

New materials for wound healing

# Skin repair kit



*If an external injury fails to get better within a few weeks, it becomes what is known as a chronic wound. Some two percent of the population in industrialized countries is afflicted by such wounds. Apart from an abundance of wound dressings, treatment options up until now have been very limited. Bayer Innovation (BIG) is currently developing an entire range of products for the treatment of these complex symptoms.*

"Pain, pain, go away..." With young children, a few words of comfort, some TLC and a plaster are often enough to help them to forget about scratches or minor cuts and grazes. This is because wound healing in those of tender years is usually straightforward and takes but a few days. The body repairs the damage virtually unaided. In later life, however, things are different. "In old age and also in conditions such as diabetes, the body is unable to get wounds to heal of their own accord," explains Dr. Burkhard Fugmann of Bayer Innovation GmbH (BIG) in Düsseldorf. He is one of the leaders of the Wound Healing project at Bayer's BIG subsidiary. He and his colleagues are looking into treatment approaches for chronic wounds – injuries that fail

to get better even after a number of weeks. For sufferers, this often means that what was initially an apparently harmless injury turns into a serious and stressful illness. Complications such as infections usually further impair the healing process.

### Cells in overdrive and a deficiency of growth factors

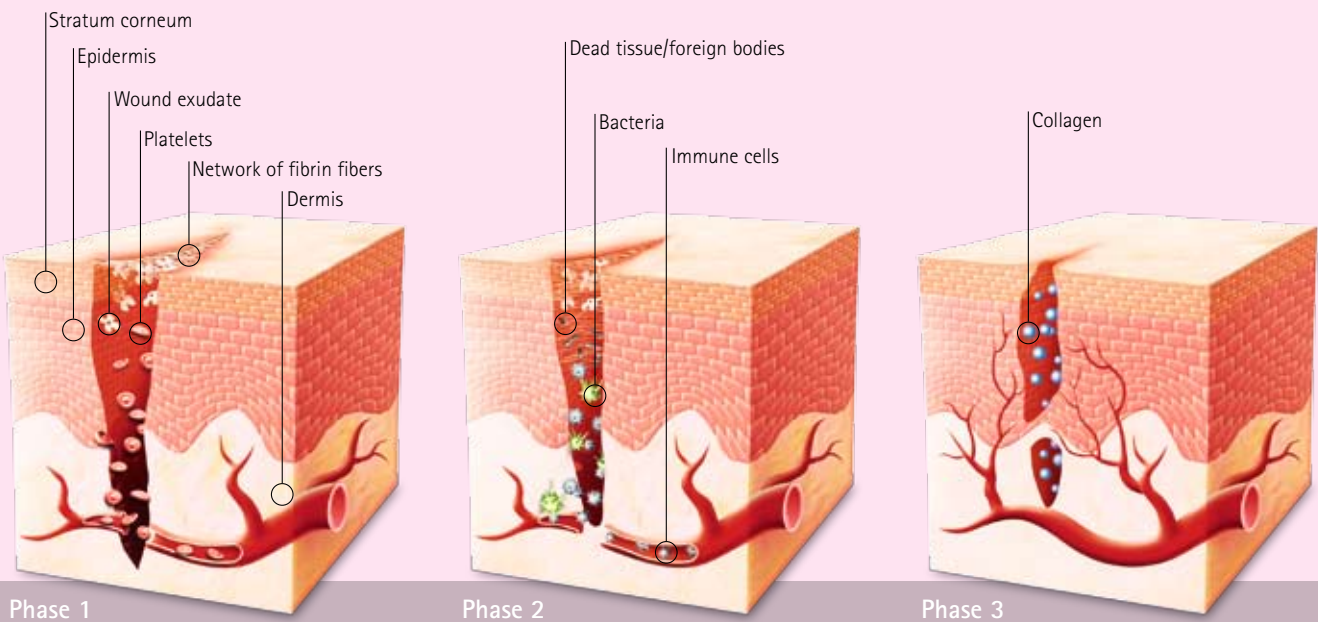
The cause of chronic wounds is an imbalance of various factors. On the one hand, cells that fuel the injury's inflammatory response and proteases (enzymes that break down protein) go into overdrive. On the other, there is a deficiency of growth factors that are needed for generating new tissue. They are destroyed

Rapid healing: wound dressings produced from novel materials (large photo) make chronic wounds heal faster. Bayer Project Managers Iwer Baecker and Dr. Burkhard Fugmann (left to right in photo, right) are coordinating the development of innovative plasters.



## Three phases of healing

Wound healing can be divided into three phases. In what is known as the coagulation and inflammation phase, blood clotting is initiated in order to stem blood flow. Wound secretion or exudate is then formed to flush pathogens and other foreign bodies out of the wound. Immune cells that have migrated to the wound likewise prevent infection by warding off germs. This inflammatory response triggers reddening and swelling of the wound area, which is often tender. At the same time, a network of fibers made of the protein fibrin is formed. One of its functions is to provide support for free skin cells. In the subsequent granulation phase, these together with the similarly fibrous protein collagen form a granular connective tissue or granulation tissue. This is transformed into mature skin only in the final regeneration phase. The silica gel wound dressings from Bayer Innovation help the wound to heal faster and promote the formation of homogenous, natural tissue.



by various agents, including proteases. These enzymes could only be blocked by suitable inhibitors which are, however, likewise in too short supply. The injured tissue is often also undersupplied with oxygen. There are various reasons why these things go wrong but a feature common to all is an underlying illness. The difficulty in getting wounds to heal is merely a consequence of this condition. "It is always necessary to treat not just the chronic wound but also the underlying disease," states Dr. Melita Dietze, co-leader of the Wound Healing project. "Failure to do so will mean that wound treatment will not be completely successful." The injuries may also nevertheless become chronic, even if the underlying disease is successfully treated.

Chronic wounds occur mainly in later life. The number of patients per year requiring treatment worldwide is already approaching 100 million, at a cost of many billions of euros. And the ever-ageing population could further magnify the problem. Research into suitable treatments is still in its infancy, however. This is why BIG's wound healing project has set itself the goal of developing new, innovative treatment methods. "We have outstanding expertise in this field in the Bayer HealthCare and Bayer Material-Science subgroups," says Fugmann, "so it's virtually a Bayer-wide initiative. Partnerships with external organizations round off the project."

One or two ideas could become ready for the market in the next few

years. For the Bayer researchers, attention is focused on three main categories: wounds in already damaged tissue, severe burns and pressure sores.

### Researchers' sights set on three wound categories

All chronic wounds are covered with wound dressings – as a barrier to invading pathogens. "Most chronic wounds contain germs," states Melita Dietze. "But provided that there is as yet no overt infection, dressing the wound is sufficient as a treatment." The dressings absorb excessive secretions, without drying out the wound. Although there are currently hundreds of different wound dressings on the market,



Germ-free production: threads are produced at high pressure from liquid silica gel and placed in molds that are laid out to dry on the changing bench by laboratory technician Kai-Michael Heuser. This results in a fibrous fleece from which the wound dressings are subsequently produced.

some requirements still remain unmet. The Bayer researchers are therefore currently developing a novel dressing made of a well-known material, silica gel. This substance has long been widely used as a food supplement and is available in tablet or capsule form as silica. In order to be able to use silica gel for wound dressings, however, it had to be produced in the form of fibers that are physically stable and yet bioabsorbable, i.e. that can be broken down within the body. This breakthrough was achieved on a laboratory scale by researchers at the Fraunhofer Institute of Silicate Research (ISC) in Würzburg. Bayer Innovation adopted this novel technology platform in late 2005 and has since been engaged in targeted product development with internal partners from Bayer HealthCare, Bayer Technology Services and Bayer Industry Services and with external partners in Europe.

On behalf of Bayer Innovation, staff at Bayer Technology Services have set

up a pilot plant in Leverkusen to produce the fibers to GMP standards. GMP stands for Good Manufacturing Practice and denotes the guidelines regulating the production of medicinal products, active substances and medical devices.

### Regeneration of blood vessels accelerated

The project managers and the scientists are agreed that the silica gel wound dressings are superior to the products currently available on the market. Various tests, for example, have shown that skin cells (fibroblasts and keratinocytes) adhere faster and better to the fiber and form new tissue. Furthermore, the three-dimensional structure of the wound closure system allows particularly rapid regeneration of blood vessels. They are particularly important to ensure that the newly formed tissue is supplied with nutrients. Wound healing takes place more swiftly than with com-

parable products and the newly formed tissue is more homogenous, has a more natural structure and is therefore of better quality.

A further advantage is that the bioabsorbable wound dressings remain stable in the wound environment for longer. In contrast, conventional bioabsorbable materials are broken down very much faster. "The material should not be broken down too quickly, as optimal cell proliferation takes place only if a minimum number of cells have docked with the scaffold," states Iwer Baecker, who heads the Bioabsorbable Silica Gel Fiber project at BIG. "If the supporting composite breaks down too rapidly or loses too much of its structure, skin cells accumulate to excess. This in turn leads to the cells being undersupplied with nutrients. The cells on the inside then eventually die and the newly formed tissue collapses." The silica gel wound dressings, on the other hand, remain in the wound both for the optimum length



Healing silica gel: this well-known material has long been used in tablet form as a dietary supplement. In association with other partners, Bayer Innovation is using this substance as a basis for the development of novel wound dressings that are absorbable within the body. Once the large sheets of fleece have dried, Kai-Michael Heuser punches pieces out of them to make individual wound dressings.

of time and with their original structure intact, before being absorbed by the body. Furthermore, active substances that further promote wound healing can be incorporated into the fibers during the manufacturing process.

### Germ-free wound dressings with active substances

Despite the virtually unlimited complexities in the production process and the various fields of application, the novel wound dressings present fewer risks. This is because, unlike many of the materials currently used, the silica gel fiber is not produced from collagen, a connective tissue protein that is obtained from human or animal tissue and may therefore be contaminated with pathogens.

Bayer's researchers have still more ideas for improving wound healing. "Up till now, all the available wound dressings have been flat," explains Fugmann. "We have therefore tried to find a material that molds itself better to the actual shape of the wound. To this end, we have initiated a joint project with

Bayer MaterialScience. With its polyurethane expertise, the development of a suitable product is looking highly promising." This, too, could additionally incorporate a special active substance that kills potential pathogens in open wounds. Some wound dressings are still coated with silver for this purpose today. This precious metal also has a harmful effect on human cells, however. Fugmann's colleagues are therefore developing products that work better against pathogens than products containing silver, yet without harming the surrounding tissue.

Bayer Innovation is also working on active substances that promote healing generally when applied to the wound. Early research worldwide in this prom-

ising market is focused on two areas in particular. Firstly, supplementation of growth factors, as levels of these in chronic wounds are too low and, secondly, inhibition of the breakdown of growth factors in the chronic wound. Researchers at Bayer Innovation want to go down both these routes, besides others. The projects are still at an early stage of development but are already showing encouraging results. So Bayer Innovation is working on several promising projects, some of which could be ready for the market in just a few years, in order to usher in a new era in wound healing. The products are to be made available individually, but will also be freely combinable, as necessary. In Fugmann's words: "a repair kit for chronic wounds".



[www.ewma.org](http://www.ewma.org)

The European Wound Management Association website has links to further information and national organizations.