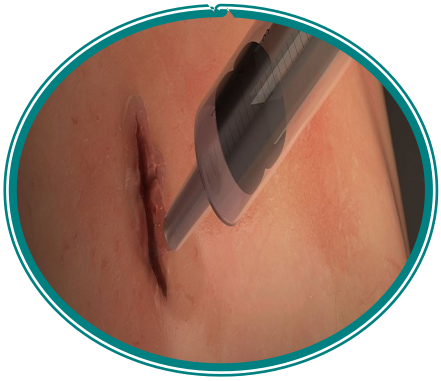
Reference:

B.M. Hover, S. Kim, M. Katz, et al. Culture-independent discovery of the malacidins as calcium-dependent antibiotics with activity against multidrug-resistant Gram-positive pathogens. Nat. Microbiol. (2018). https://doi.org/10.1038/s41564-018-0110-1

By: Amr Nowair, B. Sc.

Elastic surgical glue seals wounds in 60 seconds

Scientists have developed an elastic, adhesive surgical glue that could transform emergency treatments by sealing up critical wounds in the skin or the organs, without the need for staples or sutures.



The gel is based on methacryloyl-substituted tropoelastin (MeTro for short), a hybrid elastic protein, and can be squirted onto internal and external wounds to seal them up and encourage healing.

The material also works on internal wounds that are often in hard-to-reach areas and have typically required staples or sutures due to surrounding body fluid hampering the effectiveness of other sealants.

MeTro sets in just 60 seconds once treated with UV light, and the technology has a built-in degrading enzyme which can be modified to determine how long the sealant lasts -- from hours to months, in order to allow adequate time for the wound to heal.

The liquid or gel-like material has quickly and successfully sealed incisions in the arteries and lungs of rodents and the lungs of pigs. To be clear, for now the trials are limited to animal models. It has been successfully tested on rodent arteries and lungs in addition to pig lungs.

If the MeTro gel can be further developed into a commercial product, it could well become an essential part of a first responder's toolkit.

Reference:

N. Annabi, Y.N. Zhang, A. Assmann, et al. Engineering a highly elastic human protein–based sealant for surgical applications. Sci. Transl. Med. (2017). https://doi.org/10.1126/scitranslmed.aai7466

By: Mai Mousa, Pharm D.

Vitamin and mineral supplements, when should be taken?

Vitamins and minerals are among the most popular supplements and are taken by 48% and 39% of adults, respectively, typically to maintain health and prevent disease. Despite this enthusiasm, most randomized clinical trials of vitamin and mineral supplements have not demonstrated clear benefits for primary or secondary prevention of chronic diseases not related to nutritional deficiency. Indeed, some trials suggest that micronutrient supplementation in amounts that exceed the recommended dietary allowance (RDA) may have harmful effects, including increased mortality, cancer, and hemorrhagic stroke.

Vitamins and minerals are best obtained through a healthy and well-balanced diet. That's where the nutrients are best absorbed and are safest, and the optimal ratio of nutrients can be obtained. Moreover routine supplementation is not recommended for the generally healthy population. On the other hand, targeted supplementation may be warranted in high-risk groups for whom nutritional requirements may not be met through diet alone, including people at *certain life stages* and those with *specific risk factors.*

General Guidance for Supplementation in a Healthy Population by Life

Pregnancy

- Advised to consume adequate folic acid (0.4-0.8 mg/d) to prevent neural tube defects.
- Supplemental iron is needed if low levels of hemoglobin or ferritin are documented to prevent and treat iron-deficiency anemia.

- Prenatal multivitamin/multimineral supplements will provide folic acid as well as vitamin D and many other essential micronutrients during pregnancy.
- Calcium or high-dose vitamin D supplements during pregnancy warrants further study.

Infants and Children

- Exclusively or partially breastfed infants should receive:
    1. Supplemental vitamin D (400 IU/d) starting soon after birth and continuing until weaning to vitamin D–fortified whole milk (≥1 L/d).
    2. Supplemental iron (1 mg/kg/d) from 4 months until the introduction of iron-containing foods, usually at 6 months.
- Infants who receive formula, which is fortified with vitamin D and (often) iron, do not typically require additional supplementation. All children should be screened at 1 year for iron deficiency and iron-deficiency anemia.
- Healthy children consuming a well-balanced diet do not need multivitamin/ multimineral supplements.
- In recent years, ω-3 fatty acid supplementation has been viewed as a potential strategy for reducing the risk of autism spectrum disorder or attention-deficit/ hyperactivity disorder in children, but evidence from large randomized trials is lacking.

Midlife and Older Adults

- Adults aged ≥50 years should be advised to meet the RDA (2.4 µg/d) with synthetic vitamin B_{12} found in fortified foods or supplements.
- Regarding vitamin D, currently recommended intakes (from food or supplements) to maintain bone health are 600 IU/d for adults up to age 70 years and 800 IU/d for those aged >70 years. Some professional organizations recommend 1000 to 2000 IU/d, but it has been widely debated whether doses above the RDA offer additional benefits.

- With respect to calcium, current RDAs are 1000 mg/d for men aged 51 to 70 years and 1200 mg/d for women aged 51 to 70 years and for all adults aged >70 years. In case of increasing the risk for kidney stones and possibly cardiovascular disease, patients should be advised to eat a calcium-rich diet and take calcium supplements only if needed (often only about 500 mg/d). A recent meta-analysis suggested that supplementation with moderate-dose calcium (<1000 mg/d) plus vitamin D (≥800 IU/d) might reduce the risk of fractures and loss of bone mass density among post-menopausal women and men aged ≥65 years.

Guidance for Supplementation in High-Risk Subgroups

⇒ ***Medical conditions that interfere with nutrient absorption or metabolism:***

1. Bariatric surgery: fat-soluble vitamins, B vitamins, iron, calcium, zinc, copper, multivitamins/multiminerals.
2. Pernicious anemia: vitamin B_{12} (1-2 mg/d orally or 0.1-1 mg/mo intramuscularly).
3. Crohn disease, other inflammatory bowel disease, and celiac disease: iron, B vitamins, vitamin D, zinc, magnesium.

⇒ ***Osteoporosis or other bone health issues:*** vitamin D, calcium, magnesium (Inconsistent evidence).

⇒ ***Age-related macular degeneration:*** specific formulation of antioxidant vitamins, zinc, copper.

⇒ ***Medications (long-term use):***

1. Proton pump inhibitors (Inconsistent evidence): vitamin B_{12}, calcium, magnesium.
2. Metformin (Inconsistent evidence): vitamin B_{12}.

⇒ ***Restricted or suboptimal eating patterns:*** multivitamins/multiminerals, vitamin B_{12}, calcium, vitamin D, magnesium.

References:

- *J.E. Manson, S.S. Bassuk. Vitamin and Mineral Supplements: What Clinicians Need to Know. JAMA. (2018). https://doi.org/10.1001/jama.2017.21012*
- *National Institutes of Health Office of Dietary Supplements. https://ods.od.nih.gov. Accessed February 2018.*

By: Bassant Maher, B. Sc.

From our questions received in 2018

"Can Harvoni® (Ledipasvir/Sofosbuvir) & Daklinza® (Daclatasvir) as hepatitis C antiviral therapy lead to Bradycardia?!"

⇒ On January 2018, we received a request from a pharmacist concerning the risk of bradycardia during treatment with Harvoni® or Daklinza® as hepatitis-C antivirals.

⇒ The patient was a female aged 65 years, diagnosed with hepatitis C virus (HCV) , and had a history of hypertension & heart failure. The requester was asking about the ability of both drugs to cause bradycardia as a side effect & the possibility of administration of β-blockers at the same time for managing hypertension.

⇒ After searching in monographs for both drugs, it was found that both drugs can lead to *slow or irregular heartbeats but the incidence is not known.*

⇒ In addition, it was found that concomitant administration of amiodarone as anti-arrhythmic with Harvoni in combination with another direct-acting antiviral as Daklinza may result in a severe or life-threatening bradycardia but with unexplained mechanism.

⇒Risk factors for bradycardia in this case include:

- ***Underlying cardiac diseases.***
- ***Concomitant β-blocker therapy.***
- ***Advanced liver disease.***

⇒ So, the requester was advised to consult physician for other treatment than β-blockers for hypertension & try to avoid the combination (amiodarone, Harvoni & Daklinza). But, if there are no alternatives & this combination must be used, cardiac monitoring in an in-patient setting for the first 48 hours of co-administration is recommended. In addition, outpatient or self-monitoring of heart rate should occur daily through at least the first 2 weeks of treatment.

References:

- *S. Renet, M.C. Chaumais, T Antonini, et al. Extreme bradycardia after first doses of sofosbuvir and daclatasvir in patients receiving amiodarone: 2 cases including a rechallenge. Gastroenterology (2015). https://doi.org/10.1053/j.gastro.2015.07.051*
- *Ledipasvir and sofosbuvir monograph. https://online.lexi.com/lco/action/doc/retrieve/docid/multinat_f/5385028. Accessed February 2018.*
- *Daclatasvir monograph. https://online.lexi.com/lco/action/doc/retrieve/docid/multinat_f/5750852. Accessed February 2018.*

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