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The P50 Research Center in Perioperative Sciences: How the investment by the National Institute of General Medical Sciences in Team Science has reduced post-burn mortality

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Abstract

Since the inception of the P50 Research Center in Peri-Operative Sciences (RCIPS) funding mechanism, the National Institute for General Medical Sciences has supported a team approach to science. Many advances in critical care, particularly burns, have been driven by RCIPS teams. In fact, burns that were fatal in the early 1970s, prior to the inception of the P50 RCIPS program, are now routinely survived as a result of the P50-funded research. The advances in clinical care that led to the reduction in post-burn death were made by optimizing resuscitation, incorporating early excision and grafting, bolstering acute care including support for inhalation injury, modulating the hypermetabolic response, augmenting the immune response, incorporating aerobic exercise, and developing anti-scarring strategies. The work of the Burn RCIPS programs advanced our understanding of the pathophysiological response to burn injury. As a result, the effects of a large burn on all organ systems have been studied, leading to the discovery of persistent dysfunction, elucidation of the underlying molecular mechanisms, and identification of potential therapeutic targets. Survival and subsequent patient satisfaction with quality of life have increased. In this review article, we describe the contributions of the Galveston P50 RCIPS that have changed post-burn care and have considerably reduced post-burn mortality.

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Introduction

Multi-disciplinary research teams have contributed to improving human health via innovative research approaches and discoveries since the early 1970s. The National Institute for General Medical Sciences (NIGMS) initiated the P50 Research Center in Injury and Peri-operative Sciences (RCIPS) funding mechanism to support research across the United States, funding 32 centers (Table 1), each of which included scientifically-related projects, core facilities, and a diverse workforce. Clinician- and translational- scientists operated in an environment that encouraged multidisciplinary collaboration and novel approaches to solving clinical problems; as investigators became leaders in the critical care arena, collaborative networks across the country were created. The impact of the RCIPS discoveries changed critical care significantly. Mortality following burns has decreased as a direct result of RCIPS funding, such that burns which were fatal prior to the inception of the RCIPS program are now routinely survived (Table 2). As a result, with burn patients surviving larger burns, establishment of therapies to improve the performance of routine daily activities and quality of life has become a priority. Here we highlight some of the Galveston P50 contributions toward burn care advancement. A list of >1,000 references from all burn RCIPS, including additional publications from Galveston's RCIPS can be found at www.totalburncare.org.

Burn Survival

Survival of a burn injury was once rare, with burns covering 20% of the total body surface area (TBSA) survived only half of the time (Table 2). The advances in our understanding of the cellular mechanisms underlying burn injury have improved the standard of care, and increased survival following burn injury (Table 2) (1–3). Now a burn covering 90% of TBSA can be survived half of the time, as opposed to 60% of TBSA in the same age group prior to 1970 and the inception of the RCIPS (1). The advances in burn treatment that have contributed to the reduction in morbidity and mortality include improved resuscitation, early excision and grafting, treatment of inhalation injury, optimized nutrition, modulation of hypermetabolism, better anti-infection treatments, improved psychosocial support, rehabilitation, and anti-scarring treatments, each of which are detailed here (Table 3).

Resuscitation

With appropriate resuscitation, survival from burn shock became routine. Optimization of resuscitation protocols revealed the importance of rapid initiation, the complications induced by delayed resuscitation, the perils of over- and under-resuscitation, the benefits of guided fluid administration, utility of enteral resuscitation (especially for mass disaster scenarios), and considerations for special populations (e.g. pediatrics, pregnancy) (2, 4–8). Characterization of the hyperdynamic phase occurring 2–3 days post-burn showed low systemic vascular resistance, elevated cardiac output, systolic dysfunction, and increased myocardial energy demand (5, 9). Heart rate and energy expenditure remain elevated for up to 3 years post-burn, suggesting that interventions to correct prolonged cardiac dysfunction are needed (10). Timely assessment of intravascular volume status and urinary output guide optimal intravascular volume, osmolality, electrolyte composition, oxygen delivery, tissue

perfusion, and colloid osmotic pressure in order to prevent and mitigate organ failure (1, 4–6, 11).

Once hemorrhage and hypovolemia could be survived, sepsis became the focus. An increase in bacterial translocation and circulating endotoxin was attributed to decreased GI mucosal blood flow. In the endotoxemic phase, treatment with either the vasodilator prostacyclin or angiotensin receptor blockade normalized mesenteric blood flow, oxygen delivery/consumption and intrahepatic venous resistance (11). Additional trials testing the efficacy and safety of therapies such as antithrombin III and peroxynitrite inhibitors, which have been tested in large animal models, are warranted.

Early Excision and Grafting of the Burn Wound

Building on Janzekovitch's establishment of early excision and grafting of the burn wound, research by RCIPS investigators established this as the standard of care. Delayed admission pushed back the timing of excision/grafting, leading to more invasive wound infections, greater incidence of sepsis, elevated inflammation, and longer hospital stays (12–14). Our studies validated the safety and superiority of early excision compared to delayed (12–14).

Despite decreased mortality due to early excision and grafting, the inability to cover large burn wounds resulting from a lack of sufficient donor sites presented a significant clinical challenge. Deep partial thickness wounds requiring three weeks to heal will likely leave hypertrophic scars and disfiguring contractures (15). For large burns, allograft is applied to burned regions until sufficient donor-site grafts can be harvested or cultured epidermal autografts created (16). Graft materials are often meshed to expand the coverage material, and are superior to cultured epidermal autografts when considering length of stay and the need for reconstruction surgeries (16). Amnion can be used to cover partial thickness facial burns without exacerbating scarring. (17) Grafts often result in scars that lack elasticity and flexibility (15). Studies have focused on ways to increase graft take, and using the porcine model of excision and grafting, the slow-clotting fibrin sealant improved graft adherence following full thickness burn (18).

Other strategies were employed to develop artificial skin substitutes to rapidly cover large wounds; "Integra™", the first synthetic human skin used to cover large burn wounds, was developed with RCIPS funding awarded to Boston's Jack Burke. Galveston investigators showed that in children, Integra™ use increased bone mineral content and density while reducing resting energy expenditure and hypertrophic scarring (19).

Additional approaches for faster burn wound healing are being explored, including human trials to confirm our preclinical demonstration of the efficacy of adipose-derived stem cells for healing burn wounds (Enkhbaatar, Finnerty, Herndon, unpublished)(20).

Inhalation Injury

Improved resuscitation permitted the survival of previously-fatal burns, unmasking the role of pulmonary insufficiency in post-burn mortality, (3) and persistence of pulmonary dysfunction for up to 8 years post-burn. Several preclinical models were developed in

Galveston to study the acute and long-term effects of an inhalation injury (21, 22). The gold standard preclinical model is an instrumented ovine survival model of severe smoke inhalation injury with positive pressure ventilation at 72 hours post-exposure (21). Modifications of this model to study burn with inhalation injury allowed testing of therapies (22), such as nebulized heparin or N-acetyl cysteine, which significantly reduced mortality and re-intubation rates in burned children. The safety of nebulized epinephrine, shown to reduce lung lymph flow and protein content in the ovine model of burn and smoke inhalation injury, has now been demonstrated in a small cohort of pediatric burned subjects (Suman, Herndon, unpublished), paving the way for larger clinical trials. Following studies of tidal volume in the ovine model, comparison of high- and low-tidal volume (15 ± 3 vs. 9 ± 3 ml/kg) in pediatric burn patients with inhalation injury (23) showed significant reductions in days on a ventilator and incidence of atelectasis and acute respiratory distress syndrome with high tidal volume, establishing rationale for a larger prospective study.

The Metabolic Stress Response to Severe Burn Trauma

Increased resting energy expenditure (i.e. hypermetabolism) is a hallmark of the stress response to severe burns, (24) and metabolic dysregulation can last for months or years. Hypermetabolism complicates the task of providing burn survivors with adequate nutrition, thereby contributing to long-term morbidity. Caloric supplementation is beneficial when energy expenditure needs are met (25). Underfeeding the hypermetabolic patient exacerbates lean body mass catabolism, while overfeeding does not reverse the catabolism, but rather leads to accrual of fat mass (25, 26). Supplementation of adequate protein carbohydrate, as opposed to fat, improves net skeletal muscle protein anabolism.

Wilmore, Pruitt, and Herndon performed pioneering work to elucidate the mediators of hypermetabolism, demonstrating a clear relationship between that degree of hypermetabolism and the extent of injury, and implicating catecholamines as novel mediators of the hypermetabolic response to burns. These early observations spawned decades of research into therapeutic strategies to blunt burn-induced hypermetabolism. The observation that conductive and evaporative heat loss from burn wounds contributed to hypermetabolism led to the development of environmental and wound management approaches that remain standards of care today. Preliminary evidence suggesting that β -adrenergic receptor (β AR) blockade may be effective in reducing metabolic rate in burn victims has been confirmed by translational studies within our RCIPS (27). The non-selective β -AR antagonist propranolol effectively mitigated the hypermetabolic response to burns (26–29).

Increased ATP turnover underlies ~55–60% of the hypermetabolic stress response to burns, meaning that oxygen consumption is outpacing ATP production at the level of the mitochondrion. Studies to define the role of mitochondria in the post-burn hypermetabolic response have shown that mitochondrial respiration becomes uncoupled from ATP production in skeletal muscle (30) and white adipose tissue from burned patients (31). In other words, mitochondria produce more heat in response to burns. These new data provide novel insight into the biochemical basis of the hypermetabolic stress response to burns, and

suggest that the mitochondrion may be a future target for strategies aimed at modulating this response.

Substrate metabolism is also profoundly altered by severe burn injury. The adrenergic stress response to burns that mediates hypermetabolism also increases circulating glycerol and fatty acids from lipolysis (32). While glycerol may serve as a gluconeogenic precursor, the chronic oversupply of fatty acids into the systemic circulation contributes to hepatic steatosis (26). The role of adrenergic stress and β 2-AR agonism in mediating hyperlipolysis was confirmed, while providing evidence that the non-selective beta blocker propranolol may effectively remedy this issue.

In addition to altered lipid metabolism, glucose homeostasis is perturbed after burn (33), as patients acutely exhibit a phenomena termed stress-induced diabetes and may exhibit impaired glucose tolerance and hyperinsulinemia for months to years post burn (34, 35). Loss of central (hepatic) insulin sensitivity has been implicated as the principal contributor to poor glucose control post injury, as basal glucose release from the liver is elevated with obligatory gluconeogenesis due to increased Cori and Cahill cycle fluxes. In addition to a loss of central insulin sensitivity, the capacity for insulin stimulated glucose disposal in peripheral tissue, namely skeletal muscle, may also be diminished following severe burns. Whether this detriment in insulin sensitivity at the level of skeletal muscle is brought about by burn injury alone or through aftereffects following burn injury including infection, muscle catabolism, or enforced immobilization is difficult to delineate. Adherence to an intensive insulin protocol to maintain tight glycemic control can ameliorate this insulin resistance, however, the risk of hypoglycemia has prompted the investigation of other glucose-controlling strategies (34, 36). Fenofibrate and metformin may be useful strategies to restore central and peripheral insulin sensitivity in severely burned children (37, 38). Decreased total body fat and subcutaneous peripheral fat, in concert with prolonged systemic inflammation may drive persistent insulin resistance and predispose burn patients to subsequent cardiovascular disease and type 2 diabetes (39). Interestingly, mild obesity confers a survival benefit to burned adults, but not children, while morbid obesity has the highest mortality (40).

Altered protein metabolism is well documented in patients with massive burns and injuries (41). Herndon, Wolfe and colleagues utilized stable isotopes to trace protein metabolism in burn patients *in vivo*. These studies have contributed hugely to the understanding of burn-induced muscle catabolism and have aided in the development of therapeutic strategies for restoration of muscle mass and function following burn. Through an arterial-venous balance approach and infusion of stable isotopes of the amino acids phenylalanine, leucine, lysine, and valine, Biolo demonstrated that proteolysis was the principal mediator of altered skeletal muscle proteins turnover in burned adults. Subsequent work has underscored this finding, demonstrating that elevated muscle protein turnover persists for up to one year post burn (42). Furthermore, using five-pool modeling of amino acid kinetics in the arterial and venous blood, skeletal muscle, wound, and healthy skin, Gore and colleagues demonstrated that the marked efflux of amino acids from skeletal muscle into the blood was paralleled by a huge deposition of amino acids in burn wounds, suggesting that muscle proteolysis may support wound healing in burn patients (41).

Modulating the Hypermetabolic Response

The over-arching goal of the Galveston P50 has been to modulate the post-burn hypermetabolic response with a number of pharmacological strategies that acted by blunting muscle protein wasting, increasing muscle anabolism, or decreasing hyperglycemia, with agents that can promote the long-term restoration of muscle mass and function (23, 27, 29, 43–52).

One such agent, propranolol, is a nonselective β AR antagonist that attenuates the actions of catecholamines and limits hypermetabolism and hypercatabolism after burn, (26, 53) and stimulates muscle protein accretion (26). In burned patients, propranolol reduced tachycardia (26, 53, 54) and the percent predicted heart rate (27), attenuated resting energy expenditure (26, 53, 55), and decreased cardiac work, stress, and output (36). Propranolol also reduces cardiac stress by decreasing cardiac index in burn patients without adversely affecting peripheral perfusion (56). Improvements in body composition were also seen following propranolol administration, with resultant improvements in lean body mass (27), decreased accumulation of central fat (27), and reduced bone loss (27). With propranolol administration, blood loss was reduced during skin grafting procedures, and the number of days between procedures was less, indicating improved donor site wound healing in propranolol-treated patients (54). Mechanistic studies in the rabbit showed that propranolol increases wound healing by inducing the synthetic rate of wound protein (57). Systemic inflammation was also attenuated, with decrements in circulating concentrations of tumor necrosis factor – alpha (TNF- α) and interleukin-1 β (IL-1 β) (55). Murine models suggest that the use of propranolol may lead to increased risk of mortality in septic patients, although studies of propranolol in human burn patients showed no increased risk of infections, sepsis, or mortality (55).

Oxandrolone is a synthetic dihydrotestosterone derivative that, in the severely burned, decreases length of stay (58), improves lean body mass and muscle accretion (44, 58), increases bone mineral content and bone mineral density (45), enhances wound healing, accelerates growth rate (46), decreases the risk of osteoporosis (46), reduces protein breakdown (59), improves muscle strength (44), and improves lung function (48). In burned adults, administration of oxandrolone within 7 days of injury decreased mortality compared to untreated controls (60). In the pediatric population, oxandrolone is less virilizing than testosterone, has minimal hepatotoxicity, and is non-aromatizable, preventing conversion to estrogen and estrogen-dependent early growth plate closure in long bones (46). The benefits of oxandrolone administration persist for several years after the drug is no longer being given (43, 46, 61) and administration for two years post-burn may have even greater improvements (46).

Administration of recombinant human growth hormone (rhGH) decreased catabolism alongside increased protein synthesis, resulting in both muscle and bone growth. Patients in the rhGH cohort also experienced decreased length of stay, fewer reconstructive surgeries, and improved skin-graft donor site healing. Body composition changes attributed to rhGH included an increase in lean body mass in addition to the rhGH-treated patients attaining greater height and weight (62). Decreases in acute phase proteins, TNF- α , and IL-1 β ,

alongside increases in IGF-1, and constitutive hepatic proteins were reported with rhGH administration (63).

The effects of growth hormone are mediated via the stimulation of insulin-like growth factor 1 (IGF-1) and its binding protein, IGFBP-3. In pediatric burn patients, the administration of both IGF-1 and IGFBP-3 resulted in improved protein metabolism without hypoglycemia, one of the side effects of the administration of recombinant human growth hormone. This combination also attenuated type I and II hepatic acute phase responses, increased levels of constitutive serum protein levels, and decreased post-burn muscle catabolism (64).

Insulin administration improves clinical outcomes such as bone mineral content and muscle strength in severely burned patients (34). The use of insulin as an anti-hyperglycemia therapy in this population resulted in improved donor site healing, increased muscle protein synthesis, and decreased lean body mass loss and acute-phase responses (65, 66). When blood glucose concentrations were reduced to 130 mg/dl, significant reductions in the incidence of infections, sepsis, and mortality occurred in addition to the attenuation of the post-burn hypermetabolic and inflammatory responses (65). The increased incidence of hypoglycemia with insulin administration, and an increase in mortality (34, 65), however, led to the evaluation of other anti-hyperglycemic strategies, including metformin and fenofibrate. Metformin, a biguanide drug, has been used to control post-burn hyperglycemia without the increased risk of hypoglycemic episodes (65, 67). A randomized study showed that metformin improves glucose control by decreasing endogenous production of glucose and by increasing peripheral glucose clearance and oxidation (38, 67). In burned patients, muscle protein fractional synthetic rate increased with metformin administration, and net protein balance improved (38). Acute administration of fenofibrate increased insulin sensitivity and insulin receptor signaling, with decreased plasma glucose concentrations and increased mitochondrial ATP production (37).

The role of hypercortisolemia in the post-burn response was examined via administration of the cortisol synthesis inhibitor ketoconazole (68). Although cortisol production was significantly reduced, ketoconazole did not affect the catabolic, inflammatory, or hypermetabolic responses, indicating that high levels of cortisol may not contribute significantly toward the post-burn hypermetabolic response.

Combinations of the drugs described above were also trialed to determine whether the combination could be more efficacious than the individual therapies. In order to test the hypothesis that co-administration of propranolol and rhGH would synergistically reduce hypermetabolism and catabolism to markedly improve patient outcomes, a small pilot study was performed. The significant reduction of heart rate and rate of free fatty acid release supported this hypothesis. However, later studies in larger cohorts did not confirm the benefits of combined propranolol and rhGH therapy (53, 63). Similarly, the combination of propranolol with rhGH did not improve anabolism over the effect achieved with propranolol alone (53), however, peripheral lipolysis and inflammation – two side effects attributed to the administration of rhGH, were significantly reduced with the co-administration of propranolol (63). Although propranolol did diminish the side effects induced by rhGH, synergy in the mechanisms of action was not found.

The combination of propranolol with oxandrolone has demonstrated synergism; the post-burn growth arrest was attenuated, and the subsequent growth rate significantly improved with the combined administration of oxandrolone and propranolol (61). Further study of the effects of propranolol in combination with oxandrolone are needed to determine how adults are affected, the effects on hypertrophic scarring and other tissue-specific responses, and to determine the sex-dependence of outcomes following the administration of this androgen to female and male burn patients.

Infection, Inflammation, and Altered Immunity

Infection and sepsis are now the leading causes of death following burn injury and substantially influence morbidity in surviving patients. Within minutes of a major burn injury, profound immune alterations occur, rendering the host unable to generate novel cell-mediated immune responses. The host is left dependent on innate immunity and existing responses, with increased mortality observed when these remaining mechanisms are defective or rendered inactive (69). Accordingly, stimulation of the remaining functional immune mechanisms has been investigated in response to viruses, bacteria, and fungi that are problematic for burned patients (20, 69–71). Burn-induced immune alterations also include decreased natural killer cell activity, (69, 70) and the formation of immunologically anergic M2b monocytes in peripheral blood (72, 73). The formation of these anergic monocytes is induced by catecholamines, but can be blocked by propranolol administration in burned children (74).

Burn also impairs the antigen-specific adaptive system. Burn-associated T cells (BA2T cells, CD8+, CD11b+, γ/δ +) mediate increased susceptibility to viral pathogens, *Candida albicans*, cytomegalovirus, and other opportunistic pathogens (71); the actions of these cells are countered by regulatory T cells (CD4+, CD28+ T cell receptor α/β) during healing, and can be countered by IL-12. Greater understanding of post-burn alterations in host immunity will allow improvements burn care and survival. To this end, the genomic response to burn in white blood cells involves the majority of the genome with enduring perturbations (75). The unique differences in the genomic response to burns in mice and humans (76) emphasize the importance of conducting experiments in animal models, such as our humanized mouse model (70), or with cells obtained from patients (72, 73).

The past decade of biomarker research has resulted in the elucidation of characteristic post-burn protein expression profiles. Systemic release of large quantities of pro- and anti-inflammatory proteins affect organ function, immune function, and the hypermetabolic and hypercatabolic responses (77–81). Understanding the post-burn release of inflammatory mediators may be essential to predict untoward outcomes and provide treatment personalized to optimize outcomes (77–81). Sixteen cytokines are elevated immediately following burn injury (79, 82), with some perturbations persisting (18). The most favorable window for intervention appears to be during the first post-burn week when release of inflammatory proteins is greatest (79, 82). Plasma protein expression, and the accompanying hypermetabolic response, vary with sex (83), presenting a potential barometer for monitoring efficacy of various interventions. Early elevation of cytokine expression was indicative of future sepsis development, with elevated IL-6 and IL-12 p70 and lower TNF

indicating an elevated risk of death by sepsis (77). Additional work demonstrated an association between IL-8 concentrations and infection risk (84). Similar studies confirmed the predictive potential of cytokine expression for inhalation trauma (77) and survival (80, 81). We have not yet determined how best to modulate this pathophysiological response to improve outcomes, although agents such as propranolol, oxandrolone, insulin, and recombinant growth hormone impact cytokine release (27, 43, 55, 58, 63, 65).

Additional plasma proteins modulated by burn injury may be predictive of death (80). Similarly, triglyceride elevation was associated with poor post-burn outcomes, including increased inflammation and hypermetabolism (32). C-reactive protein, a marker of post-burn inflammation, is not an adequate marker for infection and sepsis in the severely burned patient. The accuracy of prediction of patient outcome based on clinical characteristics such as burn size, presence of inhalation injury, and patient age can be improved upon by incorporating expression of a panel of biomarkers, including acute phase proteins, cytokines, and clinical chemistries, into the predictive models (80, 81).

Post-Burn Exercise

The importance of strengthening the patient's physical condition became a crucial aspect of recovery upon realization of the reduction of daily activities in burn survivors (85). The first exercise program improved strength and muscle function, and demonstrated that a structured exercise program during the rehabilitative stage led to beneficial results in the severely burned (51). The program included moderate intensity, progressive resistance and aerobic exercises and was conducted three times a week for twelve weeks (51). The twelve week in-hospital exercise program led to improvements in cardiopulmonary and muscle function, which were still lower in burned survivors randomized to exercise when compared to a non-burned control group, but significantly higher in relation to the non-exercise group of burned children (50). Recent work suggests that despite activation of the satellite cells, the stem cells responsible for skeletal muscle regeneration, by burn injury a concurrent increase in apoptosis of these cells results in a net loss of the cells needed to regenerate lean muscle tissue (41). The combination of exercise programs with other approaches for improving physical outcome was also tested. Patients receiving growth hormone and enrolled in an exercise program had greater muscle strength following the conclusion of a twelve week exercise program (52). However, this study also identified that exercise in the burn patient had to be studied further as body temperature elevations may not be compensated for correctly in these patients (86). One of the next studies established practice guidelines for safely exercising: controlled exercise programs with moderately-intense exercises for not more than 20 minutes, in an environment kept at room temperature (22°C), in patients with less than 75% of TBSA burned. (86) The benefits of participating in an exercise program persisted beyond the period while the patient was actively participating; three months after discharge, lean body mass and muscle strength remained significantly higher compared to the non-exercise control group (49). This benefit is lost by two years post-burn, suggesting that continuing exercise maintenance programs after discharge would benefit severely burned children even more (87). Additional studies in children less than 7 years of age, demonstrated that the addition of music or oxandrolone to the exercise regimen synergistically improved outcomes (44, 88). Exercise programs, in conjunction with general

wellness programs, also improve psychological outcomes (47). Exercise was initially started 6–9 months post-burn, transitioned to immediately post-discharge, and now is being studied for even earlier implementation.

Despite the myriad benefits of exercise training to severely burned patients, exercise programs are not the standard of care at most institutions. Due to the utility of exercise in restoring function in burn survivors, we advocate the incorporation of structured exercise programs into the outpatient care following discharge from the acute unit. Indeed, early outpatient exercise training implemented at the time of hospital discharge represents an additional intervention for the improvement of muscle mass and function after severe burn injury (87). Further, alternative rehabilitation achieved via community based training programs conducted in centers close to the patient's home enables improvements in body lean mass, strength, and cardiopulmonary capacity (89).

Post-Burn Hypertrophic Scarring

Quality of life in burn survivors may be compromised due to the physical appearance of scars, reduced function of scarred joints, or by persistent itch and pain emanating from scars (90). Lessening the impact of the extensive scarring that affects 70–90% of severely burned patients has become a research priority, prompting the development of reliable animal models to study post-burn wound healing and hypertrophic scarring (15, 18, 91, 92) to parallel studies of the patients themselves.

Various strategies have been trialed to reduce post-burn scarring in the clinic (15–17, 19). Burn patients who develop hypertrophic scarring frequently have delayed wound healing due to chronic inflammation or infection (15). One of the most effective methods for reducing inflammation in the burn wound, early excision and grafting, also reduces hypertrophic scarring (12–14). Splints were widely used in the past to minimize scar contraction and hypertrophy (93). Pressure garments have also been efficacious for reducing scarring, but should be worn for up to 2 years post-burn or until the scar matures (15). Additional effective therapies for reducing the already formed post-burn hypertrophic scar include surgical release, laser therapy, or sub- and intracuticular fat injection (20).

Scar severity can be assessed with photographic planimetry and evaluation using various scar scoring scales (94, 95). A scale for assessing photographs of post-burn scarring was validated in severely burned children (95). Assessment of scar color and pigmentation is possible with the derma-spectrometer and chromometer, while the pneumatonometer and durometer measure scar pliability, and scar vascularity and perfusion can be estimated with laser doppler ultrasound (94).

These methods were used to assess the effects of administration of 0.05 mg/kg/day rhGH for one year compared to placebo on hypertrophic scarring (96). Although scar severity was similar in both groups, donor site healing time decreased significantly in GH-treated patients (96). Patients receiving rhGH underwent significantly fewer reconstructive surgeries, indicating a reduction in function-impairing scar contractures in the rhGH-treated patients. Significant reduction of scarring was achieved with 0.1 and 0.2 mg/kg/d rhGH (62). This

decrease in scarring is attributed to increased patient activity and use of affected joints during the scar maturation phase in rhGH-treated patients.

Chronic increases in catecholamine concentrations following burn injury may be the main culprit underlying increased post-burn hypermetabolism, elevated inflammation, and hypertrophic scarring. Catecholamines act on cell proliferation and extracellular matrix remodeling mainly through the beta-adrenergic receptors. Studies have demonstrated that wound protein synthesis can be bolstered with propranolol treatment (57); use of propranolol decreases the average number of days between skin grafting procedures – which suggests faster donor site wound healing in patients randomized to propranolol (54). Studies into the effect of propranolol on hypertrophic scarring are continuing.

To understand the molecular mechanisms underlying post-burn hypertrophic scarring, dermal fibroblasts from hypertrophic scars and non burned skin from burned patients have been used to elucidate the roles of various signaling pathways in the fibrotic response (15, 97, 98). The role of IL-6 trans-signaling STAT3, BRD4, and CDC9 in mediating extracellular matrix production and myofibroblast transdifferentiation in post-burn scar have recently been elucidated (98). The reduced sensitivity of fibroblasts from hypertrophic scar to IL-6 may effectively suppress extracellular matrix remodeling, leading to excessive collagen accumulation. Smad 2 and Smad ubiquitination regulatory factor 2 (Smurf2), mediators of TGF- β activity, were also implicated in the progression of hypertrophic scarring (97). Collagen III accumulation in post-burn scars is greater than in non hypertrophic scars for up to 24 months post-injury. During this same time frame, collagen I protein expression does not change, suggesting that collagen III can be useful for differentiating between hypertrophic and non- hypertrophic scars (99), and may serve as an indicator of therapeutic efficacy.

Conclusion

The NIGMS investment in research infrastructure, including administrative and clinical research support, database curation, biospecimen repositories, and an established network of clinical research sites capable of performing complex clinical trials, enabled the success of the RCIPS programs. Specialized techniques developed through the projects and cores benefitted the larger research community, including stable isotope methodologies; microfluidics, proteomics, immunologic, and genomics technologies; and animal models of burn, infection, and inhalation injury (5, 11, 17–19, 21, 23, 25, 26, 30, 31, 38, 70, 75, 76, 80, 88, 91, 93–95, 99). The Burn P50 RCIPs, along with the associated post-doctoral T32 training grants, P01 program project grants, and multi-institutional U54 grants funded by the NIGMS, and more recently, the Clinical and Translational Science Award (CTSA) from the NCATS, have expanded our understanding of burn pathophysiology, and importantly have improved the care of the severely burned (Table 3), reducing morbidity and mortality in the severely burned. The life-saving advancements would not have occurred in such a short period of time without P50 RCIPS funding and the creation of research centers that became the foci of burn and critical illness research and care. Other acute care surgery fields could benefit from similar focused funding for team science to support major advancements in patient outcomes.

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Table 1
National Institute for General Medical Sciences P50 Research Centers in Peri-operative Sciences.

Project No.	Year P50 Founded	Title	PIs	Institution	Papers
GM021700	1974	Burn Trauma Center	Burke, John Tompkins, Ronald Gary	Massachusetts General Hospital	773
GM017961	1975	Body Compositional Changes in Severe Trauma	Hardy, James D.	University of Mississippi Med Ctr	73
GM022550	1975	Burn Research Center	Curren, P. William Carrico, Charles J.	University of Washington	132
GM015428	1975	Center for Comprehensive Clinical Study of Trauma	Altmeier, William A.	University of Cincinnati	209
GM014546	1975	Influence of Acute Illness and Injury on Energy Exchange	Kinney, John M.	Columbia University	172
GM015426	1975	On-Line Computer Study of Therapy for Human Shock	Powers, Samuel R. Bourke, Robert S. Shah, Dhirajm Fortune, John B.	Albany Medical College	453
GM015768	1975	Sequence of Organ Failures Following Trauma	Border, John R. Schenk, Worthington G	State University of New York at Buffalo	98
GM017366	1975	The Effects and Treatment of Major Trauma	Egdahl, Richard H. O'Hern, Jane S.	Boston University Medical Campus	60
GM018470	1975	Trauma Center Project	Blaisdell, F. William Sheldon, George Trunkey, Donald D.	University of California, San Francisco	420
GM021797	1976	Program Study of the Traumatized Patient	Carrico, Charles J.	University of Washington	65
GM023095	1976	Trauma and Burn Research Center	Moody, Frank G. Warden, Glenn	University of Utah	413
GM024990	1978	Systemic Response to Mechanical and Thermal Injury	Carrico, Charles J.	University of Washington	62
GM026145	1979	Burn and Trauma Research Center	Curren, P. William Shires, G. Tom; Goodwin, Cleon W.	Weill Medical College of Cornell University	279
GM027345	1980	A Study of Wound Healing and Wound Infection	Hunt, Thomas K. Banda, Michael J.	University of California, San Francisco	229
GM021681	1980	Circulatory and Fluid Volume Changes in Burns	Baxter, Charles R.	UT Southwestern Medical Center	77

Project No.	Year P50 Founded	Title	PIs	Institution	Papers
GM029327	1981	Trauma—Regulators & Modulators of the Catabolic State	Wilmore, Douglas W.	Brigham and Women's Hospital	195
GM036428	1985	Trauma—Regulators and Modulators of Catabolic State	Wilmore, Douglas W.	Brigham and Women's Hospital	173
GM038529	1987	Pathogenesis of Multiple Organ Failure	Moody, Frank G.	University of Texas Health Science Center Houston	61
GM049222	1993	Trauma Primes Cells	Harken, Alden H.	University of Colorado Denver	222
GM038529	1994	Pathogenesis of Multiple Organ Failure	Moore, Frederick A.	University of Texas Health Science Center Houston	877
			Mercer, David W.		
			Holcomb, John B.		
			Moody, Frank G.		
GM027345	1995	A Study of Wound Healing, Inflammation, and Infection	Hunt, Thomas K.	University of California, San Francisco	92
GM052585	1995	Augmented Injury Due to Autologous Inflammatory Attack	Moore, Francis D.	Brigham and Women's Hospital	105
GM021700	1995	Burn Trauma Center	Tompkins, Ronald Gary	Massachusetts General Hospital	281
GM021681	1995	Pathophysiological, Biochemical Changes of Thermal Injury	Horton, Jureta W.	UT Southwestern Medical Center	231
			Idris, Ahamed H.		
			Nwariaku, Fiemu E.		
			Baxter, Charles R.		
GM049222	1995	Trauma Primes Cells	Banerjee, Anirban;	University of Colorado Denver	207
			Harken, Alden H.		
GM053789	1996	Mechanisms of Trauma-Induced Immune Dysregulation	Billia, Timothy R.	University of Pittsburgh at Pittsburgh	496
GM060338	2000	Assess Anabolic Agents/Exercise in Burned Children	Herndon, David N.	University of Texas Medical Branch at Galveston	508
GM069790	2004	Mesenteric Lymph Linking Gut & Distant Organ Injury	Deitch, Edwin A.	University of Med/Dent of NJ—NJ Medical School	141
GM076659	2006	Protocolized Care for Early Septic Shock (ProCESS)	Angus, Derek C.	University of Pittsburgh at Pittsburgh	254
GM111152	2014	PICS: A New Horizon for Surgical Critical Care	Moore, Frederick A.	University of Florida	46

Table 2Survival from burn injury through the years by age group.[/]

Group/Institution	LA ₅₀ (%)			
	0–14 years	15–44 years	45–64 years	>65 years
Bull & Fisher (1942–1952)	49	46	27	10
2807 Patients	(n = 1366)	(n = 967)	(n = 330)	(n = 144)
Bull (1967–1970)	64	56	40	17
1917 Patients	(n = 962)	(n = 565)	(n = 246)	(n = 144)
Curreri & Abston (1975–1979)	77	63	38	23
1508 Patients	(n = 803)	(n = 413)	(n = 178)	(n = 114)
SHC/UTMB (1980–89)	98	70	46	19
2164 Patients	(n = 1524)	(n = 450)	(n = 127)	(n = 63)
SHC/UTMB (1989–2013)	98	82	78	35
1722 Patients	(n = 1083)	(n = 420)	(n = 152)	(n = 67)

[/]Survival depicted as the burn area lethal to 50% of patients.Abbreviations: LA₅₀, burn area lethal to 50% of patients; SHC, Shriners Hospitals for Children®—Galveston; UTMB, University of Texas Medical Branch

Table 3

Status of contributions of Burn RCIPS programs to improving burn care

Contribution	Status
Optimized resuscitation	SOC
Comprehensive volume status assessment and hemodynamic monitoring with Pulse index Continuous Cardiac Output	SOC-G
Guided fluid resuscitation with decision support system	RCU-G, adult patients Investigational for others
Early excision and grafting	SOC
Cultured epithelial autograft as a salvage procedure for massive burns	As needed when other approaches unsuccessful
Amnion for face	RCU-G
Fibrin sealant for graft adherence	RCU-G
Integra	RCU
Adipose derived stem cells for use on burn wounds	Investigational
Nebulized heparin	SOC
N-acetyl cysteine	SOC
Nebulized epinephrine	Investigational
Greater tidal volume	Investigational
Caloric supplementation guided via resting energy expenditure and Galveston formula	SOC-G
Beta-blockade with propranolol to attenuate the hypermetabolic response	SOC-G for pediatric patients Investigational for adults
Oxandrolone	SOC at some burn hospitals
Oxandrolone / Propranolol	Investigational
Supplemental Insulin to control hyperglycemia	SOC
IGF1/BP3	Investigational
Fenofibrate	Investigational
Metformin	Investigational
Growth hormone	Investigational
Growth hormone + propranolol	Investigational
Biomarkers to guide treatment	Investigational

Contribution	Status
Splints for immobilization	SOC
Pressure garments	SOC
Surgical release of scar	SOC
Fat injections to mitigate scarring	Investigational
Laser therapy	RCU
Scar assessments photographically & with devices	Investigational
Exercise program with aerobic & resistance components	SOC-G
Exercise with music	Investigational
Early exercise while in ICU	Investigational

Standard of Care (SOC): widely considered standard of care for treating burns patients

SOC-G: standard of care in Galveston burn units

Routine clinical use (RCU): frequently used technique but may not be the standard of care

RCU-G: in routine clinical use in Galveston

Investigational: in clinical trials or needing further investigation