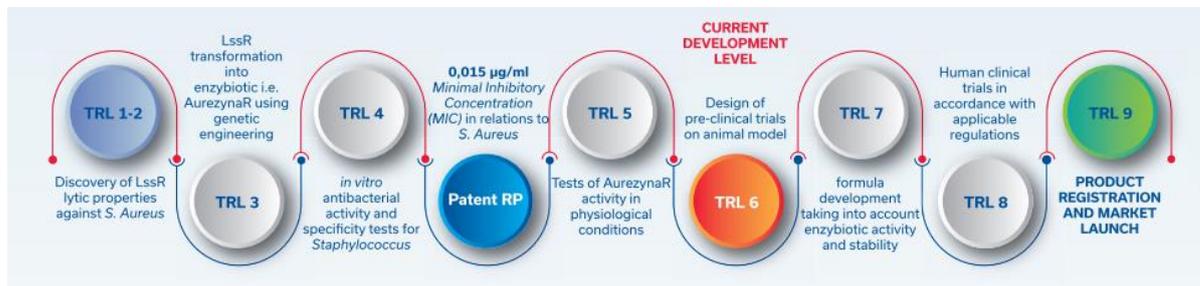


AuresineR – a rescue for wounds and problematic skin

Become a co-creator of an innovative product

Enzybiotic **AuresineR** stands a chance to become one of the most effective methods of treatment for hard-to-heal wounds (diabetic foot, decubitus pressure ulcers, burns) and dermatologic conditions such as atopic dermatitis, impetigo, psoriasis or prurigo nodularis. Enzybiotics are novel biological anti-bacterial agents which induce immediate bacterial cells lysis without damaging natural human microbiome. They also deplete antibiotic-resistant strains, which is of particular significance now that antibiotic-resistance is an escalating issue. The protein has been patented (UP RP-243304) and affects exclusively *Staphylococcus* bacteria.

With the support of the public, the research team of Protein Engineering Laboratory of the MMRI PAS have developed the invention up to TRL 5 (*Technology Readiness Level*). A grant application has been submitted to the Medical Research Agency for preclinical trials of the enzybiotics application in atopic dermatitis treatment. Further research on the application of AuresineR to eradicate staphylococci from hard-to-heal wounds is also feasible.



The inventors

Izabela Sabała MD PhD and **Elżbieta Jagielska MD** from the Protein Engineering Laboratory of the MMRI PAS have been investigating proteins and their antibacterial properties for years. The scientific activities pertain to both basic research, such as the structural characterization of proteins, their interaction with cell walls or their physiological role in bacteria, and the developmental and industrial research on the use of lytic potential of bacteriolytic enzymes. Izabela Sabała MD PhD and Elżbieta Jagielska MD co-authored many publications, patents and patent applications concerning new enzybiotics.

A global problem

Staphylococcus aureus (*S. aureus*) is the most common pathogen which causes skin infections worldwide regardless of the climate, geographical region and patient's age. *S. aureus*-related infections can be very severe and potentially fatal.

In 2019, *S. aureus*, along with *Escherichia coli*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, accounted for 30.9% of the 7.7 million infection-related deaths worldwide. In 2019, *S. aureus* alone was the major cause of bacteria-related mortality in 135 countries and resulted in 1,105,000 deaths¹. Currently, over 90% of *S. aureus* produce penicillinase and is resistant to penicillin. Methicillin-resistant nosocomial strain of *S. aureus* also remains a global challenge². Improper use of antimicrobials (especially antibiotics) foster the environment that promotes the selection of strains that are resistant to currently available antimicrobial treatment, thereby posing a serious risk to patient health. *Staphylococcus aureus* is associated with infections of hard-to-heal wounds and a great number of cutaneous disorders. Patients with diabetic foot and decubitus pressure ulcers constitute the largest proportion (43%) of individuals affected by chronic wounds and wounds-related infections³.



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Diabetic foot syndrome

According to the International Diabetes Federation, the number of people with diabetes was expected to increase from 366 million in 2011 to 552 million in 2030⁵. Unfortunately, the figures proved underestimated as the number of diabetic patients already exceeded half a billion in 2021. In addition, almost 183 million people with diabetes have not been diagnosed, and about 4 million people have developed diabetic foot syndrome which is the most common cause of non-traumatic amputations

¹ M. S. Linz, A. Mattappallil, D. Finkel, D. Parker, *Clinical Impact of Staphylococcus aureus Skin and Soft Tissue Infections*, *Antibiotics* (Basel). 2023 Mar 11; 12(3):557.

² R. Bagdonas, A. Tamelis, R. Rimdeika, *Staphylococcus aureus infection in the surgery of burns*, *Medicina (Kaunas)*. 2003; 39(11):1078-81.

³ *Chronic Wound Care Market Size, Share & Industry Analysis, By Type (Diabetic Ulcers, Pressure Ulcers, Venous Leg Ulcers, and Others), By Product (Advanced Wound Dressings, Wound Care Devices, Active Therapy, and Others), By End User (Hospitals & Wound Clinics and Homecare Settings & Others), and Regional Forecast, 2024-2032*, Source: <https://www.fortunebusinessinsights.com/industry-reports/chronic-wound-care-market-100222>

⁴ R. Serra i in., *Chronic wound infections: the role of Pseudomonas aeruginosa and Staphylococcus aureus*, *Expert Review of Anti-infective Therapy* Volume 13, 2015 - Issue 5; *MRSA infection*, <https://www.mayoclinic.org/diseases-conditions/mrsa/symptoms-causes/syc-20375336>; R. D. Wolcott, *Analysis of the chronic wound microbiota of 2,963 patients by 16S rDNA pyrosequencing*, *Wound Repair Regen.* 2016 Jan-Feb; 24(1):163-74; R. Bagdonas, A. Tamelis, R. Rimdeika, *Staphylococcus aureus infection in the surgery of burns*, *Medicina (Kaunas)*. 2003; 39(11):1078-81.

⁵ J. Janik, *Diabetic tsunami*, <https://www.termedia.pl/diabetologia/Cukrzycowe-tsunami,54568.html>.

worldwide: globally, every 20 seconds one person undergoes diabetes-related limb amputation⁶. The data from the Polish Diabetes Association indicate that in Poland diabetes-related consequences have led to 7,000 so called 'major amputations', above the ankle, indicating that, on average, one individual loses a foot or part of the leg every two hours.

Atopic dermatitis - AD

The results of the study presented at the 30th Congress of the European Academy of Dermatology and Venerology indicate that 200 million adults in Europe have developed dermatologic conditions in the last year, with AD being one of the most common disorders. The disease predominantly affects children (80%), though it recurs in adults and remains a global concern⁷. AD is considered to be an inflammatory skin condition caused by the dysfunction of the skin natural protective barrier with the simultaneous occurrence of dysbiosis, i.e. an imbalance in the composition of skin-residing microorganisms, the so-called skin microbiota. Untreated AD can lead to the development of lung diseases⁸. The skin microbiota composition in AD patients may vary at different stages of the disease severity, however, there is generally a significant reduction in species diversity among the identified microorganisms, characterized by an overrepresentation of *S. aureus*, the prevalence of which escalates as skin symptoms worsen⁹. Notably, the efficacy of AuresineR varies among different staphylococcal species: the enzyme exhibits the highest activity against *Staphylococcus aureus*, while demonstrating significantly reduced activity against *Staphylococcus epidermidis*, which is one of the primary bacterial component of the natural skin microbiota.

Social and economic burden

Chronic wounds present a major challenge for healthcare systems worldwide, affecting 1-1.5% of the population with wound-related issues. It is estimated that 6.7 million patients, mainly elderly adults, suffer from hard-to-heal chronic wounds in the USA alone, which generated the costs of \$ 533 billion for the American healthcare system in 2014. Globally, wound treatment costs account for 2-4% of the healthcare budgets, however, these expenses are likely underestimated owing to insufficient data from numerous countries and an increasing population of elderly patients with diabetes¹⁰. Between 25 and 50% of hospital beds in Europe designated for acute conditions are occupied by patients with wounds, with 60% of the cases classified as hard-to-heal wounds. Wound treatment is an expensive procedure and its average cost

⁶ R. Strohal i in., *EWMA document: Debridement. An updated overview and clarification of the principle role of debridement.*, J Wound Care 2013; 22: 5.

⁷ A. Wollenberg et al., *ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children*, J Eur Acad Dermatol Venereol, 2020 Dec; 34(12):2717-2744.

⁸ L. Maintz, *From Skin Barrier Dysfunction to Systemic Impact of Atopic Dermatitis: Implications for a Precision Approach in Dermocosmetics and Medicine*, J Pers Med. 2022 Jun; 12(6): 893.

⁹ H. Kong, *Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis*, Genome Res. 2012 May; 22(5):850-9.

¹⁰ C. K. Sen, *Human Wound and Its Burden: Updated 2020 Compendium of Estimates*, Adv Wound Care (New Rochelle), 2021 May; 10(5):281-292.



in Europe reaches €6650 – €10,000. The costs of diabetic ulcers treatment depend on the disease severity, infections and concomitant vascular diseases. Annual costs in Europe are estimated at up to €10 billion. The direct costs of treatment are estimated at 2157 – 7169 € without amputation, and 14409 – 58700 € when amputation is included¹¹. In 2018 in Poland, PLN 78.2 million was spent on diabetic foot syndrome-related amputations¹². These represent the costs of public health care services that are ultimately borne by the entire population. However, it is necessary to consider additional costs incurred by the National Health Fund associated with hospitalization and indirect expenses which include paid benefits, the costs of prostheses, care and rehabilitation, as well as the reduction or loss of patient productivity.

According to the European Federation of Allergy and Airways (EFA) report of 2018, the average cost incurred by a patient with AD amounted to €927 per year. In Poland, according to the Polish Society of Atopic Diseases (PTCA), in 2018 the population of people suffering from AD was estimated at nearly 800,000 and an average annual cost per patient reached PLN 9,717, and even PLN 13,000 per year for patients with severe AD. Nearly half of the expenses are allocated to the purchase of medicinal and care products. According to the estimates by the president of the PTCA, severe AD patients spend about 40% of their entire annual consumption budget on treatment. The costs of the disease are not only incurred by the patients themselves or the National Health Fund, but also by the Social Insurance Institution (ZUS) and employers. According to ZUS data, in 2018 sickness absence among employees with AD totalled nearly 69,000 and the figure has been increasing annually. In the second quarter of 2024 alone, the number of days of AD-related sickness absence reached 20. On the other hand, according to the available reports, the global market for AD-related products, which was valued at about \$15 billion in 2020, is expected to grow to \$20 billion by 2030, which indicates an annual increase of about 10%. According to other estimates, the growth rate may even exceed 15%¹³.

Target group

Potential new product winners include patients struggling with infected wounds and dermatological diseases, medical personnel, as well as the manufacturers of dressings, products for wound cleaning and accelerated wound healing and antimicrobial agents. According to the Central Statistical Office forecasts for Poland, by 2060, the population of individuals aged 65 and older is projected to exceed 10 million, and as this demographic increases, the incidence of vascular diseases, diabetes, and pressure ulcers is also expected to rise. Moreover, the incidence of ulcers has been documented to increase with age. Chronic wounds affect almost 15% of the elderly population. In Poland, approximately 3 million people have been

¹¹ R. Strohal i in., *EWMA document: Debridement. An updated overview and clarification of the principle role of debridement.*, J Wound Care 2013; 22: 5.

¹² *Diabetes in numbers*, <https://pacjent.gov.pl/artykul/cukrzyca-w-liczbach>.

¹³ *Global Atopic Dermatitis Market Size, Share, and COVID-19 Impact Analysis, By Drug Class (Biologics, PDE4 Inhibitors), By Route Of Administration (Topical, Injectable, Oral), By Region (North America, Europe, Asia-Pacific, Latin America, Middle East, and Africa), Analysis and Forecast 2021 – 2030) Global Atopic Dermatitis Market Insights Forecasts to 2030*, <https://www.sphericalinsights.com/reports/atopic-dermatitis-market>



diagnosed with diabetes, while prediabetes has been identified in around 5 million people. Consequently, the problem of infected, hard-to-heal wounds will remain a worsening concern.

Solution

Thus, how to effectively treat infected wounds? Can a thousand amputations be avoided? The solution may lie in personalized therapy and the use of selective antibacterial agents that preserve the integrity of the natural microbiome and do promote the development of resistance. This is exactly what we have to offer: AurezinR, the enzybiotic which affects exclusively *Staphylococcus* bacteria! The product will facilitate a fundamental shift in the treatment of wounds and dermatological conditions. The product can be applied in a variety of forms: as medicinal products, dressings, dermo-cosmetics. Currently applied treatment methods are mainly based on broad-spectrum antibiotics which disrupt the commensal bacterial flora and may promote the development of antibiotic resistance. Antibiotic resistance, in turn, leads to an increase in morbidity and prolonged treatment, which results in adverse social and economic effects.

Our product is a dramatic change in the approach to the treatment of infected wounds and dermatological disorders. The final version of the enzybiotic will be created based on our further research, and we intend to implement it through commercialization with interested business partners or investors. The product developed under our project has the potential to serve as an ingredient of wound dressings and wound treatment agents or dermo-cosmetics.

For our project to be successful, preclinical trials on a wide group of patients must be conducted. This requires time, collaboration with clinical departments and healthcare professionals, along with substantial financial investment. The research team of the Protein Engineering Laboratory of the MMRI PAS can boast a unique expertise and the researchers have conducted several studies which demonstrated the effectiveness of the relevant substance. The antibacterial activity and specificity of AuresineR have been demonstrated to be higher in comparison to other widely known antibacterial agents. Additional tests on the stability of the substance, resistance induction, formulation, and patient safety are necessary for the enzybiotic to be implemented in clinical practice. This can be accomplished within 48 months; however, the project's success is highly dependent on the availability of adequate funding and strategic partnerships.

Are you interested in making a significant impact on the health of millions of patients suffering from infected wounds and dermatological conditions?

We invite you to join us as a partner in the implementation of an innovative product based on the patented enzybiotic technology.

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