

# Matrix Therapy with RGTA OTR4120 Improves Healing Time and Quality in Hairless Rats with Deep Second-Degree Burns

Gilbert Zakine, M.D., Ph.D.

Véronique Barbier, Ph.D.

Stéphanie Garcia-Filipe,  
Ph.D.

Jacqueline Luboinski, M.D.

Dulce Papy-Garcia, Ph.D.

Juan Carlos Chachques,  
M.D., Ph.D.

Alain Carpentier, M.D.,  
Ph.D.

Denis Barritault, Ph.D.

Tours, Créteil, and Paris, France

**Background:** ReGeneraTing Agents (RGTA) are biodegradable polymers engineered to mimic heparan-sulfate in the extracellular matrix of damaged tissue. RGTA improves tissue healing in several animal models by stabilizing and protecting heparin-binding growth factors and matrix proteins. RGTA restores the normal matrix architecture and supports tissue regeneration. In this study, the authors evaluated the effects of RGTA on epidermal repair and dermal remodeling in a rat burn model.

**Methods:** Deep second-degree burns were induced in 156 hairless rats, of which half ( $n = 78$ ) received topical and intramuscular RGTA immediately after the burn followed by intramuscular RGTA weekly for 1 month. The controls ( $n = 78$ ) received saline according to the same protocol. Rats were killed starting on each day of the first week and on days 14, 28, 60, 120, 240, and 365. The burns were evaluated by photography, histology, and immunohistochemistry.

**Results:** Coagulation necrosis involved the entire epidermis and superficial adnexa. Compared with the controls, speed of epidermal repair, as assessed between days 3 and 7 based on cell-layer number and anticytokeratin-14 staining, was faster in the RGTA group; and the zone of stasis, as assessed based on secondary vascular lesions in the dermis, was smaller. On day 7, reepithelialization was complete in both groups. On days 14 and 28, the remodeled dermal zone was smaller in the RGTA group.

**Conclusion:** RGTA accelerated epidermal repair and protected the dermis from secondary effects of heat as quantified by zone-of-stasis size and extent of dermal remodeling. (*Plast. Reconstr. Surg.* 127: 541, 2011.)

**A**fter a thermal burn injury to the skin, the epidermis heals from the keratinocytes of the adnexa and basal layer. The dermis undergoes prolonged remodeling, healing from the fibroblasts. Healing is regulated by growth factors, which are polypeptides produced by various cell

types in response to tissue injury. Growth factors stimulate cell proliferation, migration, and differentiation. They play a major role in burn injury healing, being expressed during the phases of proliferation, migration, matrix synthesis, and contraction.<sup>1-5</sup> Significant acceleration of healing in several animal models of wound repair<sup>6,7</sup> and in a partial-thickness burn-repair model<sup>8,9</sup> was obtained by topically applying recombinant growth factors such as epidermal growth factor, keratinocyte growth factor, basic fibroblast growth factor (bFGF), transforming growth factor (TGF)- $\alpha$ , and platelet-derived growth factor (PDGF).

*From the Plastic, Reconstructive, and Cosmetic Surgery and Burn Center, Trousseau Hospital, CHRU de Tours; Laboratory CRRET, UMR CNRS 7149, Paris 12 University; OTR3 SAS; the Department of Pathology, Rothschild Hospital; and the Department of Cardiovascular Surgery, Broussais Hospital and Georges Pompidou Hospital. Received for publication June 19, 2010; accepted August 10, 2010.*

*Presented at the 14th International Congress of the International Confederation for Plastic Reconstructive and Aesthetic Surgery, in Berlin, Germany, June 26 through 30, 2007, and the 18th Annual Meeting of the European Association of Plastic Surgeons, in Gent, Belgium, May 24 through 26, 2007.*

*Copyright ©2011 by the American Society of Plastic Surgeons*

DOI: 10.1097/PRS.0b013e318200a910

**Disclosure:** Only Drs. Barbier and Barritault have an interest in the product described in this article. None of the other authors has a financial interest in any of the products, devices, or drugs mentioned in this article.

ReGeneraTing Agents (RGTA) are polymers chemically derived from dextran by means of a sequence of controlled substitutions.<sup>10–12</sup> They replicate some of the effects of heparan sulfate on heparin-binding growth factors (HBGFs) such as FGF, vascular endothelial growth factor (VEGF), PDGF, and TGF- $\beta$ , stabilizing and protecting them from enzymatic degradation, heat, and pH variations, and potentiating their biological effects. RGTA are selected for their ability to interact with HBGFs and their absence of anticoagulant activity. RGTA increase the speed and quality of tissue healing in several animal models of injury to a variety of tissues (e.g., skeletal muscle, myocardium, bone, skin, cornea).<sup>13–19</sup> RGTA may hold promise for accelerating reepithelialization and/or improving skin repair in patients with burn injuries, thereby decreasing mortality, morbidity, hospital length of stay, and treatment costs, and improving functional and cosmetic outcomes.

To assess the effects of RGTA therapy on burn injuries, we designed an experimental study in hairless rats. We hypothesized that RGTA accelerates and/or improves repair of the epidermis and dermis in rats with second-degree burns.

## MATERIALS AND METHODS

### RGTA

RGTA are compounds, usually derived from dextran by means of a sequence of controlled substitutions. In this study, we used the RGTA called OTR4120. Briefly, carboxymethyl dextran was prepared from T40 dextran (average  $M_r$ , 37,000; Pharmacia Fine Chemicals, Uppsala, Sweden) by carboxymethylation of OH residues with monochloroacetic acid. The presence of carboxymethyl groups was confirmed by infrared spectroscopy, which showed an absorption band at 1650  $\text{cm}^{-1}$ . Then, OTR4120 was obtained from carboxymethyl dextran by O-sulfonation. The presence of sulfate groups was confirmed by infrared spectroscopic identification of two absorption bands at 1250 and 1025  $\text{cm}^{-1}$ , respectively.

Chemical characterization of OTR4120 was based on the degree of substitution of each individual group per glucosidic unit. A degree-of-substitution value of 3 indicates maximum substitution, because one glucosidic unit contains three reactive OH groups at the C<sub>2</sub>, C<sub>3</sub>, and C<sub>4</sub> positions, respectively. Each degree-of-substitution value was determined by acidimetric titration and elementary analysis and confirmed by <sup>1</sup>H-nuclear magnetic resonance. The average molecular weight of OTR4120 (64,100) was estimated by high-perfor-

mance size-exclusion chromatography. OTR4120 had no major anticoagulant activity (<15 IU/mg, compared with 170 IU/mg for heparin).

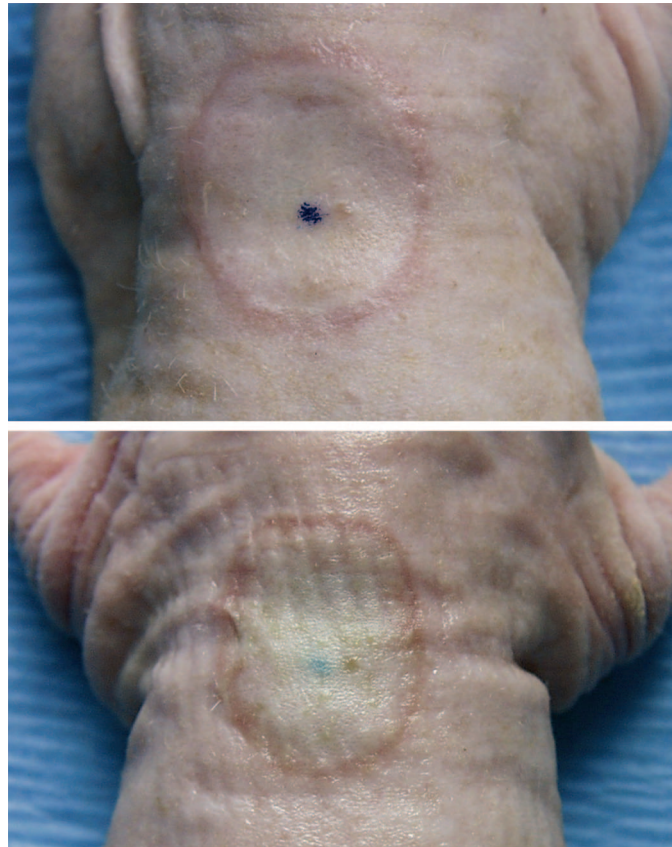
### Hairless Rat Model of Burn Injury

All study procedures were approved by the local institutional animal care and use committee and complied with the *Guide for the Care and Use of Laboratory Animals* (European Convention no. 2001-131 of February 6, 2001). We used 3-month-old female hairless rats ( $n = 156$ ) weighing 300 g (Iffa-Credo, Lyon, France). The smaller number of hair follicles makes the hairless rat a better animal model than the Wistar rat for studying burn injuries and skin repair.

Burn injuries were induced and evaluated under pentothal anesthesia. Deep second-degree (partial-thickness) burns were induced by applying a hot brass cylinder (2 cm in diameter, 100°C) to the skin of the dorsal aspect of the neck for 4 seconds (Fig. 1). The application time, cylinder temperature, and pressure applied were determined in a previous study.<sup>16</sup> The cylinder was heated by being placed in boiling water before inducing each lesion, so its temperature was 100°C (at atmospheric pressure averaging 1013 hPa), pressure of application of the metal bar was its weight, and duration of application was 4 seconds. The pressure exerted by the brass cylinder was constant during the 4 seconds.

The 156 rats with burn injuries were allocated at random to RGTA treatment ( $n = 78$ ) or saline ( $n = 78$ ). RGTA was administered topically and given as an intramuscular injection in the leg immediately after burn induction and then intramuscularly once per week for 1 month. The RGTA solution for topical administration contained 100  $\mu\text{g}/\text{ml}$  of RGTA in phosphate-buffered saline solution. The dosage for systemic RGTA administration was 1 mg/kg per injection; the determination of this dosage was based on previous studies.<sup>13,16</sup> The 78 controls received topical and intramuscular saline according to the same protocol. Vehicle was physiologic serum in both modes of administration. Topical application was indeed sufficient to obtain the effect as described in the previous articles.<sup>16</sup> In both groups, an occlusive paraffin gauze dressing was placed on the burn injury and changed three times per week. Before the first dressing and at each dressing change, photographs of the burn injury were taken and the size of the wound was measured.

Six rats in each group were killed on each day of the first week and then on days 14, 28, 60, 120, 240, and 365. The burn injury with at least 1 cm of surrounding normal skin was excised, fixed in



**Fig. 1.** The burn is made on the back of a hairless rat by the application a brass cylinder at 100°C for 4 seconds. (Above) Aspect of the burn on the day of injury. (Below) Aspect of the burn at day 3.

formaldehyde for at least 48 hours, embedded in paraffin, and cut into sections. The average was three sections per microscopic slide at three or four positions, close to the center, and as many as needed to cover the width of the burn; altogether, six to eight slides at a given time and a given animal. Analysis was blinded to the histologic assessor. Sections stained with hematoxylin-eosin-saffron were examined by light microscopy to evaluate fibroblast counts and appearance, neoangiogenesis, inflammation, changes in pilosebaceous units, and thickness and appearance of the epidermis. The number of keratinocyte layers was counted at the center of the injury, where the burn was deepest. Sirius red stain was used to assess collagen fiber density under a polarizing microscope. To evaluate the extent of epidermal healing, immunohistochemical studies were performed on days 3, 4, 5, and 6 using anti-cytokeratin 14 antibody (antibody 7800; Abcam, Cambridge, United Kingdom), a marker for pluripotent keratinocytes. Anti-cytokeratin 14 labels newly formed epidermis but not differentiated keratinocytes. The antigen unmasking solution was

H-3300 (Vector Laboratories, Inc., Burlingame, Calif.); the saturation buffer was phosphate-buffered saline with 5% fetal calf serum, 1% gelatin, either 2% (saturation solution) or 1% (dilution solution) blocking reagent (BM 1096176; Boehringer Mannheim, Mannheim, Germany), 0.2% Tween, and 1% goat serum. For statistical comparisons, *t* tests were used. Data are reported as means  $\pm$  SEM, and values of  $p < 0.05$  were considered significant.

## RESULTS

### Epidermal Regeneration

Examination of the deep second-degree burn injuries showed keratinocyte necrosis, edema, neutrophil infiltrates, and cleavage of the epidermis from the dermis after day 1. On day 3, coagulation necrosis was seen throughout the entire thickness of the epidermis and in the superficial part of the dermis and adnexa. Between day 3 and day 7, epidermal repair proceeded faster in the RGTA group than in the control group (Table 1 and Fig. 2). Thus, the mean number of keratin-

**Table 1. Mean Number of Keratinocyte Layers in the RGTA Group and in the Control Group\***

Day	RGTA Group (n = 78)	Control Group (n = 78)	p
1	0	0	NS
2	0	0	NS
3	1.5 ± 0.79	0.67 ± 0.74	NS
4	4.17 ± 0.69	2.17 ± 1.07	0.0055
5	7.67 ± 1.7	5.0 ± 1.41	0.0224
6	10.83 ± 1.07	7.17 ± 1.57	0.0015
7	11.0 ± 1.29	9.5 ± 0.96	0.042
14	10.67 ± 0.94	7.5 ± 0.96	0.0004
28	6.83 ± 0.69	6.33 ± 0.47	NS
60	6	6	NS
120	6	6	NS
240	6	6	NS
365	6	6	NS

NS, not significant.

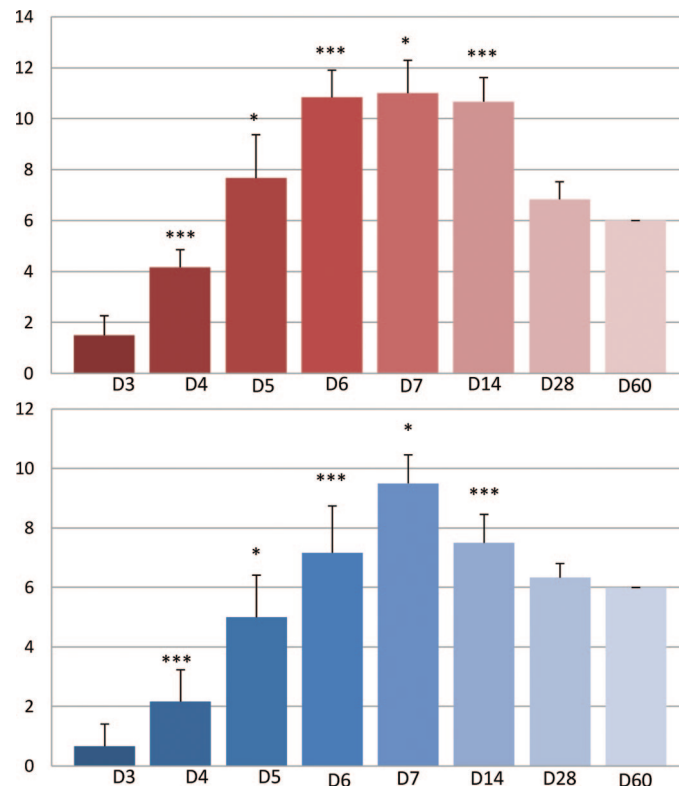
\*Each subgroup contained six animals (sample size = 6).

ocyte layers on day 3 (Fig. 3), day 4 (Fig. 4), day 5 (Fig. 5), day 6 (Fig. 6), and day 7 (Fig. 7) was greater in the RGTA group than in the control group. Necrotic material from the epithelium, superficial dermis, and adnexa was completely eliminated by day 7, when the thickness of the new

epidermis was 0.10 mm with four layers of granulomatous cells in the RGTA group and 0.09 mm with three layers of granulomatous cells in the control group. New epithelium was visible at the infundibulum of the pilous folliculi.

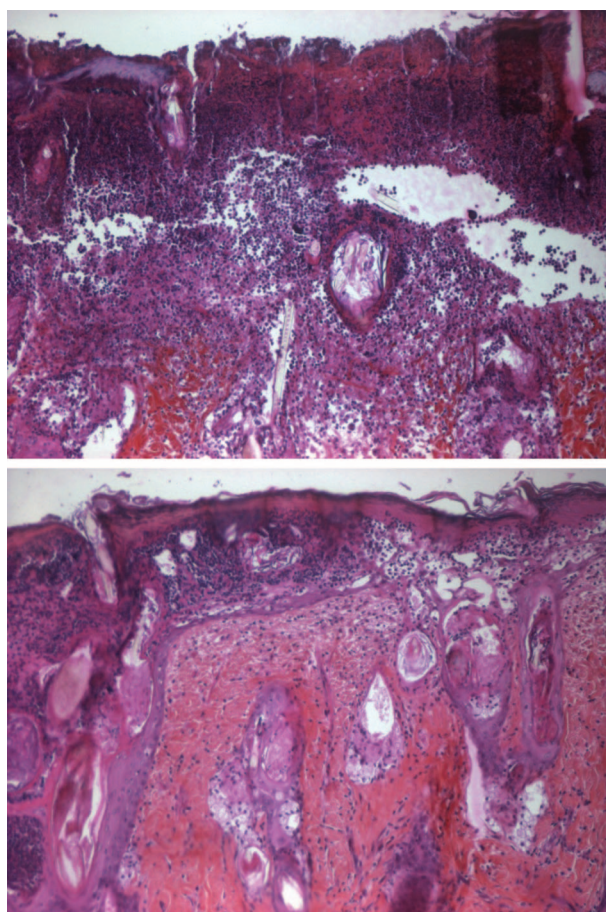
The number of keratinocyte layers decreased subsequently, to  $10.67 \pm 0.94$  in the RGTA group and  $7.50 \pm 0.96$  in the control group by day 14. Epidermal thickness was 0.14 mm with three layers of granulomatous cells in the RGTA group, indicating epidermal hyperplasia, compared with 0.09 mm with two layers of granulomatous cells in the control group. On day 28, the number of layers was similar in the two groups and close to that in normal epidermis ( $6.83 \pm 0.69$  in the RGTA group and  $6.33 \pm 0.47$  in the control group). Mean thickness of the epidermis on day 28 was 0.13 mm in the RGTA group, indicating mild hyperplasia, and 0.09 mm in the control group. From day 60 onward, the number of layers was six in both groups, and epidermal thickness was 0.08 to 0.09 mm, as in normal rat epidermis.

Immunostaining for cytokeratin 14 showed faster epidermal regeneration in the RGTA group



**Fig. 2.** Evolution of the mean number of keratinocyte layers. RGTA administration increases the mean number of keratinocyte layers between day 3 and day 7 (*above*) in comparison with the control group (*below*). At day 1 and day 2, this number was 0; on and after day 60, this number was 6.



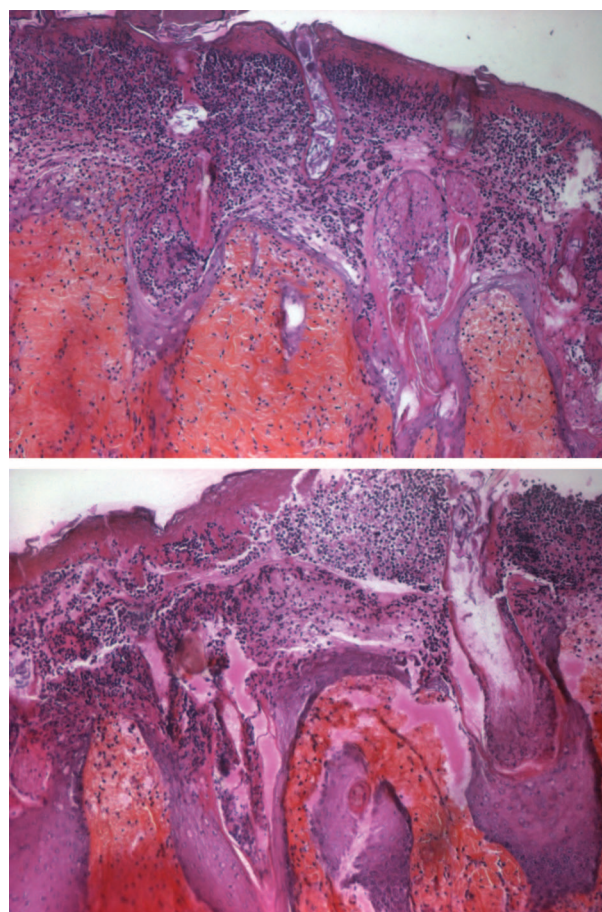


**Fig. 3.** Histologic study on day 3 at 100× magnification. (Above) Control group with no layers. (Below) RGTA group with one layer.

(Fig. 8). Cytokeratin 14 labeling, indicating the presence of newly forming epidermis, appeared earlier (on day 3) and decreased earlier (on day 5) in the RGTA group than in the control group. The suprabasal layer of the new epidermis, composed mostly of regenerating keratinocytes, was strongly stained.

### Dermis Remodeling

In the deep part of the reticularis dermis and in the hypodermis, vascular congestion and an infiltrate composed of lymphocytes, histiocytes, mast cells, and a few neutrophils were noted. In the RGTA group, the number of newly formed blood vessels in the deep part of the dermis was larger than in the control group. Between the necrotic zone and underlying zone of inflammation was a zone of reticularis dermis that showed no inflammatory reaction but contained necrotic fibroblasts, necrotic vessels, and altered collagen fibers, consistent with previous descriptions of the

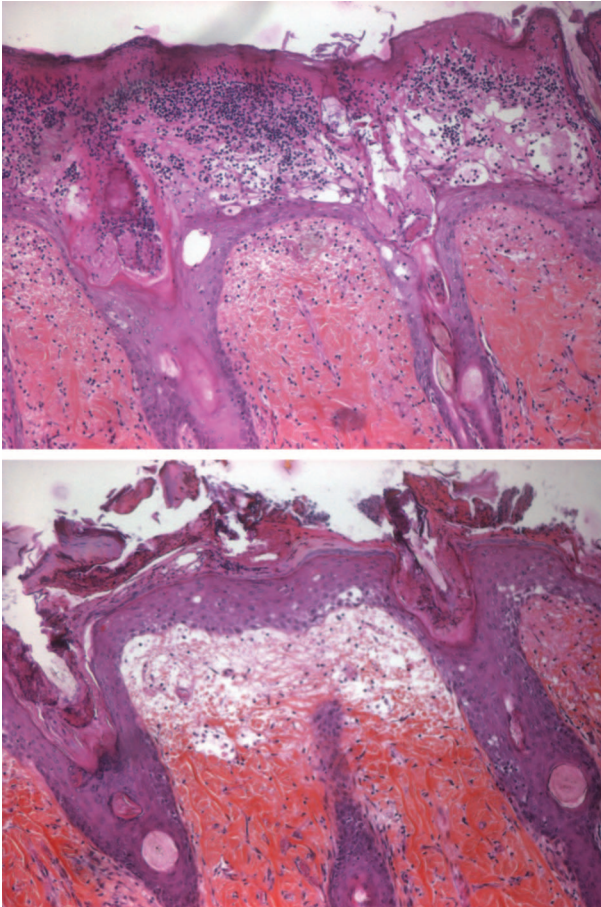


**Fig. 4.** Histologic study on day 4 at 100× magnification. (Above) Control group with two layers. (Below) RGTA group with five layers.

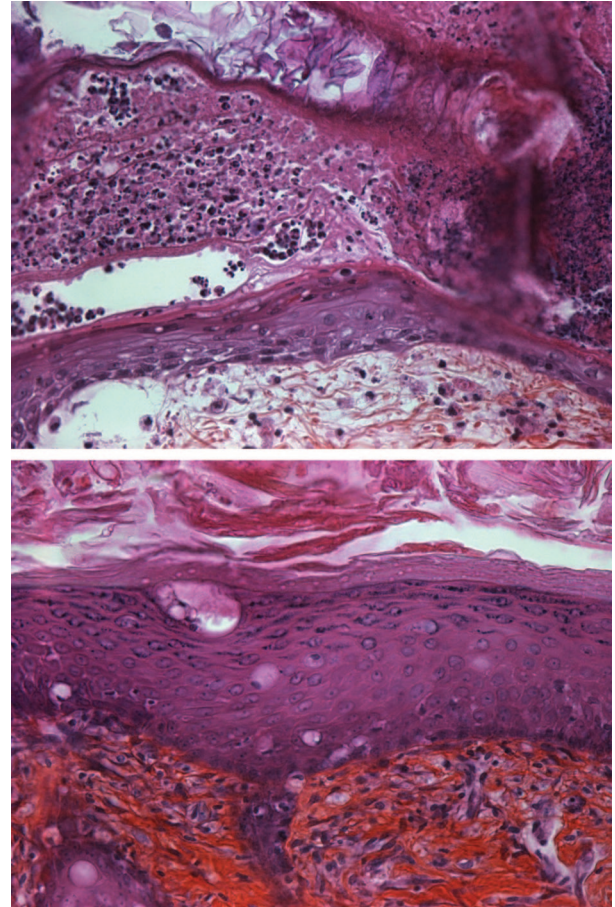
zone of stasis.<sup>20,21</sup> The zone of stasis reflects delayed vascular lesions that develop between the burn injury and the adjacent healthy tissue when the temperature is between 48°C and 52°C and the duration of heat exposure is sufficient.<sup>20</sup> Mean thickness of the zone of stasis on day 3 was 0.43 mm and 30 percent of the total dermis in the RGTA group, compared with 0.65 mm and 47 percent of the total dermis in the control group. The zone with necrosis of the pilosebaceous adnexa was 0.39 mm thick in the RGTA group and 0.58 mm thick in the control group. Thus, on day 3, the zone of stasis was smaller in the RGTA group than in the control group.

On day 7, new blood vessels and numerous mast cells were visible in the subcutaneous tissue and hypodermis. In the RGTA group, the number of small vessels exhibiting the characteristics of newly formed vessels was larger than in the control group, and the fibroblasts were hyperplastic. Active dermal remodeling was noted between day 7 and day 120. On day 14, dermal hyperplasia and





**Fig. 5.** Histologic study on day 5 at 100 $\times$  magnification. (Above) Control group with four layers. (Below) RGTA group with eight layers.



**Fig. 6.** Histologic study on day 6 at 250 $\times$  magnification. (Above) Control group with six layers. (Below) RGTA group with ten layers.

fibroblast density were greater in the RGTA group than in the control group; whereas on day 28, dermal thickness was similar in the two groups. From day 28 onward, the thickness of remodeled dermal zone was  $0.49 \pm 0.08$  mm in the RGTA group compared with  $0.84 \pm 0.15$  in the control group.

Burn injury size was not significantly different between the two groups. Between day 0 and day 60, the mean transverse dimension decreased from 20 mm to 13 mm, and the mean craniocaudal dimension remained unchanged at 25 mm.

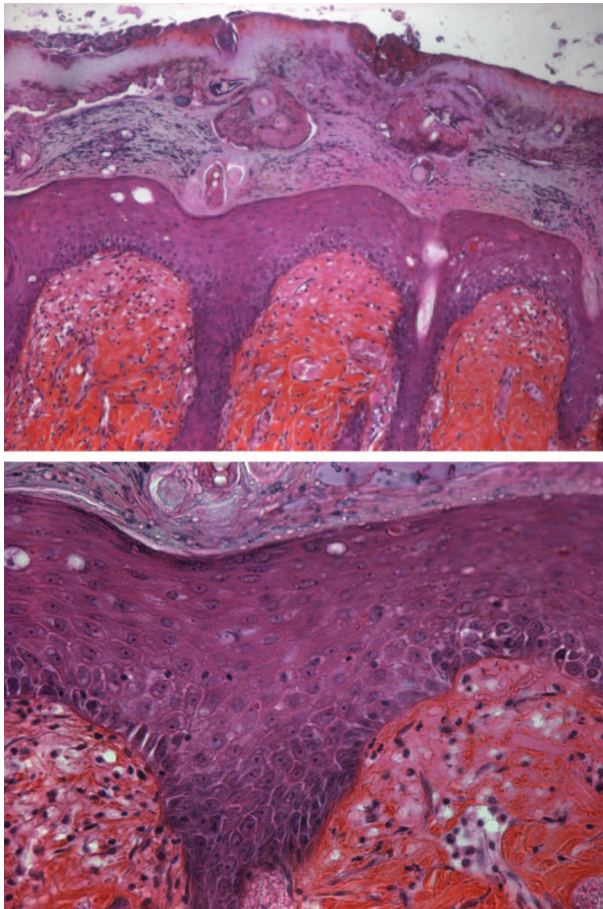
## DISCUSSION

In this study, OTR4120 improved the speed and quality of burn injury healing when administered topically and systemically in very low dosages, as a single dose or as repeated doses. Young adult female hairless rats allow easier evaluation than Wistar rats of burn injuries and their repair. Other animal models used to study burns include the micropig<sup>22</sup> and the hairless dog.<sup>23</sup> We induced

superficial partial-thickness burn injuries at the dorsal aspect of the neck, where the skin was thinnest. The epidermis is thicker in hairless rats than in Wistar rats, the hair canals contain lamellar cornified tissue instead of hair, and some of the hair follicles deep in the dermis exhibit cyst formation. The normal hairless rat skin has six cell layers, including two layers of granulomatous cells, which are in the stratum basale. We assessed the effect of RGTA treatment on several aspects of skin repair, namely, reepithelialization and production of collagen fibers.

RGTA should have stimulated the production of new vessels within the first few days. This can explain that the zone of stasis was smaller on day 3 in the RGTA group than in the control group. On day 7, neovascularization was complete. Epidermal repair was also complete on day 7 in both groups. However, the epidermis seemed more mature in the RGTA group, where three layers of granulomatous cells were visible, compared with four in the control group. On each day during the





**Fig. 7.** Samples of RGTA group on day 7 with 12 layers, (above) at 100 $\times$  and (below) at 250 $\times$  magnification.

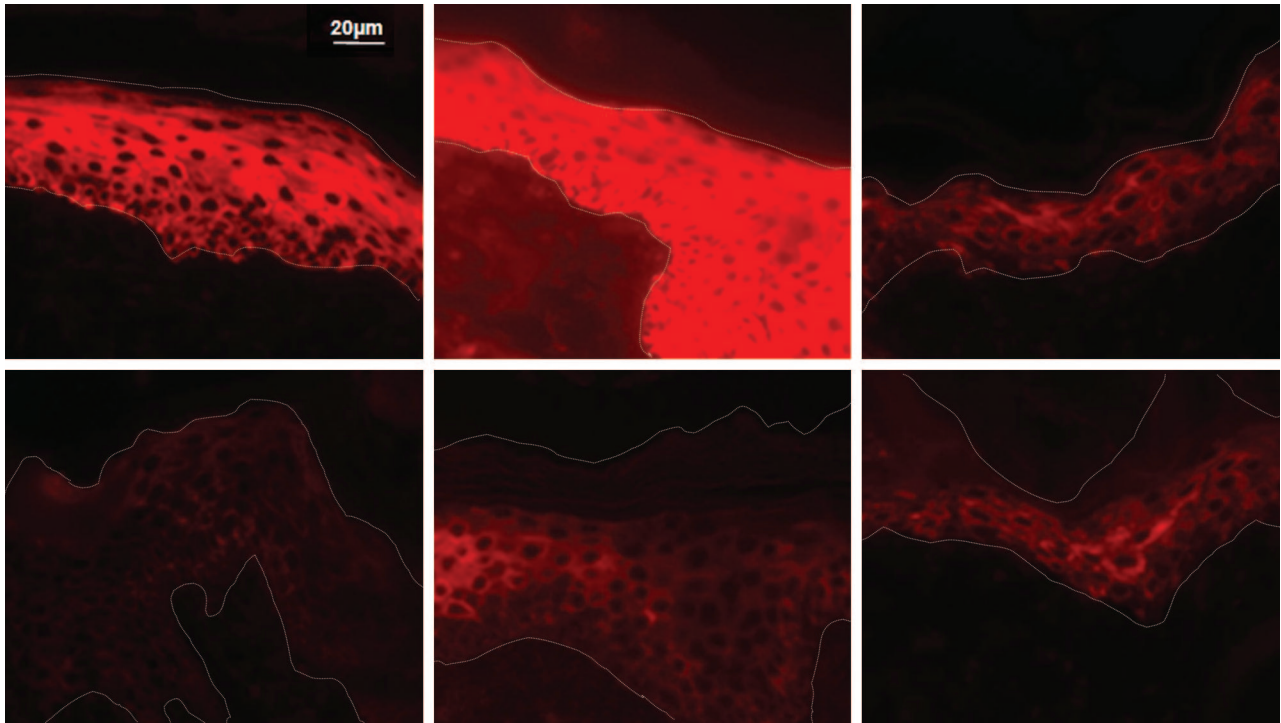
first week, the stage of epidermal repair was approximately 1 day earlier in the RGTA group. Between day 7 and day 30, the epidermis was thicker in the RGTA group. The quality of the newly formed epidermis seemed similar in the two groups. The adnexa were destroyed gradually, with no difference between the two groups.

On day 14, fibroblast density was greater in the RGTA group. This effect might be ascribable to the protective effect of RGTA on FGF, which is chemotactic and mitogenic for fibroblasts in vitro and in vivo. FGF protection also explains the earlier development of a myofibroblastic appearance in the RGTA group. The greater degree of scar contraction in the RGTA group, in both the craniocaudal and the transverse directions, may be related to the larger number of myofibroblasts.

For our immunohistochemical study, we chose anti-cytokeratin 14, because keratin 14 is a marker of choice for monitoring keratinocyte division and epithelium restoration in skin. Dividing keratino-

cytes of stratified epithelium express keratin 5 and keratin 14,<sup>24</sup> whereas keratinocytes in simple epithelial tissue express keratin 8 and keratin 18. As the basal cells stop dividing and engage in the terminal differentiation pathway that ultimately results in squame production, keratin 5 and keratin 14 gene expression stops and keratin 1 and keratin 10 production begins. When keratinocytes of stratified tissues withdraw from the cell cycle and begin to differentiate, they down-regulate the transcription of keratin 5 and keratin 14, which are often coexpressed. The skin of mice lacking keratin 14 (keratin 14-null mice) blisters on exposure to physical stress, as a result of mechanically induced degeneration of the epidermal basal layer,<sup>25</sup> and genetic alterations in the keratin 14 network are responsible for epidermolysis bullosa in humans.<sup>26</sup> In our study, cytokeratin 14 staining intensity on day 3 was more marked in the RGTA group than in the control group. On day 4, cytokeratin 14 expression peaked in the treated group, where it was far greater than in the control group. On day 5, cytokeratin 14 expression was noted throughout the epithelium in the RGTA group but was confined to the stratum granulosum and stratum spinosum. Thus, cytokeratin expression was more marked and showed faster kinetics in the RGTA group, in keeping with the histologic evidence of faster reepithelialization.

RGTAs stimulate the repair and regeneration of damaged tissues. They mimic the effects of heparan sulfates on HBGFs in vitro and increase the speed and quality of tissue healing in several animal models, including a model of crushed muscle.<sup>13</sup> RGTA therapy prevents muscle-flap atrophy in a cardiomyoplasty model.<sup>14</sup> RGTAs increase the speed of healing after colonic anastomosis surgery and improve endothelialization.<sup>27</sup> Furthermore, RGTAs improve healing of the cornea,<sup>19</sup> mucosa,<sup>28,29</sup> myocardium,<sup>30</sup> and skin.<sup>16–18</sup> The healing effects of RGTAs probably involve protection of HBGF against thermal and enzymatic degradation, resulting in increased HBGF bioavailability.<sup>10</sup> This mechanism was established in a recent study of the interaction between OTR4120 and endogenous VEGF.<sup>31</sup> Most of the HBGFs play a key role in burn injury healing. Among them, VEGF, a compound released by keratinocytes, macrophages, and fibroblasts, has a powerful angiogenic effect<sup>32</sup> and is related to the induction of endothelial cell division.<sup>33</sup> FGF-2, a major mediator of wound angiogenesis<sup>34</sup> and epithelialization, accelerates reepithelialization<sup>35</sup> by improving keratinocyte division and granulation tissue formation<sup>36</sup> by stimulating the synthesis of



**Fig. 8.** Immunostaining with cytokeratin 14 antibody (*above*) versus control (*below*). (*Left*) Day 3. (*Center*) Day 4. (*Right*) Day 5. Immunostaining cytokeratin 14 antibody (in  $\text{cm}^{-1}$ ) was more intense, and appeared (day 3) and decreased earlier (day 5) in the RGTA group than in the control group.

matrix components such as collagen, fibronectin, and proteoglycan. Topical application accelerated healing of burn injuries in a pig model<sup>9</sup> and improved wound epithelialization in diabetic mice.<sup>37</sup> In humans, topical application of FGF-2 to burns<sup>38</sup> and chronic dermal ulcers<sup>39</sup> was followed by accelerated healing.

Keratinocyte growth factor (KGF)-1 and KGF-2 are important regulators of keratinocyte proliferation. In a murine wound model, KGF-1<sup>40</sup> or KGF-2<sup>41</sup> administration improved reepithelialization and collagen synthesis by fibroblasts by means of increased release of PDGF, TGF- $\beta$ , and FGF-2 by epithelial cells. In rats, KGF-2 accelerated the epithelialization of cutaneous meshed grafts<sup>42</sup> and improved epidermal and dermal healing.

PDGF is mitogenic for fibroblasts and improves collagen production.<sup>43</sup> It accelerates healing of wounds in diabetic mouse<sup>44</sup> and of chronic ulcers in humans.<sup>45</sup> TGF- $\beta$  increases and regulates angiogenesis by means of extracellular matrix synthesis, fibroblast activation, and collagen and fibronectin production.<sup>46</sup> The mechanisms of action of OTR4120, the RGTA tested in this study, can probably be summarized as follows. After a burn injury, activation of neighboring tissues leads to cell proliferation and migration

to the injury site, allowing skin repair. OTR4120 replaces destroyed heparan sulfate on heparin-binding sites, if any are available. Heparin-binding sites are located on most extracellular matrix proteins (e.g., collagens, laminin, fibronectin, elastin). Binding of OTR4120 should have promoted recovery of the original scaffold of extracellular fibers, thereby ensuring normal extracellular matrix architecture, with normal location of the HBGFs produced by neighboring cells. By restoring the normal architecture of the matrix scaffold, HBGFs in the appropriate dosage would be expected to improve skin repair.

Topical OTR4120 therapy proved dramatically effective in the treatment of patients with grade 4 nonhealing arteritic skin ulcers. Clinical trials including burn patients are under way.

## CONCLUSIONS

RGTA administration to hairless rats with burn injuries accelerated reepithelialization and seemed to protect the dermis from the delayed effects of heat as quantified based on zone-of-stasis thickness. Over the longer term, RGTA limited the extent of dermal remodeling.



**Gilbert Zakine, M.D., Ph.D.**

Department of Plastic Reconstructive and Aesthetic  
Surgery  
Burn Center  
Trousseau Hospital  
CHRU de Tours  
37044 Tours, France  
zakinegilbert@yahoo.fr

## ACKNOWLEDGMENT

*This work is dedicated to the memory of Professor Jean Pierre Caruelle, who died in January of 2007.*

## REFERENCES

- Robson MC. Growth factors as wound healing agents. *Curr Opin Biotechnol*. 1991;2:863–867.
- McGrath MH. Peptide growth factors and wound healing. *Clin Plast Surg*. 1990;17:421–432.
- Clark RAF. Wound repair. In: *The Molecular and Cellular Biology of Wound Repair*. 2nd ed. New York: Plenum; 1996.
- Rumalla VK, Borah GL. Cytokines, growth factors, and plastic surgery. *Plast Reconstr Surg*. 2001;108:719–733.
- Zakine G. Growth factors, modulating growth factors and burn (in French). *Burns* 2005;6:8–17.
- Shukla A, Dubey MP, Srivastava R, Srivastava BS. Differential expression of proteins during healing of cutaneous wounds in experimental normal and chronic models. *Biochem Biophys Res Commun*. 1998;244:434–439.
- Breuing K, Andree C, Helo G, Slama J, Liu PY, Eriksson E. Growth factors in the repair of a partial thickness porcine skin wounds. *Plast Reconstr Surg*. 1997;100:657–664.
- Cribbs RK, Luquette MH, Besner GE. Acceleration of partial-thickness burn wound healing with topical application of heparin-binding EGF-like growth factor (HB-EGF). *J Burn Care Rehabil*. 1998;19:95–101.
- Danilenko DM, Ring BD, Tarpley JE, et al. Growth factors in porcine full and partial thickness burn repair: Differing targets and effects of keratinocyte growth factor, platelet-derived growth factor-BB, epidermal growth factor, and neu differentiation factor. *Am J Pathol*. 1995;147:1261–1277.
- Tardieu M, Gamby C, Avramoglou T, Josefowicz J, Barritault D. Derivatized dextrans mimic heparin as stabilizers, potentiators, and protectors of acidic or basic FGF. *J Cell Physiol*. 1992;150:194–203.
- Ledoux D, Papy D, Escartin Q, et al. Human plasmin enzymatic activity is inhibited by chemically modified dextrans. *J Biol Chem*. 2000;275:29383–29390.
- Meddahi A, Lemdjabar H, Caruelle JP, Barritault D, Hornebeck W. FGF protection and inhibition of human neutrophil elastase by carboxymethyl benzylamide sulfonate dextran derivatives. *Int J Biol Macromol*. 1996;18:141–145.
- Desgranges P, Barbaud C, Caruelle JP, Barritault D, Gautron J. A substituted dextran enhances muscle fiber survival and regeneration in ischemic and denervated rat EDL muscle. *FASEB J*. 1999;13:761–766.
- Zakine G, Martinod E, Fornes P, et al. Growth factors improve latissimus dorsi muscle vascularization and trophicity after cardiomyoplasty. *Ann Thorac Surg*. 2003;75:549–554.
- Blanquaert F, Saffar JL, Colombier ML, Carpentier G, Barritault D, Caruelle JP. Heparan-like molecules induce the repair of skull defects. *Bone* 1995;17:499–506.
- Garcia-Filipe S, Barbier-Chassefiere V, Alexakis C, et al. RGTA OTR4120, a heparan sulfate mimetic, is a possible long-term active agent to heal burned skin. *J Biol Mater Res A* 2007;80:75–84.
- Barbier-Chassefiere V, Garcia-Filipe S, Yue XL, et al. Matrix therapy and regenerative medicine, a new approach for chronic wound healing. *J Biomed Mater Res A* 2009;90:641–647.
- Tong M, Zbinden MM, Hekking IJ, Vermeij M, Barritault D, van Neck JW. RGTA OTR 4120, a heparan sulphate proteoglycan mimetic, increases wound breaking strength and vasodilatory capability in healing rat full-thickness excisional wounds. *Wound Repair Regen*. 2008;16:294–299.
- Khammari Chebbi C, Kichenin K, Amar N, et al. Pilot study of a new matrix therapy agent (RGTA OTR4120) in treatment-resistant corneal ulcers and corneal dystrophy (in French). *J Fr Ophtalmol*. 2008;31:465–471.
- Zawacki BE. Reversal of capillary stasis and prevention of necrosis in burns. *Ann Surg*. 1974;180:98–102.
- Jackson D. The diagnosis of the depth of burning. *Br J Surg*. 1953;40:588–596.
- Sullivan TP, Eaglstein WH, Davis SC, Mertz P. The pig as a model for human wound healing. *Wound Repair Regen*. 2001;9:66–76.
- Matsumura H, Yoshizawa N, Kimura T, Watanabe K, Gibran NS, Engrav L. A burn wound healing model in the hairless descendant of the Mexican hairless dog. *J Burn Care Rehabil*. 1997;18:306–312.
- Fuchs E, Green H. Changes in keratin gene expression during terminal differentiation of the keratinocyte. *Cell* 1980;19:1033–1042.
- Lloyd C, Yu C, Cheng J, et al. The basal keratin network of stratified squamous epithelia: Defining K15 function in the absence of K14. *J Cell Biol*. 1995;129:1329–1344.
- Coulombe PA, Hutton ME, Letai A, Hebert A, Paller AS, Fuchs E. Point mutation in human keratin 14 genes of epidermolysis bullosa simplex patients: Genetic and functional analyses. *Cell* 1991;66:1301–1311.
- Desgranges P, Caruelle JP, Carpentier G, Barritault D, Tardieu M. Beneficial use of fibroblast growth factor 2 and RGTA, a new family of heparan mimics, for endothelialization of PET prostheses. *J Biomed Mater Res*. 2001;58:1–9.
- Morvan FO, Baroukh B, Ledoux D, et al. An engineered biopolymer prevents mucositis induced by 5-fluorouracil in hamsters. *Am J Pathol*. 2004;164:739–746.
- Escartin Q, Lallam-Laroye C, Baroukh B, et al. A new approach to treat tissue destruction in periodontitis with chemically modified dextran polymers. *FASEB J*. 2003;17:644–651.
- Yamauchi H, Desgranges P, Lecerf L, et al. New agents for the treatment of infarcted myocardium. *FASEB J*. 2000;14:2133–2134.
- Rouet V, Hamma-Kourbali Y, Petit E, et al. A synthetic glycosaminoglycan mimetic binds vascular endothelial growth factor and modulates angiogenesis. *J Biol Chem*. 2005;280:32792–32800.
- Senger DR, Galli SJ, Dvorak AM, Peruzzi CA, Harvey VS, Dvorak HF. Tumor cells secrete a vascular permeability factor that promotes accumulation of acid fluid. *Science* 1983;219:983–985.
- Connolly DT, Heuvelman D, Nelson R, et al. Tumor vascular permeability factor stimulates endothelial cell growth and angiogenesis. *J Clin Invest*. 1989;84:1470–1478.
- Folkman J, Klagsbrun M. Angiogenic factors. *Science* 1987;235:442–447.
- Hebda PA, Klingbeil CK, Abraham JA, Fiddes JC. Basic fibroblast growth factor stimulation of epidermal wound healing in pigs. *J Invest Dermatol*. 1990;95:626–631.
- Gospodarowicz D, Neufeld G, Schweigerer L. Fibroblast growth factor: Structural and biological properties. *J Cell Physiol Suppl*. 1987;Suppl 5:15–26.

37. Greenhalgh DG, Sprugel KH, Murray MJ, Ross R. PDGF and FGF stimulate wound healing in the genetically diabetic mouse. *Am J Pathol.* 1990;136:1235–1246.
38. Fu XB, Shen Z, Chen Y, et al. Randomised placebo-controlled trial of use of topical recombinant bovine basic fibroblast growth factor for second-degree burns. *Lancet* 1998; 352:1661–1664.
39. Fu XB, Shen Z, Chen Y, et al. Recombinant bovine basic fibroblast growth factor accelerates wound healing in patients with burns, donor sites and chronic dermal ulcers. *Chin Med J.* 2000;113:367–371.
40. Staiano-Coico L, Krueger JG, Rubin JS, et al. Human keratinocyte growth factor effects in a porcine model of epidermal wound healing. *J Exp Med.* 1993;178:865–878.
41. Jimenez PA, Rampy MA. Keratinocyte growth factor-2 accelerates wound healing in incisional wounds. *J Surg Res.* 1999; 81:238–242.
42. Soler PM, Wright TE, Smith PD, et al. In vivo characterization of keratinocyte growth factor-2 as a potential wound healing agent. *Wound Repair Regen.* 1999;7:172–178.
43. Heldin CH, Westermark B. Platelet-derived growth factor mechanism of action and possible in vivo function. *Cell Regul.* 1990;1:555–566.
44. Brown RL, Breeden MP, Greenhalgh DG. PDGF and TGF- $\alpha$  act synergistically to improve wound healing in the genetically diabetic mouse. *J Surg Res.* 1994;56:562–570.
45. Pierce GF, Tarpley JE, Tseng J, et al. Detection of platelet-derived growth factor (PDGF)-AA in actively healing human wounds treated with recombinant PDGF-BB and the absence of PDGF in chronic nonhealing wounds. *J Clin Invest.* 1995; 96:1336–1350.
46. Sporn MB, Roberts AB. A major advance in the use of growth factors to enhance wound healing. *J Clin Invest.* 1993;92: 2565–2566.

## Baker Gordon Videos



**Baker Gordon**  
Educational Symposium

PRS proudly presents  
select lectures and  
procedural videos from  
the 2010 Baker Gordon  
Symposium. To begin  
watching the Masters at  
work in our first two  
entries, visit the [Baker  
Gordon Video  
Collection](#).

*Now Available!*

View Baker Gordon Videos at [PRSJJournal.com](http://PRSJJournal.com)