Intelligent Polymers

An interdisciplinary team of Polish scientists has developed innovative "smart" biomaterials to aid in the treatment of painful burn wounds.

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Burns are among the most common injuries, and one of the most painful types we can incur in daily life. While mild burns cause redness and discomfort that typically resolve within a few days, more severe burns – classified as second or third degree – require medical intervention and often extended hospitalization.

The World Health Organization (WHO) estimates that globally, approximately 11 million burn injuries each year require medical attention, with 180,000 resulting in death. Children, particularly those under five, are especially at risk. In developing countries with lower safety standards, burns are the fifth most common cause of injury in children.

When left untreated or poorly managed, burns can lead to complications such as wound infections, scarring, skin contractures, and electrolyte imbalances. In extreme cases, particularly with extensive burns, *burn shock* can occur, posing a life-threatening risk. The aftermath of burns often involves not only prolonged hospital stays, surgeries, and rehabilitation but also long-term effects on a patient's quality of life and ability to work.

Given that other medical conditions also contribute to the formation of skin wounds, the effective treatment and healing of wounds – while minimizing patient suffering – remains a major medical and societal challenge. Comprehensive, multidisciplinary approaches that reduce infections, alleviate pain, and accelerate wound healing are critical for advancing burn care.

Burn treatment methods

How burns are treated depends on the severity of skin damage, the size and location of the wound, and the stage of healing. Success largely relies on a prompt and appropriate response to the injury, along with access to suitable dressings and medical care. Effective treatment requires rapid wound cleaning and the application of a specialized dressing tailored to the wound's needs. Such dressings should protect the damaged epithelium, minimize pathogen colonization, regulate moisture, remove excess exudate, and facilitate gas exchange. Additionally, they should be stable and exhibit low adhesion to the skin.

Various types of dressings are available, including sterile gauze, hydrogels, hydrocolloid dressings, hydrofiber dressings, alginate dressings, and dressings infused with antibacterial agents such as silver, iodine, or manuka honey. Sterile dressings prevent infections, hydrogels and hydrocolloids create a moist environment conducive to healing, while alginate dressings absorb excess wound exudate. These dressings are typically made from natural polymers (e.g., chitosan, cellulose, hyaluronic acid, or gelatin) and/or synthetic polymers (e.g., PVP, PEG, PLGA).

For severe burns, the most effective treatment is a graft of the patient's own healthy skin tissue, known as an *autologous graft*. However, this approach is not feasible for large wounds. In such cases, biological or bioengineered skin substitutes become necessary. Biological dressings include allogeneic or xenogeneic skin

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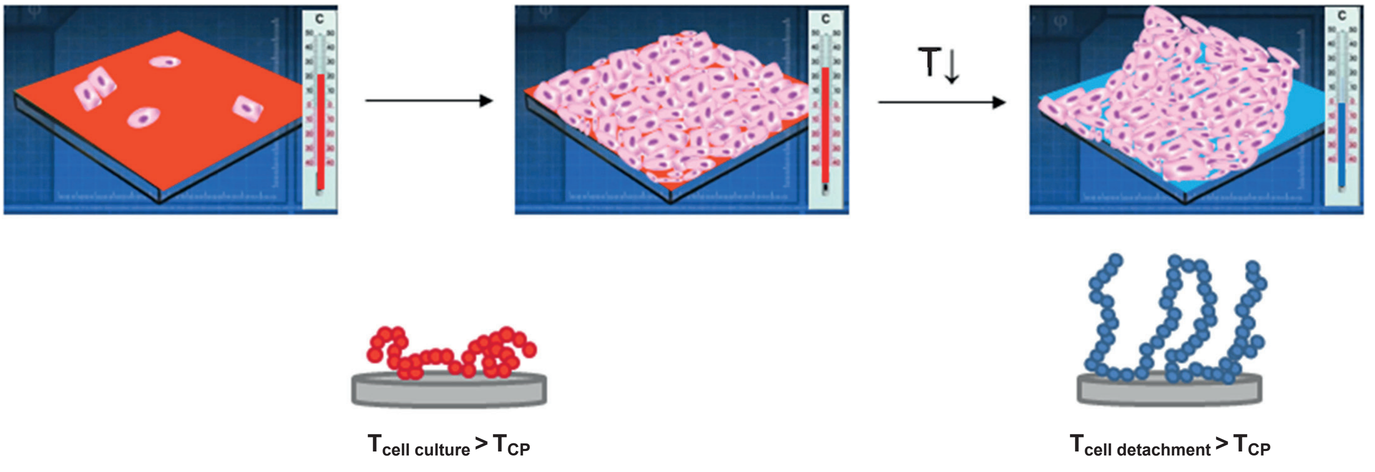
Culture and detachment of a cell sheet using a thermoresponsive polymer layer



grafts, though these carry risks such as rejection, scarring, and pathogen transmission. Other innovative skin substitutes, such as amniotic membranes, which stimulate healing, or fish skin, rich in collagen and with antibacterial properties that help reduce scarring, are also being increasingly used in wound treatment.

Bioengineered skin substitutes are materials that can be used independently and include collagen, glycosaminoglycans, polyglycolic acid, hyaluronic acid, or biodegradable polymer matrices. These materials are often enriched with skin cells – such as epithelial cells, fibroblasts, keratinocytes, and melanocytes – as well as nutrients and growth factors. This approach allows for the creation of materials that resemble natural skin more closely than traditional grafts or synthetic dressings.

However, despite advancements in wound dressings, an ideal biomaterial replicating natural skin's structure and restoring its full functionality – including pigmentation, blood vessels, and nerves – has yet to be developed. Research continues to focus on improving existing materials. The introduction of advanced systems, such as *intelligent polymer materials* (also known as "smart" polymer materials), offers hope for innovative breakthroughs in wound treatment.

Biomaterials

Intelligent polymer materials are composed of macromolecules that can reversibly respond to changes in their environment, such as temperature, pH, light, biologically active substances, or magnetic fields. In response to a stimulus, these materials can modify their structure, shape, physicochemical properties, or functionality. When used in burn wound treatment, they offer numerous promising solutions, such as active dressings that aid healing by precisely releasing and delivering substances at the right time and dose, regenerative scaffolds that support tissue reconstruction, or technologies that enable real-time wound monitoring.

For extensive burns and chronic wounds, the best treatment option is an autologous skin graft. However, this is often not feasible due to a lack of donor sites or the patient's health condition. An alternative solution involves cultivating skin cells in vitro and applying them to the wound. This approach integrates intelligent polymers with tissue engineering to produce scaffolds with thermoresponsive properties.

The essence of this procedure lies in coating the scaffold with a thermoresponsive polymer, which changes its properties under changing temperature and provides an attractive surface for skin cells. In specific cultivation conditions, cells proliferate on the scaffold, forming a sheet that includes the essential extracellular matrix. When the temperature is lowered, the cells detach easily from the surface, in the form of an intact sheet. The temperature at which an intelligent polymer undergoes a significant change in its properties is referred to as the *cloud point temperature* (T_{CP}). This method of culturing cells and harvesting them from thermoresponsive surfaces significantly reduces cell damage compared to traditional mechanical or enzymatic methods used to detach cells from the substrate.

Joining forces

The growing challenges in burn treatment have motivated the scientific community to develop scaffolds using thermoresponsive polymers to culture patient skin cells in sheet form. An interdisciplinary research team of scientists from Centre of Polymer and Car-

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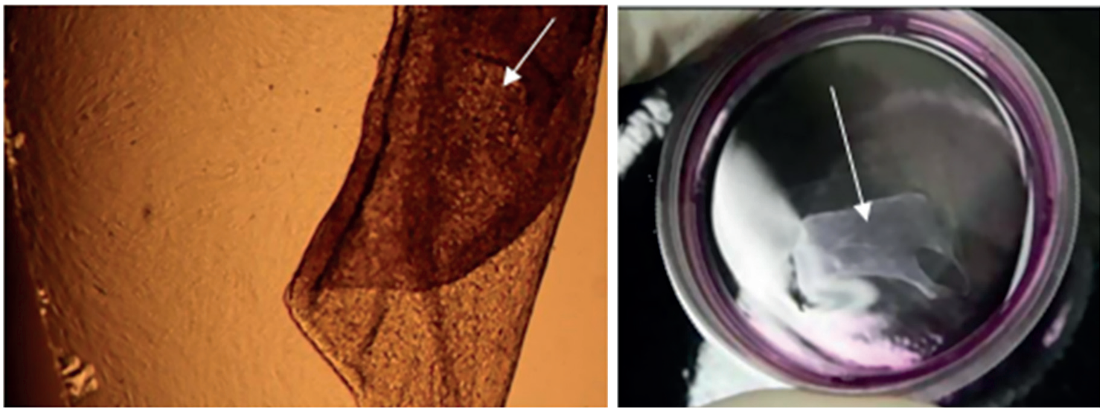
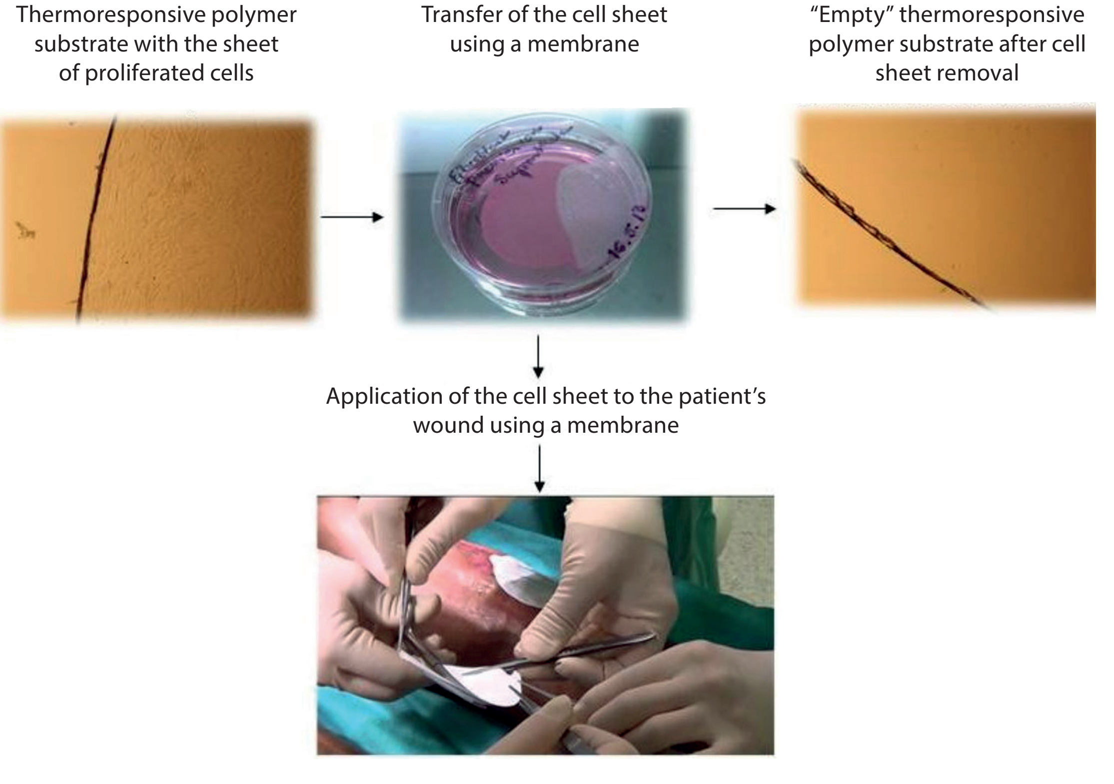
Detaching a fibroblast sheet



bon Materials of the Polish Academy of Sciences in Zabrze, the Medical University of Silesia in Katowice, and the Institute of Applied Radiation Chemistry at the Lodz University of Technology, supported by physicians from the Dr. Stanisław Sakiel Center for Burn Treatment in Siemianowice Śląskie, has been working together for years to create innovative intelligent polymer materials for tissue culture and to optimize tissue engineering methods, particularly for skin reconstruction. This collaboration has resulted in the development of synthetic substrates made from intelligent polymers enriched with biological components, successfully used for cultivating sheets of skin cells.

The thermoresponsive substrates were created using specially designed oxazoline and oligo(ethylene glycol) methacrylate polymers. At the culture temperature (37°C), the polymer layer on the substrate promoted the proliferation of fibroblasts, keratinocytes, and their co-cultures. Lowering the temperature altered the polymer layer's properties, which changed the interaction between the cells and the substrate, allowing the cells to detach as an intact sheet without damaging their structure. The properties of the intelligent polymer enabled precise manipulation of the patient's cell layers. Importantly, biological studies of the cells cultured under these conditions showed



no changes in genotoxicity or phenotype, confirming that the culture conditions were optimal and did not influence cell functionality.

These promising results led to a medical experiment conducted at the Center for Burn Treatment under hospital conditions. Autologous fibroblasts were isolated from dermis tissue collected during a graft procedure and cultured to full confluence. The resulting cell suspension was applied to a thermoresponsive substrate, and after achieving the necessary adhesion and proliferation, the fibroblast sheet was transferred to the operating room. The sheet was detached from the substrate by cooling and applied to the wound using a Suprathel membrane. Using forceps, the medical team placed the graft onto the cleansed chronic wounds on the patient's right and left lower legs. The experiment confirmed the suitability of thermoresponsive polymer substrates, demonstrating that using such cultured skin cells accelerated the wound healing of the patient.

Another innovative approach being developed by the research team involves creating a laminated dressing that combines the properties of polymer hydrogels and the amniotic membrane, which is widely used as a skin substitute in burn treatment. In this process, a physically cross-linked cryogel of poly(vinyl alcohol) was coated with an amniotic membrane. Following gamma irradiation, a sterilized polymer material permanently bonded to the amniotic membrane was obtained. Preliminary biological studies suggest that this laminated dressing is a promising alternative to the amniotic membrane alone. It combines the membrane's beneficial properties with those of a hydrogel dressing, providing a moist environment, the ability to encapsulate bioactive substances, and ease of preparation.

Choosing materials that enable the rapid and safe proliferation of large numbers of skin cells and developing effective dressings are critical for successful wound treatment. These advancements can accelerate healing and reduce the risk of complications. While intelligent polymers and their derivatives hold significant promise for burn wound treatment, further research is needed to enhance their biocompatibility and biodegradability. Additionally, the higher production costs of intelligent polymers compared to traditional dressings could be a barrier to widespread clinical use. Designing materials suitable for all stages of chronic wound healing remains a challenge, necessitating the development of multifunctional systems that release therapeutic substances and provide antimicrobial effects. The effectiveness of intelligent polymer materials must be confirmed through rigorous clinical trials, and their advantages over conventional methods must be experimentally validated. Establishing clear performance and quality control standards is also essential to ensure the safety and consistency of these products.

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Further reading:

Utrata-Wesolek A., Oleszko-Torbus N., Bochenek M., Kosowski D., Kowalczuk A., Trzebicka B., Dworak A., Thermoresponsive polymer surfaces and their application in tissue engineering, *Polimery* 2018, vol. 5.

Kawecki M., Kraut M., Klama-Baryła A., Łabuś W., Kitala D., Nowak M., Glik J., Sieroń A.L., Utrata-Wesołek A., Trzebicka B., Dworak A., Szweda D., Transfer of fibroblast sheets cultured on thermoresponsive dishes with membranes, *Journal of Materials Science: Materials in Medicine* 2016, vol. 27.

Dworak A., Utrata-Wesołek A., Oleszko N., Wałach W., Trzebicka B., Anioł J., Sieroń A.L., Klama-Baryła A., Kawecki M., Poly(2-substituted-2-oxazoline) surfaces for dermal fibroblasts adhesion and detachment, *Journal of Materials Science: Materials in Medicine* 2014, vol. 25(4).

Dworak A., Utrata-Wesołek A., Szweda D., Kowalczuk A., Trzebicka B., Anioł J., Sieroń A.L., Klama-Baryła A., Kawecki M., Poly[tri(ethylene glycol) ethyl ether methacrylate] – Coated Surfaces for Controlled Fibroblasts Culturing, *ACS Applied Materials & Interfaces* 2013, vol. 5.