PERSPECTIVE ARTICLE

Human skin wounds: A major and snowballing threat to public health and the economy

Chandan K. Sen, PhD[1]; Gayle M. Gordillo, MD[1]; Sashwati Roy, PhD[1]; Robert Kirsner, MD[2]; Lynn Lambert, CHT[1,3]; Thomas K. Hunt, MD[4]; Finn Gottrup, MD[5]; Geoffrey C. Gurtner, MD[6]; Michael T. Longaker, MD[6]

1. Department of Surgery, The Ohio State University Comprehensive Wound Center, Columbus, Ohio,
2. Department of Dermatology, University of Miami Miller School of Medicine, Miami, Florida,
3. National Healing Corporation, Boca Raton, Florida,
4. Department of Surgery, University of California-San Francisco, San Francisco, California,
5. Department of Dermatology, Copenhagen Wound Healing Center, Bispebjerg University Hospital, Copenhagen, Denmark, and
6. Department of Surgery, Stanford University School of Medicine, Stanford, California

Reprint requests:
Chandan K. Sen, Department of Surgery, The Ohio State University Comprehensive Wound Center, Columbus, OH 43210.
Email: chandan.sen@osumc.edu

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ABSTRACT

In the United States, chronic wounds affect 6.5 million patients. An estimated excess of US$25 billion is spent annually on treatment of chronic wounds and the burden is rapidly growing due to increasing health care costs, an aging population and a sharp rise in the incidence of diabetes and obesity worldwide. The annual wound care products market is projected to reach $15.3 billion by 2010. Chronic wounds are rarely seen in individuals who are otherwise healthy. In fact, chronic wound patients frequently suffer from "highly branded" diseases such as diabetes and obesity. This seems to have overshadowed the significance of wounds per se as a major health problem. For example, NIH's Research Portfolio Online Reporting Tool (RePORT; http://report.nih.gov/), directed at providing access to estimates of funding for various disease conditions does list several rare diseases but does not list wounds. Forty million inpatient surgical procedures were performed in the United States in 2000, followed closely by 31.5 million outpatient surgeries. The need for post-surgical wound care is sharply on the rise. Emergency wound care in an acute setting has major significance not only in a war setting but also in homeland preparedness against natural disasters as well as against terrorism attacks. An additional burden of wound healing is the problem of skin scarring, a $12 billion annual market. The immense economic and social impact of wounds in our society calls for allocation of a higher level of attention and resources to understand biological mechanisms underlying cutaneous wound complications.

CHRONIC WOUNDS

Chronic wounds are rarely seen in individuals who are otherwise healthy. In fact, chronic wound patients frequently suffer from ''highly branded'' diseases such as diabetes and obesity. The purpose of this article is to highlight the significance of investing in the development of wound sciences as an interdisciplinary field with lucrative translational opportunities to manage public health. The term comorbidity refers to the association of two distinct diseases in the same individual at a rate higher than expected by chance. As a result, the true impact of chronic wound is diminished. From a funding standpoint, it is seen only in parts, i.e., foot ulcers as a complication of diabetes or pressure ulcers as a complication of spinal cord injuries, and never as the sum of these parts. This seems to have overshadowed the significance of wounds per se as a major health problem. For example, NIH's Research Portfolio Online Reporting Tool (RePORT; http://report.nih.gov/), directed at providing access to estimates of funding for various disease conditions does list rare diseases such as Pick's disease but does not list wounds. Pick's disease is a rare neurodegenerative condition that is just one of the causes of the clinical syndrome now known as frontotemporal lobar degeneration.[1] Current advances in wound research have led to solutions that have markedly improved patient care.[2–8] Experimental observations have helped formulate guidelines of care providing the basis for uniform care across the United States.[9–13] Strengthening of wound healing research, in light of the rapidly growing threat, deserves a higher level of prioritization.

Chronic wounds are those that have failed to proceed through an orderly and timely reparative process to produce anatomic and functional integrity of the injured site.[14] Often disguised as a comorbid condition, chronic wounds represent a silent epidemic that affects a large fraction of the world population and poses a major and gathering threat to the public health and economy of the United States. In developed countries, it has been estimated that 1–2% of the population will experience a chronic wound during their lifetime.[15] In the United States alone, chronic wounds affect 6.5 million patients.[16,17] In the Scandinavian countries, the associated costs account for 2–4% of the total health care expenses.[18]

The burden of treating chronic wounds is growing rapidly due to increasing health care costs, an aging population and, in the United States and beyond, a sharp increase in the incidence of diabetes and obesity worldwide. It is claimed that an excess of US$25 billion is spent annually on treatment of chronic wounds.[19] To that, add the rapidly expanding need for wound care of our veterans, and the need to prioritize wound care and research would appear to be compelling. At present, over 1,000 outpatient wound centers are in operation in the United States, not including all the wound care rendered by clinicians in their offices, by inpatient acute care hospitals, long-term facilities, and nursing homes.[20] According to a new report by Global Industry Analysts, the annual wound care products market would reach US$15.3 billion by 2010. The United States represents the world's largest and the fastest growing market.[21] The amount of money spent on wound care, the loss of productivity for afflicted individuals and the families that care for them, and their diminished quality of life come at great cost to our society.

PRESSURE ULCERS

An infected pressure ulcer, secondary to spinal cord injury, caused the untimely death of the actor Christopher Reeve, known for playing "Superman." According to the National Pressure Advisory Panel, a pressure ulcer is localized injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear and/or friction. Vulnerable patients include the elderly, stroke victims, patients with diabetes, dementia, those in wheelchairs, bedridden, or suffering from impaired mobility or sensation. Paralysis on the operating room table and sedentary stays in the ICU are also situations that can initiate pressure sore development in otherwise healthy patients. Patients 65 years of age and older accounted for 72% of all patients hospitalized during which pressure ulcers were noted. Of those patients with pressure ulcers who were hospitalized, nearly nine of every 10 were covered by government health programs—66% by Medicare and 23% by State Medicaid programs. Patients with pressure ulcers are usually admitted to the hospital for a medical reason other than pressure ulcer. For patients with pressure ulcers, the most common primary diagnoses for hospitalizations include septicemia, pneumonia, urinary tract infections, congestive heart failure, respiratory failure, and complicated diabetes mellitus.[22] It appears that the prevalence of pressure ulcers increases with underlying disease. For example, in the United States, the National Pressure Ulcer Advisory Panel reports that the prevalence of pressure ulcers in a critical care setting is 22%.[23] Comparably, the prevalence of pressure ulcers among hospital inpatients in Europe is typically above 20%.[24] Almost one-third were severe ulcers at grade 3 or 4 and most (50–80%) were hospital acquired. In Scandinavia, the prevalence of open pressure ulcers vary between 13 and 27%.[25–28] In Denmark, it was found that 58% of open pressure ulcers were not documented either in the medical record or in the nurse record.[25] This merely reflects that pressure ulcers and chronic wounds tend to develop in a debilitated patient population. Even though a great deal of effort is expended to try and prevent pressure ulcers, it is still extremely difficult and expensive to adequately relieve pressure.[29–33] This is a global problem that does not seem to be unique to any specific region of the world.

Pressure ulcers can be a major source of infection and lead to complications such as septicemia, osteomyelitis, and even death. It is estimated that there are over 7.4 million pressure ulcers in the world where estimation was possible, i.e., excluding the vast number of developing countries.[34] Annually, 2.5 million pressure ulcers are treated in the United States in acute care facilities alone.[35] According to data from the Department of Health and Human Services' Agency for Healthcare Research and Quality, the number of hospitalized patients with pressure sores increased by 63% during the period 1993–2003. The price of managing a single full-thickness pressure ulcer is as much as US$70,000, and US expenditures for treating pressure ulcers have been estimated at US$11 billion per year.[36,37] During the first 2 weeks of admission alone hospital-acquired pressure ulcers occur in approximately 9% of hospitalized patients.[38] The average length of stay in the hospital for treatment of a pressure ulcer is 13 days.[22] Development of a pressure ulcer increases the mortality rate by 7.23%.[39] The additional average charge for a hospital stay per case related to pressure ulcers is US$43,180.[40] About 15% of patients in acute care facilities and up to 29% of patients in long-term care facilities will experience a pressure ulcer.[41] The development of pressure ulcers may also have important legal consequences. For example, the failure to prevent pressure ulcers in long-term care settings has resulted in increasing litigation, with settlements favoring long-term care residents in up to 87% of cases.[42,43] The number of hospital patients who develop pressure ulcers has increased by 63% over the last 10 years and nearly 60,000 deaths occur annually from hospital-acquired pressure ulcers.[44]

Pressure ulcers now have even graver implications for health care.[45] According to the Centers for Medicare and Medicaid Services (CMS), in FY2007, there were 257,412 preventable pressure ulcers reported as secondary diagnoses in hospitals.[40] Starting in October 2008, CMS no longer pays for hospital-acquired pressure ulcers,[46] because they can "reasonably be prevented through the application of evidence-based guidelines." The financial implications of this new policy are substantial. Starting in October 2008, CMS discontinued assigning a higher payment to hospitals for pressure ulcers that develop during hospitalization.[46] This proposed ruling was finalized on August 1, 2007, when CMS included pressure ulcers as one of the at least two conditions that were required to be selected. CMS refers to this as the present on-admission hospital-acquired conditions. Reduction of facility-acquired pressure ulcers and improvement of outcomes through better practices and research is therefore a matter of high priority.

THE RISING THREAT BECAUSE OF DIABETES

Over 23 million people, or 7.8% of the US population, suffer from diabetes. While 17.9 million have been diagnosed, 5.7 million are unaware that they have the disease.[47] During the period 2005–2007, the total incidence of diabetes increased by 13.5%.[48] Worldwide there are major differences in the prevalence of diabetes. The highest prevalence of diabetes was found in Nauru (30.7%) while the Middle East regions rank among the highest, with United

Arab Emirates at > 20%.[49] In Europe and the Scandinavia, the prevalence is estimated at 5–7%[24] and this is expected to increase significantly during the next 20 years, especially in the elderly.[50] In Denmark, the prevalence of diabetes (types 1 and 2) is expected to double in the next 15–20 years (the Danish Diabetic Association).

Diabetic neuropathy, defined by damage to the foot's sensory nerves, contributes to foot deformities and/or ulcers that increase the chance of lower-extremity amputations (LEAs) unless treated. It is estimated that up to 25% of all diabetics will develop a diabetic foot ulcer.[51] About 71,000 nontraumatic lower-limb amputations were performed in people with diabetes in 2004.[47] Sixty-seven percent of all LEA patients have diabetes.[52,53] At US$38,077 per amputation procedure, diabetes-related amputations cost approximately US$3 billion per year.[54] Every year 5% of diabetics develop foot ulcers and 1% require amputation.[55] Recurrence rate of diabetic foot ulcers is 66% and the amputation rate increases to 12% with subsequent ulcerations.[55] The age-adjusted LEA rate for people with diabetes (5.5 per 1,000 people with diabetes) was 28 times that of people without diabetes (0.2 per 1,000 people). Patients with diabetes-related LEAs were on average 66 years of age, while those with non–diabetes-related LEA were on average 71 years of age.[52] Amputation rates increase with age. For example, in 2003, the LEA rate per 1,000 people with diabetes was 3.9 among people under age 65, 6.6 among people aged 65–74, and 7.9 among people aged 75 or older.[56] Amputation rates are also influenced by race, with the age-adjusted LEA rate per 1,000 people with diabetes was 5.0 among blacks compared with 3.2 among whites. Additionally, it appears that men are more likely to have an amputation, with the age-adjusted LEA rate among men (5.8 per 1,000 persons with diabetes) being approximately twice that among women.[56] In Denmark, optimal vascular surgery and wound management in a multidisciplinary setup resulted in a 75% decrease in the incidence of major amputations.[18, 57]

FROM FOOT ULCERS TO AMPUTATION

The diabetic foot constitutes a tremendous challenge for patients, caregivers, and the health care system. Up to 25% of individuals with diabetes will develop a foot ulcer during their lifetime.[51] Adjusting for health-care inflation in 2007, foot ulcers cost between US$7,439 and US$20,622 per episode.[58] Ulcers and other foot complications are responsible for 20% of the nearly 3 million hospitalizations every year related to diabetes. Many of these patients eventually must undergo LEAs as a result of infection brought on by untreated foot ulcers.[59] It is estimated that 12% of individuals with a foot ulcer will require amputation.[55] The 5-year survival rate after one major LEA is about 50%.[60] Once amputation occurs, 50% of patients will develop an ulcer in the contralateral limb within 5 years.[55] According to estimates, a total of US$9 billion was spent on the treatment of diabetic foot ulcers in 2001.[61]

VENOUS ULCERS

In the United States, it has been estimated that venous ulcers cause the loss of 2 million working days per year.[62] Venous ulcers account for 70–90% of ulcers found in the lower leg.[63] The prevalence of venous ulcers in the United States is approximately 600,000 annually.[64] In individuals 65 years and older, venous leg ulcers affect approximately 1.69% of the population in the United States.[41] Venous leg ulcers cost approximately US$9,600 to treat.[41] The annual cost of treating venous ulcers to the US health care system is estimated at US$2.5–US$3.5 billion.[63] Up to one-third of treated patients experience four or more episodes of recurrence.[62] These figures are consistent with what is observed in Europe and Scandinavia. In a Spanish study with mean age of patients of 76 years, 81% of all of the leg ulcers occurred in patients over 65 years of age.[65] In Ireland, the prevalence of leg ulcers in the general population is estimated at 0.12%. This increases to 1.2% in the population over 70 years of age.[66] The cost impact of leg ulceration is not well documented in Europe and estimates differ widely in their methodology.[24] The costs of treating patients with a leg ulcer in specialized wound centers in Germany demonstrated that average cost per patient ranged from €9,900 to €10,800.[67] Most of the cost was contributed by the cost of inpatient treatment. In Scandinavia, the annual expenses per patient for treating a venous leg ulcer have been estimated to be €3,000–€6,000.[68,69] Similar to what is noted in the United States, a high recurrence rate is observed. One reason could be that it is estimated that almost half of the patients with an active open ulcer treat themselves in Sweden.[70]

THE AGING POPULATION AS AN INCREASED RISK FACTOR FOR CHRONIC WOUNDS

The biomedical and socioeconomic burdens posed by wound complications are worsened by the aging global population. The population of the aged in both Europe and the United States is expected to increase by 13–15%, even as the overall population of Europe may experience a slight decline. As the global population ages, so does the nursing home population, and this will lead to more pressure ulcers. In Europe, similar to that in the United States, aging of the population is associated with increase in the number of patients with a chronic wound. In the 17 years between 2008 and 2025, the total population of Europe is expected to increase by < 1%.[24] During this interval of time, the population aged 65 and above is expected to increase by 13% (25.5 million), and the proportion of the population aged 65 and above will increase from 17% in 2008 to 22% in 2025.[24] It is estimated that by 2050, the total population of Europe will be static or declining, while the population aged 65 and above will have increased by 50 million (59%). The number of Americans aged 45–64 has increased by 39% during this decade. The population aged 65 and over will increase from 35 million in 2000 to 40 million in 2010 (a 15% increase) and further increase to 55 million in 2020 (a 36% increase for that decade). The oldest old, those over 85 years old, is projected to increase from 4.2 million in 2000 to 6.1 million in 2010 (a 40% increase) and then to 7.3 million in 2020 (a 44% increase for that decade).[71] Peripheral artery disease, the circulatory disease commonly associated with nonhealing wounds, affects about 8 million Americans and 12–20% of Americans aged 65 and older.[72]

THE RISING THREAT BECAUSE OF OBESITY

According to the Centers for Disease Control and Prevention and World Health Organization (WHO), in adults a body mass index (BMI) of 25 or more is considered "overweight" and a BMI of 30 or more is considered "obese." In 2007, > 1.1 billion adults worldwide were overweight and 312 million of them were obese.[73] The WHO estimates that by 2015, the number of overweight people worldwide will increase to 2.3 billion and > 700 million will be obese.[72] According to the WHO, the United States ranks fifth among all countries for obesity-related deaths.[1] Two-thirds of Americans are overweight, defined as having a BMI > 25. Americans spend close to US$117 billion on obesity-related complications, with another US$33 billion spent annually in attempts to control or lose weight. Nearly half the costs of obesity are paid out by tax-supported health insurance. As the number of larger patients increases, so do the health problems related to obesity, including wound healing. Clearly, the prevalence of morbid obesity, along with related comorbidities, is sharply increasing in the United States, confounding wound care for persons at heightened risk for skin ulceration. Obesity-related changes in body systems impede wound healing.[74] Wound complications in the obese patients include infection, seromas, anastomatic leaks, and incision dehiscence. Limited tissue perfusion is also an issue of concern in most assessments.[75–77] Obesity is responsible for changes in skin barrier function, sebaceous glands and sebum production, sweat glands, lymphatics, collagen structure and function, wound healing, microcirculation and macrocirculation, and subcutaneous fat.[78] Obesity has a clear but not yet precisely defined effect on the immune response through a variety of immune mediators, which leads to susceptibility to infections.[79]

DISABILITIES AND LOST WAGES CAUSED BY CHRONIC WOUNDS

Patients suffering from chronic wounds frequently find themselves in situations of having to choose between commitments to their work and compliance with medical management for the ulcers.[80–82] Others that are less fortunate may be permanently impaired from performing their occupational job.[83,84] As a whole on an annual basis, skin disorders account for US$39 billion of lost wages and medical care involving 65 million Americans.[85] Chronic wounds lead to disability and disability worsens wound outcomes, resulting in a vicious cycle.[86] Psychological status of mobile amputees is noted to be better than that of the diabetic foot ulcer patients.[87] Disability and loss of wages related to chronic wounds represents a heavy socioeconomic burden.[88] Venous ulcers alone lead to loss of an estimated 2 million workdays/year. It may also cause early retirement, which is found in up to 12.5% of workers with venous ulcers.[89] It is estimated that chronic venous ulcers cost US$2 billion annually to lost wages and workdays.[88,90] Eighty-one percent of 73 patients interviewed with leg ulcer believed that their mobility was adversely affected by the ulcer. In younger, working patients, leg ulceration correlated with time lost from work, job loss, and adverse effects on finances. Fifty-eight percent of patients found caring for the ulcer burdensome. There was a strong correlation between time spent on ulcer care and feelings of anger and resentment. Sixty-eight percent of patients reported that the ulcer had a negative emotional impact on their lives, including feelings of fear, social isolation, anger, depression, and negative self-image.[80] Accurate assessment, prompt treatment, and suitable follow-up are essential components in minimizing the potential long-term disability caused by chronic wounds.[84,91,92] Pain is also a major problem for venous leg ulcer patients.[93] Persisting pain and pain at dressing changes is commonly encountered.[94] Pain results in lower activity, depression, irritation, and reduced social activity. Furthermore, 73% has a disturbed sleep and 50% had their mood affected. Recently a foam dressing containing Ibuprofen has been introduced in order to solve some of the pain problem.[95]

ACUTE WOUNDS

Acute wound care is indicated in all patients with surgical and traumatic wounds, abrasions, or superficial burns. Every time an incision is made a wound is created. Wound infections are the most expensive complications following surgery and still after many years are a major source of bacteria that drive the nosocomial infection rates in hospitals. We must develop and apply new concepts of preventing and treating these wound infections. According to the latest data from the National Center for Health Statistics, 40 million inpatient surgical procedures were performed in the United States in 2000, followed closely by 31.5 million outpatient surgeries. The need for postsurgical wound care is sharply on the rise with the expectation to reach more than 38.0 million by 2012.[96] Furthermore, the long-term infections that follow the implantation of prosthetic devices is currently an unconquerable problem faced by an increasing number of patients. In European hospitals, the overall rates of surgical site infection (SSI) range between 3 and 4% of patients undergoing surgery. Depending on the nature of surgery in question, the incidence of SSI ranges between < 1 and > 10%.[24] In the future, as the population ages, the incidence of SSI is expected to sharply increase because the incidence is connected to age with a doubling of the rate in patients older than 64 years.[97]

Emergency wound care in an acute setting has a major significance not only in a war setting but also in homeland preparedness against natural disasters as well as against terrorism attacks. The soft tissue and musculoskeletal systems have the highest incidence of bodily injury in survivors of bombings. The most extreme of these injuries, the traumatic amputation, is reported to occur in 1–3% of blast victims.[98] Acute wound care may be of very high value in occupational health because of the nature of related infection. An important factor in the failure of a sore to heal is the presence of multiple species of bacteria, living cooperatively in highly organized biofilms. The biofilm protects the bacteria from antibiotic therapy and the patient's immune response. Among others, cutaneous wounds lend themselves to infection by methicillin-resistant *Staphylococcus aureus*.[99] Comparison of infectious complications in patients with mutilating wounds due to trauma during corn harvesting with those in patients with factory-related hand injuries of similar severity showed that more Gram-negative rods were recovered from environmental cultures of corn-harvesting machines and corn

plants than from those of factory machinery.[100] Many species of Gram-negative bacteria are pathogenic. This pathogenic capability is usually associated with certain components of Gram-negative cell walls, in particular the lipopolysaccharide, which triggers an innate immune response characterized by cytokine production and immune system activation. Gram-negative rod infection poses a substantial public health threat, more so than that posed by factory wounds themselves. Hospital discharge data derived from the 2002 Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project were reviewed by Hostetler and colleagues to look at the demographics and health care resource utilization for this patient population. Data were collected for 55,795 injury-related hospitalizations with an acute wound, representing an estimated 272,278 such hospitalizations in the United States. Overall, 96.9% of patients had an open wound and 5.8% of those acute wound patients and 17.8% of burn wound patients were discharged to home health care. After controlling for demographics, comorbidities, and hospital characteristics, the likelihood of having an acute wound that required home health care referral was significantly increased with increased age (odds ratio [OR]: up to 10.91), insurance (OR: 2.08–7.04), diabetes (OR: 1.26–2.81), and obesity (OR: 1.41).[101] Thus, a significant number of acute wounds do not go on to resolve uneventfully and consequently utilize significant health care resources.

SCAR AND FIBROSIS

An additional burden of wound healing is the problem of scarring, which can have profound functional and aesthetic consequences.[102] Hypertrophic scarring commonly occurs following burns.[103] A scar represents the sum of the injury, the reparative process, and subsequent interventions to improve the scarring process.[104] Scars may have long-lasting functional, cosmetic, as well as psychological consequences for the patient. Both normal and hypertrophic scars remain difficult to treat and impossible to prevent. Analysts at Nomura Code, the investment bank that focuses on life sciences, ''conservatively'' estimate the market for an antiscarring drug at US$12 billion in skin application alone.[105]

EDUCATION

At present, American medical students receive very little education in the science and care of wounds during their medical studies. The mean hours of education in physiology of tissue injury at 50 American medical schools are 0.5 and 0.2 hours, respectively, in the first and second years and none in the third and fourth years. The mean hours of directed education in the physiology of wound healing are 2.1 and 1.9 hours in the first and second years.[106] In Europe, at present there is no consensus on the minimum education program necessary to qualify as an acceptable expert in wound care. For medical doctors, a standardized pregraduate and postgraduate education is essential. In Denmark, medical students have the option to follow the work at the two existing major national wound-healing centers during their rotation between specialties.[107] A specialized 2-year postgraduate wound care education program for physicians is currently under development. In Europe, different initiatives have been launched. The umbrella organization for European societies (European Wound Management Association) has developed an educational program primarily directed at nurses. It is the hope that this program will establish European standards of wound care education. Given the current and projected burden that wound-related complications may place on our public health and economy, it is important to objectively revisit the investment needs in education of wound care.

CLOSING REMARKS

The immense economic and social impact of wounds in our society calls for allocation of a higher level of research resources to understand biological mechanisms underlying the complexities noted in problem wounds. Listing of such allocation in databases such as the NIH RePORT will enable year-by-year tracking and should help attract a wider interdisciplinary interest in the science and care of wound healing. For detailed experimental queries, the development of animal models would enable in-depth study of biological mechanisms as a function of time.[108–110] Wound healing represents the outcome of a large number of interrelated biological events that are orchestrated over a temporal sequence in response to injury and its microenvironment. Investment in approaches that query global changes in wound tissue proteome,[111,112] as well as coding[109,113–115] and noncoding[116,117] genome, seems prudent. Effective application of systems biology tools[82,118] to manage vast ''omics'' datasets will facilitate supervised generation of novel hypotheses. The study of chronic wounds presented clinically is highly valuable but poses numerous practical challenges. Development of technologies such as laser capture microdissection enables the collection of ''omics'' data from single as well as multicellular regions of a tissue biopsy.[115] Approaches directed at the mathematical modeling of wound healing lend themselves to systems biology tools and have the potential to contribute to clinical wound management in the near future. Finally, the rapidly developing field of tissue engineering and stem cell biology represents the backbone of the future of wound sciences.[119,120]

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