# Composite Tissue Allotransplantation

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**Summary:** Recently, composite tissue allotransplantation was introduced as a potential clinical treatment for complex reconstructive procedures, including tumor ablative operations, traumatic injuries, and extensive tissue loss secondary to burns. Composite tissue allotransplantations consist of heterogeneous tissues including skin, fat, muscle, nerves, lymph nodes, bone, cartilage, ligaments, and bone marrow, all presenting with different antigenicity. Thus, composite tissue allotransplantations are considered to elicit a stronger response compared with solid organ transplants. This article outlines different experimental models and current clinical applications of composite tissue allotransplantation. (*Plast. Reconstr. Surg.* 124: 327e, 2009.)

Composite tissue allotransplantation has considerable potential for application in the field of reconstructive surgery. The immunology of composite tissue allotransplantation is complex because the grafts are composed of a variety of tissues, such as skin, fat, muscle, nerves, lymph nodes, bone, cartilage, ligaments, and bone marrow, representing different antigenicities. Each of these components elicits a different immune reaction, making graft acceptance and tolerance more difficult to achieve compared with solid organ transplants. These tissues are structurally, functionally, and aesthetically important to patients who are in need of functional restoration of complete musculoskeletal defects when standard reconstructive options are exhausted and autologous tissues are not avalible.[1–5]

## CURRENT CLINICAL APPLICATIONS

To date, there are more than 50 composite tissue allograft transplants performed worldwide, including hand, abdominal wall, knee, flexor tendon apparatus, nerve, larynx, skeletal muscle, tongue, trachea, scalp, penis, and partial face transplants.

### Hand

The first hand transplantation was performed before the cyclosporine A era of immunosuppression, in 1963.[6] The hand was rejected 3 weeks after transplantation. Since the first successful hand transplantation in 1998, in Lyon,[7] a total of 26 hand transplants (seven bilateral) and one thumb transplant have been reported worldwide.[8]

The most significant complications related to hand transplantation are rejection episodes. Because of repeated rejection episodes that required increased systemic immunosuppression, the first hand transplant recipient stopped taking his medication, and this led to rejection and amputation of the transplanted hand.[9] This case shows the importance of patient selection and also demonstrates the reversibility of hand transplantation for cases with undesired complications or for patients with unsatisfactory results.[10]

Immunosuppressive protocols used in hand transplants are similar to those used in solid organ transplants and mainly include a combination of tacrolimus, mycophenolate mofetil, and prednisone for induction therapy and tacrolimus and mycophenolate mofetil or tacrolimus and prednisone for maintenance therapy. Episodes of rejection have been treated with an increase in the prednisone dosage and with topical application of steroids and tacrolimus.[10–12]

### Abdominal Wall

Levi et al. reported nine cadaveric abdominal wall composite allograft transplants in eight patients.[13] The abdominal wall composite allograft included one or both rectus abdominis muscles,

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fascia, subcutaneous tissue, and skin. Recipients received either isolated small bowel or multivisceral allografts. Seven patients received the anti-CD52 monoclonal antibody alemtuzumab and one patient received daclizumab as an induction agent. Maintenance immunosuppression was based on tacrolimus (10 $\mu$g/liter) without corticosteroids. Intravenous corticosteroids were used for the treatment of rejection. Six of eight patients are alive; five have functioning, viable abdominal wall composite grafts. A mild attack of rejection of the skin of the abdominal wall was seen in two patients, and they completely recovered with corticosteroid therapy.

**Knee**

In 1994, Hofmann et al. used vascularized bone allotransplantations to treat sequelae of tumors and trauma of the lower extremities.[14] Three patients received a femoral diaphysis and five patients received a whole knee joint with its extensor system. Recipients received an immunosuppressive protocol consisting of cyclosporine A, azathioprine, antithymocyte globulin, and methylprednisolone. In the femur recipients, immunosuppressive therapy was stopped 2 years after transplantation. Four patients after 2 to 5 years of follow-up revealed a favorable integration of allograft and a satisfactory range of motion of the knee joint.[15] However, one femur allograft and three knee allografts were removed and replaced with autografts or prosthetic devices because of infection.

**Flexor Tendon Apparatus**

In 1988 and 1989, Guimberteau et al. reported two cases of vascularized digital flexor tendon apparatus allotransplantation.[16] The grafts were revascularized onto the recipient's ulnar vessels. Both patients received cyclosporine A monotherapy at 6 mg/kg/day for 6 months. The grafts were accepted without rejection and the vessels remained patent. After 1-year follow-up, both patients revealed a satisfactory range of motion of proximal and distal interphalangeal joints.[11,16]

**Nerve**

In 2001, Mackinnon et al. presented the clinical outcome of nonvascularized peripheral nerve allografts in seven patients who had traumatic peripheral nerve deficits.[17] Before transplantation, to decrease the immunogenicity of the allografts, the grafts were harvested from cadaveric donors and preserved for 7 days at 5°C.

Five patients received cyclosporine A, azathioprine, and prednisone. Tacrolimus replaced cyclosporine A for the last two patients. The immunosuppressive therapy was maintained for 6 months after evidence of nerve regeneration distal to the graft. The mean time of immunosuppression was 18 months. Rejection was noticed in one patient, and this led to graft loss. The other six patients had sensory recovery and three patients had motor recovery.

**Larynx**

In 1998, Strome performed the successful larynx transplantation.[18] The patient was a 40-year-old man who had been aphonic since the age of 20 after traumatic avulsion of his larynx. The patient received an allograft of the complete pharyngolaryngeal system, including six tracheal rings and thyroid and parathyroid glands based on bilateral superior thyroid arteries and the right internal jugular and left middle thyroid veins. Both superior laryngeal and right recurrent laryngeal nerves were included.

The patient received muromonab-CD3, cyclosporine A, methylprednisolone, and mycophenolate mofetil during the first week after surgery. Subsequently, the patient received cyclosporine, mycophenolate mofetil, and prednisone in progressively decreasing doses. At 15 months, one episode of rejection was observed and treated with high doses of prednisone. Then, cyclosporine A was replaced with tacrolimus. Currently, the patient talks with a natural and intelligible voice and feeds himself without aspiration, and the sensation of taste and odor have improved.[19]

**Muscle**

In 1998, vascularized skeletal muscle allografting was performed to cover a large defect in the scalp of a renal transplant patient who was on chronic immunosuppressive therapy.[20] The patient received methylprednisolone and rabbit antithymocyte globulin before revascularization. He was returned immediately to his baseline immunosuppressive regimen of prednisone and cyclosporine A. At 2 weeks postoperatively, a muscle biopsy revealed perivascular lymphocytic infiltration. Mycophenolate mofetil was administered and the dose of cyclosporine A was increased. At 18 weeks postoperatively, mycophenolate mofetil was stopped and the patient was kept on chronic cyclosporine A and prednisone. This patient is still under immunosuppression, with no reported complications.

**Tongue**

On July 19, 2003, the world's first tongue transplantation was performed in a patient with tongue



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cancer.[21] Although the recipient was discharged from the hospital 1 month later, the tongue still cannot be moved, but the patient can already swallow some of his own saliva. At 8-month follow-up, there were no signs of rejection and the patient had some useful sensation, with the ability to swallow his saliva and some fluids. Although the surgeon from the transplant team commented that the tongue is just a muscle and that it should thus work out, unfortunately, some muscle wasting was occurring. However, it was thought to be unlikely that the sense of taste would return. The long-term results of this transplantation are of interest to many surgeons.

### Trachea

In 1979, Rose et al. reported a heterotopic implantation performed by wrapping the trachea in the sternocleidomastoid muscle.[22] At 9-week follow-up, under no immunosuppressive protocol, no signs of rejection or ischemia were reported.

Levashov and colleagues reported the second patient who received an allograft replacement of the distal trachea wrapped with omentum. Although the functional outcome 2 months after transplantation was good, progressive stenosis occurred and the patient ultimately needed permanent stenting of the trachea.[23] In 2004, Klepetko et al. reported heterotopic tracheal transplantation with omentum wrapping in the abdomen.[24] Triple immunosuppressive therapy was started with intravenous cyclosporine A, mycophenolate mofetil, and corticosteroids and maintained orally thereafter. The tracheal allograft was harvested and gross, microscopic, and angiographic examination revealed mechanically stable, viable, and excellent vascularization of the tracheal wall 8 months after surgery.

### Scalp Transplantations

To date, the only successful scalp transplantation was performed between identical twins[25] without need for any immunosuppression. From her identical twin, the patient received two free scalp flaps based on superficial temporal arteries. At 6-month follow-up, without any immunosuppressive regimen, the flaps provided adequate hair growth.

The second scalp transplant was performed recently in a 72-year-old woman with stage IIIC recurrent cutaneous malignant melanoma on the vertex.[26] Wide excision of the tumor, including the scalp, facial/cervical skin, and two ears, was performed. The defect was reconstructed by means of composite tissue allotransplantation, including scalp and both external ears transplanted from a brain-dead young man. The patient received tacrolimus, mycophenolate mofetil, steroids, and Zenapax (Hoffmann-La Roche, Inc., Nutley, N.J.) as an immunosuppressive protocol. The follow-up of 4 months was presented.

### Penis Transplantation

In 2006, Hu et al. reported their preliminary results of penile transplantation.[27] A 44-year-old male recipient with a traumatic penile defect that occurred 8 months earlier was matched with a 22-year-old, male, brain-dead donor. Transplantation included anastomosis of the urethra corpus spongiosum and corpus cavernosum, and sutures of the deep dorsal vein, dorsal artery, dorsal nerve, and superficial dorsal vein. Zenapax, mycophenolate mofetil, and methylprednisolone were administered immediately preoperatively and intraoperatively. Maintenance immunosuppression was based on mycophenolate mofetil, prednisone, and cyclosporine A. The Foley catheter was removed at the end of postoperative day 10, and the patient voided without difficulty. There was no sign of rejection or infection. At day 14 postoperatively, because of a severe psychological problem of the recipient and his wife, the transplanted penis was cut off. Pathologic examination showed no rejection. This transplant also raises many technical, ethical, and social concerns.[27–29]

## RECENT PARTIAL FACE TRANSPLANTATIONS

On November 27, 2005, a French team led by Dr. Dubernard carried out the world's first partial face transplantation using the nose, lips, and chin from a brain-dead living donor to repair the face of a 38-year-old woman who had been bitten by a dog. One week after surgery, the patient started to eat and drink. In addition to the immunosuppressive protocol [i.e., Thymoglobulin (SangStat Medical Corp., Fremont, Calif.), tacrolimus, mycophenolate mofetil, and prednisone], injection of stem cells from the donor's bone marrow was given to help prevent tissue rejection.[30–34] In this patient, the functional and aesthetic results 18 months after transplantation were satisfactory.[35]

In April of 2006, a Chinese surgery team led by Dr. Guo Shuzhong performed the world's second partial face transplant.[36] The patient, a 30-year-old farmer, was severely disfigured after he was mauled by a black bear in 2004. There was no upper lip, all the upper teeth were exposed, and the patient also



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had lost the front wall of his maxillary sinus and part of his cheekbone, leaving him prone to infections. From the donor, surgical team took the entire nose, upper lip, some soft tissue from the left side of the face and more than two-thirds from the right side (including skin, subcutaneous tissue, and muscle), along with bone from the nose and malar area. The major difference from the French case was that the Chinese surgical team included bone and salivary gland tissue in the partial face transplant.[36]

In January of 2007, the world's third partial face transplant was performed by a French team at Henri-Mondor Hospital in Paris.[8,37] Unfortunately, detailed reports related to the last two face transplants have not yet been published. However, we know from some anecdotal and brief media and meeting comments that patients and grafts are continuing to survive, with few episodes of acute rejection. There are no scientific data available on the current status of these partial face transplant recipients.[8]

On December 9, 2008, Siemionow et al. performed the first near-total face transplantation in the United States, replacing 80 percent of the patient's traumatic facial deficit with a composite allograft from a brain-dead donor. This largest, and most complex, face allograft in the world included more than 535 cm of facial skin, functional units of full nose with nasal lining and bony skeleton, lower eyelids and upper lip, underlying muscles, and bones including orbital floor, zygoma, maxilla, alveolus with teeth, hard palate, parotids and pertinent nerves, arteries, and veins. Immunosuppressive treatment consisted of thymoglobulin, tacrolimus, mycophenolate mofetil, and prednisone. The functional and aesthetic outcome is thus rewarding and confirms feasibility of performing complex reconstruction of severely disfigured patients in a single surgical procedure of facial allotransplantation.[38,39]

## EXPERIMENTAL MODELS

During the past 20 years of research in the field of composite tissue allotransplantation, we have gone from designing, developing, and testing different composite tissue allotransplantation models to applying different immunosuppressive protocols for tolerance induction[40–83] (Table 1).

### Hind-Limb Allograft Transplantation Models

We have performed over 1000 hind-limb transplantations across the major histocompatibility complex barrier between fully allogeneic Brown Norway ($RT1^n$) and semiallogeneic Lewis–Brown Norway ($RT1^{1+n}$) donors and Lewis ($RT1^1$) recipients. Different immunosuppressive protocols including cyclosporine A monotherapy, cyclosporine A combined with topical fluocinolone acetonide, tacrolimus (FK-506) monotherapy, combined cyclosporine A/$\alpha\beta$–T-cell receptor monoclonal antibody, FK-506/$\alpha\beta$–T-cell receptor monoclonal antibody, and cyclosporine A/antilymphocyte serum therapies were used for different dose and time regimens. Combined protocols of cyclosporine A/$\alpha\beta$–T-cell receptor monoclonal antibody resulted in long-term survival and donor-specific tolerance in the hind-limb allografts recipients. Transplants under combined cyclosporine A/$\alpha\beta$–T-cell receptor monoclonal antibody therapy survived over 350 days[42–46] (Fig. 1).

We also evaluated the role of host thymus in tolerance induction in limb allograft transplants across the major histocompatibility complex barrier and a 7-day cyclosporine A/$\alpha\beta$–T-cell receptor monoclonal antibody protocol. We confirmed that the presence of recipient thymus was imperative for induction of donor-specific tolerance and resulted in indefinite survival (mean survival time, 370 days) of rat hind-limb allografts under a cyclosporine A/$\alpha\beta$–T-cell receptor monoclonal antibody protocol.[47]

### Cremaster Muscle Composite Tissue Allograft Transplantation Model

We have developed a composite tissue allotransplantation model with which to study the microcirculatory hemodynamics during acute allograft rejection and to test the effects of surgical trauma on ischemia-reperfusion injury. The donor cremaster muscle allografts were prepared as a tube flap, harvested on the common iliac vessels, and transplanted to the neck region of the recipient. We found that cremaster muscle transplantation in mice is a reliable and reproducible model with a 95 percent success rate. The model offers the unique possibility of studying different hemodynamics and leukocyte-endothelium interaction during acute allograft rejection and in response to ischemia-reperfusion injury.[48] This model was not designed to investigate long-term survival of allografts; thus, no long-term results of allografting are available.

### Hind-Limb/Cremaster Transplantation Model

To determine the potential use of antibodies to adhesion molecules in composite tissue allografts, we investigated the effects of anti–intercellular adhesion molecule-1 and anti–lymphocyte function-associated molecule-1 monoclonal antibody treatment in a rat hind-limb cremaster transplantation model. This model allows monitoring directly, in vivo, microcirculation responses such as rolling, adhering, and transmigrating neutro-



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**Table 1. Experimental Models of CTA and Their Reasons for Development**

| Experimental Models of CTA | Reasons for Developments of the CTA Models |
|---|---|
| 1. Hind-limb allograft transplantation models | To test the efficacy of different immunosuppressive protocols, including CsA monotherapy; CsA combined with topical fluocinolone acetonide; FK-506 monotherapy; combined CsA/αβ-TCRmAb, FK-506/αβ-TCRmAb, and CsA/ALS therapies for different dose and time regimens in a highly immunologically challenging model of CTA, including multiple vascularized tissue types (e.g., skin, muscle, bone marrow). |
| 2. Cremaster muscle CTA transplantation model | To study the microcirculatory hemodynamics during acute allograft rejection and to test the effects of surgical trauma on ischemia-reperfusion injury. |
| 3. Hind-limb/cremaster transplantation model | To investigate the effects of anti–ICAM-1 and anti–LFA-1 monoclonal antibody treatment in a CTA model. This model provides important information on the hemodynamics and sequence of events occurring during rejection of CTAs. |
| 4. Composite vascularized skin and femoral bone transplantation models | To introduce composite vascularized skin/bone transplantation models for future vascularized bone marrow–based tolerance induction studies. |
| 5. Bone marrow transplantation models | To investigate the effect of different routes and dosages of donor-derived bone marrow cell transplantation on donor-specific tolerance induction and chimerism across the MHC barrier under a short, 7-day protocol of CsA monotherapy and combined CsA/αβ-TCRmAb therapy. |
| 6. Vascularized skin allograft transplantation model | To test the potential of different shorter (given for only 7 days) immunosuppressive protocols, including αβ-TCRmAb, CsA, or FK-506 monotherapy or combined regimens of αβ-TCRmAb/CsA and αβ-TCRmAb/FK-506 therapy to extend survival and to induce chimerism in an immunologically challenging model of vascularized skin allografts. |
| 7. Vascularized bone marrow transplantation model | To introduce a new inset technique of vascularized femoral bone allograft to the recipient inguinal region. |
| 8. Bilateral vascularized femoral bone marrow transplantation model | First, as an isograft, to investigate the feasibility of BVFB transplantation based on abdominal aorta and inferior vena cava. Second, as an allograft, to test the potential of BVFB for tolerance induction across the MHC barrier under a combined CsA/αβ-TCRmAb protocol given for 7 days. |
| 9. Vascularized laryngeal allograft transplantation model | To apply the αβ-TCRmAb protocol along with tacrolimus to the existing rat model of laryngeal transplantation as a tolerance-inducing strategy. |
| 10. Full face/scalp transplant model | To evaluate the feasibility, technical aspects, survival rates, and complications of composite face/scalp flap transplantation in the rat model. |
| 11. Modifications of full face/scalp transplantation model | To improve the survival of full face/scalp allograft recipients; two different modifications of the arterial anastomoses in the recipients are introduced. |
| 12. Hemiface transplantation model | To evaluate technical and immunologic aspects and potential clinical applicability of the hemiface transplant model compared with the full face transplant model. |
| 13. Composite hemiface/calvaria transplantation model | To augment the face/scalp transplantation model in the rat by combining it with vascularized calvarial bone based on the same vascular pedicle as a new treatment option for coverage of severe craniofacial defects. |
| 14. Composite hemiface/mandible/tongue allograft transplant model | To extend application of the face/scalp transplantation model in the rat by incorporation of the vascularized mandible, masseter, and tongue as a new reconstructive option for large soft- and hard-tissue defects of the head and neck region. Thus, this experimental model enhances knowledge about the immune reconstitution and immune responses following face transplantation with vascularized bone marrow. |
| 15. Rat maxilla allotransplantation model | To test the effects of vascularized maxilla allotransplantation on the substructures of the maxilla, including teeth, and for studying the immunologic and wound-healing aspects of the procedure. |
| 16. Combined semimembranous muscle and epigastric skin flap model | To introduce a new combined muscle and skin flap model for microcirculatory, pharmacologic, physiologic, biochemical, and immunologic studies. |
| 17. Composite osteomusculocutaneous sternum, ribs, thymus, pectoralis muscles, and skin allotransplantation model | To introduce a highly antigenic new composite vascularized sternal bone marrow transplant model including sternum, ribs, thymus, muscle, and skin that can be applied for augmentation of hematopoietic activity for chimerism induction after transplantation. |
| 18. Composite osteomusculocutaneous hemiface/nose, lower lip, and premaxilla allograft transplantation | To evaluate the effect of allogeneic transplantation on the substructures of the vascularized premaxilla, nose, and whiskers with the trigeminal and facial nerves for evaluation of the allotransplanted sensory and motor nerves and for studying the immunologic and wound-healing aspects of the procedure. |
| 19. Vascularized iliac osteomyocutaneous transplantation model | To introduce a new vascularized bone marrow transplant model combination with a high antigenic load of a large vascularized skin component. |
| 20. Total abdominal wall transplantation model | To introduce a model with a large antigenic load of vascularized skin, which is considered the most immunogenic tissue in the body. This model allows study of the migration of donor passenger leukocytes of skin origin (dendritic cells) into lymphoid organs of recipients, contributing to long-term allograft survival and tolerance. |
| 21. Penile allotransplantation model | To introduce the model of functional penis transplantation, which is a unique graft that can be applied for penile reconstruction after trauma and cancer ablative surgery, because standard penile reconstructive procedures are not satisfactory. |

CTA, composite tissue allotransplantation; CsA, cyclosporine A; TCRmAb, T-cell receptor monoclonal antibody; ALS, antilymphocyte serum; FK-506, tacrolimus; BVFB, bilateral vascularized femoral bone; MHC, major histocompatibility complex; ICAM-1, intercellular adhesion molecule-1; LFA-1, lymphocyte function-associated molecule-1.



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**Fig. 1.** Hind-limb transplant model. The appearance of the transplanted hind limb (Lewis–Brown Norway to Lewis) at day 350 under combined cyclosporine A/$\alpha\beta$–T-cell receptor monoclonal antibody therapy showing no signs of rejection.

phils and lymphocytes in response to antibody therapy. This unique approach provides important information on the hemodynamics and sequence of events that occur during rejection of composite tissue allotransplants.[49] Monoclonal antibodies against anti–lymphocyte function-associated molecule-1 or intercellular adhesion molecule-1 alone inhibit the activation of leukocytes at the microcirculatory level but do not prolong graft survival. Thus, the first clinical signs of rejection were observed on the ninth day in groups treated with anti–intercellular adhesion molecule-1 and anti–lymphocyte function-associated molecule-1. However, the combination of anti–intercellular adhesion molecule-1 and anti–lymphocyte function-associated molecule-1 monoclonal antibodies significantly prolonged allograft survival until day 13 in this composite tissue transplantation model.[49]

### Composite Vascularized Skin and Femoral Bone Transplantation Models

To test the role of bone morrow in acceptance of vascularized allografts, we have designed a model of combined vascularized groin skin flap (combined with bone) transplantation. Transplantations were performed between genetically identical Lewis rats. Combined vascularized skin (groin) and femoral bone flaps were transplanted based on the femoral vessels. All flaps survived over 100 days following transplantation. Histologic examination of the femoral bone revealed active hematopoiesis, with viable compact and cancellous bone components at day 100 following transplantation.[50] Based on this study, we introduced composite vascularized skin/bone transplantation models for bone marrow–based tolerance induction studies.[51]

### Bone Marrow Transplantation Models

We investigated the effect of different routes and dosages of donor-derived bone marrow cell transplantation on donor-specific tolerance induction and chimerism across the major histocompatibility complex barrier under a short, 7-day protocol of cyclosporine A monotherapy and combined cyclosporine A/$\alpha\beta$–T-cell receptor monoclonal antibody therapy. Bone marrow cells were transplanted between Brown Norway donors and Lewis recipients. Intraosseous transplantation of donor-specific bone marrow cells was 75 percent more efficient in induction of donor-specific chimerism compared with intravenous transplantation, and the level was 50 percent higher in animals receiving $70 \times 10^6$ bone marrow cells (9.9 percent) when compared with animals receiving $35 \times 10^6$ bone marrow cells (4.9 percent)[52,53] (Fig. 2).

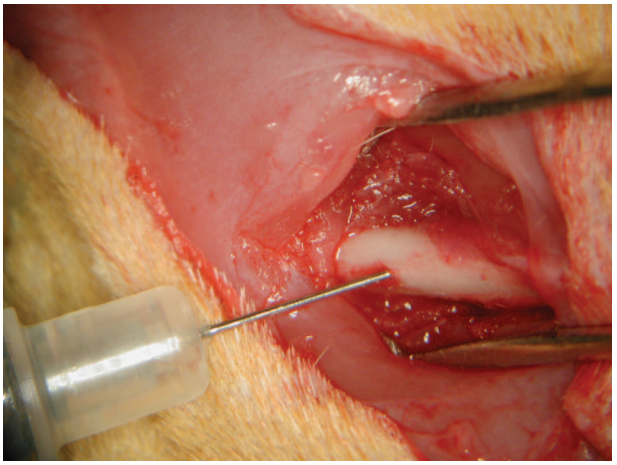


**Fig. 2.** Intraosseous bone marrow transplantation model.



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We also investigated the effect of crude bone marrow cotransplantation on vascularized skin allograft survival. The use of combined cyclosporine A and αβ–T-cell receptor monoclonal antibody therapy for 35 days with crude bone marrow transplantation extended skin allograft survival up to 65 days in a vascularized skin allograft model between semiallogeneic Lewis–Brown Norway donors and Lewis recipients.[54]

### Vascularized Skin Allograft Transplant Models

The efficacy of different immunosuppressive protocols and their potential to extend survival and to induce chimerism was tested in the most immunologically challenging model of vascularized skin allografts. Transplantations across strong major histocompatibility complex barriers were performed between fully allogeneic ACI donors and Lewis recipients. Skin flaps, based on the femoral artery and vein, were harvested from the donor groin and transplanted to the recipient's groin (Fig. 3). Animals received either αβ–T-cell receptor monoclonal antibody, cyclosporine A, or FK-506, or a combined immunosuppressive protocol consisting of αβ–T-cell receptor monoclonal antibody/cyclosporine A and αβ–T-cell receptor monoclonal antibody/FK-506 therapy given for only 7 days.[55]

There was no significant difference between monotherapy groups. Thus, transplants under immunosuppressive monotherapy were rejected between 14 and 20 days in the cyclosporine A therapy group, between 14 and 19 days in the FK-506 therapy group, and between 10 and 14 days in the αβ–T-cell receptor monoclonal antibody group. However, survival under the combined FK-506/αβ–T-cell receptor monoclonal antibody treatment (survival was up to 39 days ) and cyclosporine A/αβ–T-cell receptor monoclonal antibody treatment (survival was up to 84 days) protocols were effective in inducing and maintaining chimerism and substantially extended the survival of vascularized bone marrow transplants across the major histocompatibility complex barrirer.[55]

To introduce a new vascularized skin and muscle flap model, a combined semimembranous muscle and epigastric skin flap model was developed.[56] In addition, a total abdominal wall transplantation model was developed (all transplants showed viable islands at posttransplant day 200 under a cyclosporine A monotherapy protocol) as a new large vascularized skin allotransplantation model.[57]



**Fig. 3.** Vascularized skin (groin) allograft transplant model. (*Above*) Appearance of the harvested vascularized skin allograft from semiallogeneic Lewis–Brown Norway donors. (*Center*) Vascularized groin skin transplants based on the femoral vessels were performed between semiallogeneic Lewis–Brown Norway donors and Lewis recipients (early posttransplant view). (*Below*) The recipient of skin (groin) allograft 63 days after transplantation shows no sign of rejection under low-dose cyclosporine A monotherapy.



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### Vascularized Bone Marrow Transplantation Models

The hind-limb allograft in rat was the first vascularized bone marrow transplantation model to be successful in delivery of donor-specific chimerism and developed our interest in the role of vascularized bone marrow transplantation. We performed 52 hind-limb transplantations between Lewis–Brown Norway ($RT1^{1+n}$) donors and Lewis ($RT1^{1}$) recipients to investigate the role of shorter $\alpha\beta$–T-cell receptor/cyclosporine A protocols on tolerance induction. The impact of 21-, 7-, and 5-day protocols of combined $\alpha\beta$–T-cell receptor monoclonal antibody/cyclosporine A treatment on tolerance induction was tested. All transplants under combined $\alpha\beta$–T-cell receptor/cyclosporine A therapy survived over 350 days. All recipients at day 100 following transplantation uniformly accepted skin allografts from the donor (Lewis–Brown Norway) and the recipient (Lewis) but rejected third-party (ACI) grafts. We confirmed that the 5-day protocol was long enough to maintain immunologic unresponsiveness of a new repertoire of recipient T cells, which led to the engraftment of donor hematopoietic stem cells.[44]

We also introduced a new technique for insetting vascularized femoral bone allograft into the recipient inguinal region. Vascularized femoral bone allograft was harvested based on the lateral femoral circumflex and superficial circumflex iliac arteries (Fig. 4). In the recipient, the vascular anastomoses were performed to the femoral vessels and flap insetting was completed in the inguinal region. More than 50 transplantations were performed, and the patency of the anastomosis and viability of the bone morrow were confirmed in all animals.[58]

To introduce new vascularized bone marrow transplantation models, we have recently developed a composite vascularized sternal bone marrow transplant model[59] (long-term survival of the allotransplants was 130 days following transplantation) and a vascularized iliac osteomyocutaneous transplantation model (histologic examination of allotransplants did not reveal any signs of rejection at day 200 following transplantation).[60]

### Bilateral Vascularized Femoral Bone Marrow Transplantation Model

To test the potential of vascularized bone marrow transplantation for tolerance induction, we introduced bilateral vascularized femoral bone isograft and allograft transplant models based on the abdominal aorta and the inferior vena cava.

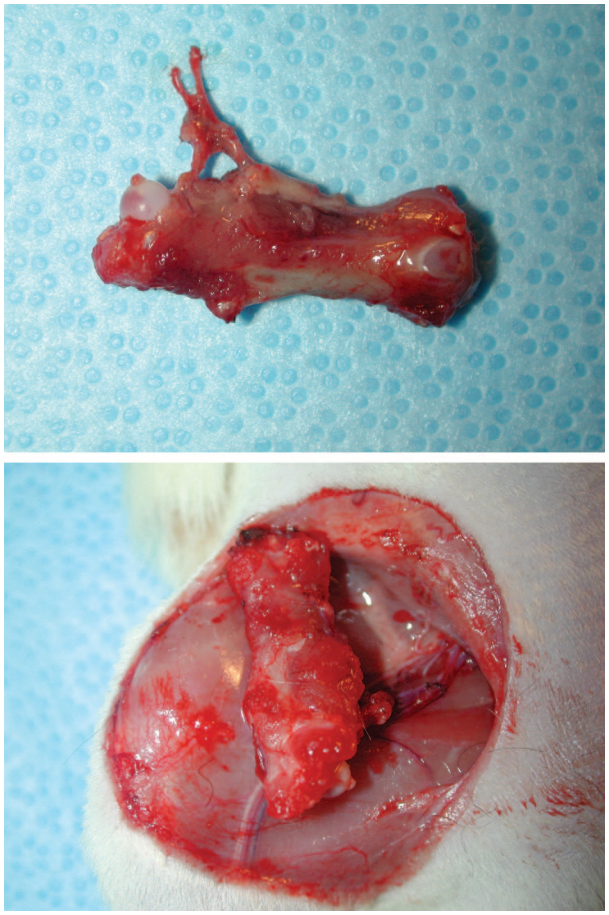


**Fig. 4.** Vascularized bone marrow transplantation model. (*Above*) Appearance of the harvested vascularized femoral bone allograft based on the lateral femoral circumflex and superficial circumflex arteries. (*Below*) In the recipient, the vascular anastomoses were performed to the femoral vessels, and flap insetting was completed in the inguinal region.

Isotransplants were performed between Lewis rats. In the recipient, the harvested isograft transplants were transferred into the abdominal cavity.[61] The vascular pedicles of transplants into the abdominal cavity were patent and the bones were viable during the follow-up period of 63 days. We have confirmed the feasibility of bilateral vascularized femoral bone transplantation based on the abdominal aorta and the inferior vena cava.[61]

As in allografts, the efficacy of bilateral vascularized femoral bone in induction of chimerism across the major histocompatibility complex barrier was tested under a combined cyclosporine A/$\alpha\beta$–T-cell receptor monoclonal antibody protocol given for 7 days. Allotransplantations were performed between Brown Norway donors and Lewis recipients. At day 21, the peak level of donor-specific chimerism of 24.2 percent was con-



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firmed in peripheral blood of bilateral vascularized femoral bone recipients. At day 63, the level of chimerism declined to 1.5 percent and was maintained at this level thereafter. Histologic examination revealed viable bone marrow cells up to 35 days following transplantation. This bilateral vascularized femoral bone transplant model can be applied as augmentation therapy of bone marrow transplants in tolerance induction protocols.[62]

### Vascularized Laryngeal Allograft Transplantation Model

In 1992, Strome et al. developed a vascularized laryngeal allograft transplantation model to reexamine the potential for clinical application, and this model contributed to the first successful human larynx transplant in 1998. Over 1500 rat transplants later, numerous modifications have improved the applicability of this model to the composite tissue allotransplantation field.[63,64]

In a collaborative study, we applied the $\alpha\beta$–T-cell receptor monoclonal antibody protocol along with tacrolimus to the existing rat model of laryngeal transplantation as a tolerance-inducing strategy. Larynges were transplanted from Lewis–Brown Norway ($RT1^{l/n}$, F1) donors to Lewis ($RT1^{l}$) recipients. Recipients received 7 days of treatment with tacrolimus and mouse antirat $\alpha\beta$–T-cell receptor monoclonal antibodies. All 10 recipients survived until they were killed at 100 days. Histologic examination suggested functional allograft tolerance. In this rat laryngeal transplantation model, functional tolerance was induced under a combined tacrolimus and $\alpha\beta$–T-cell receptor protocol.[65]

### Face Transplantation Models

We have introduced different models of face transplantation.[66–82]

#### Full Face/Scalp Transplant Model

We performed full face/scalp allograft transplantation across the major histocompatibility complex barrier in a rodent model. Transplants were performed between semiallogeneic Lewis–Brown Norway ($RT1^{l+n}$) and fully allogeneic ACI ($RT1^{a}$) donors and Lewis ($RT1^{l}$) recipients. In this model, cyclosporine A (16 mg/day) was started on the day of surgery and tapered to 2 mg/kg over a 4-week period. Long-term survival (>200 days) was achieved without any signs of rejection with low-dose (2 mg/kg/day) cyclosporine A therapy[68,69] (Figs. 5 through 7).

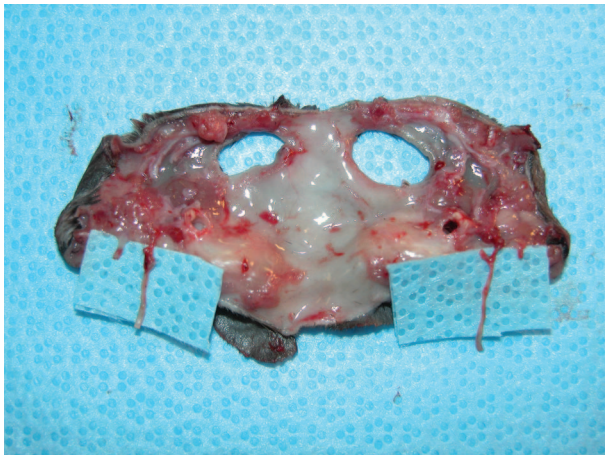


**Fig. 5.** The full face/scalp allograft transplantation model. Full face/scalp flaps including the external ears and scalp, based on the common carotid artery and external jugular vein, were harvested from the donors.

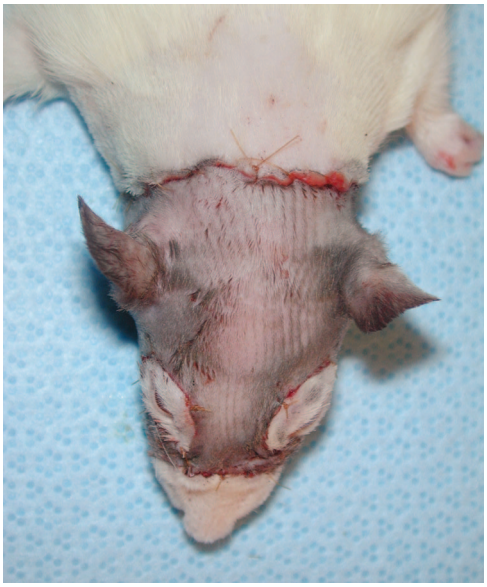


**Fig. 6.** Immediate posttransplant view of the full face/scalp allograft recipient. Transplantation was performed between fully allogeneic ACI donors and Lewis recipients.

#### Modifications of the Full Face/Scalp Transplant Model

To improve the survival of full face/scalp allograft recipients, two different modifications of the arterial anastomoses in the recipients were introduced. The unilateral common carotid artery of the recipient was used to vascularize the full face/scalp flap. These arterial modifications have significantly reduced the complications associated with the bilateral common carotid arterial anastomoses and subsequently the postopera-



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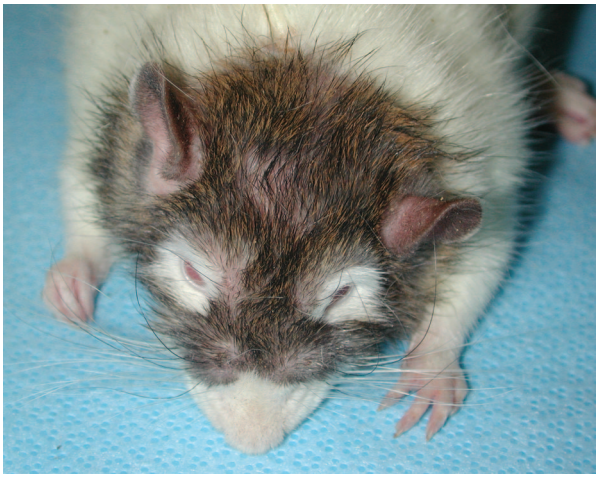


**Fig. 7.** Late posttransplantation views of full face/scalp allograft recipient on low-dose cyclosporine A monotherapy at day 200, showing no signs of rejection.

tive mortality of the animals. Transplants in which the unilateral common carotid artery was used yielded 100 percent survival over 200 days following transplantation.[70]

### Hemiface Transplant Models

We introduced a hemifacial allograft transplant model that is technically less challenging compared with the full face/scalp model. The same low-dose cyclosporine A monotherapy (2 mg/kg/day) immunosuppressive protocol was used during the follow-up period. Long-term survival was achieved in 100 percent of Lewis–Brown Norway (up to 400 days) and ACI (up to 330 days) recipients[71] (Fig. 8).

In addition, we introduced more complex hemiface transplant models, including composite hemiface/calvarium[72] (long-term survival of the allotransplants was 220 days), hemiface/mandible/tongue[73–78] (long-term survival of the allotransplants was over 300 days) (Fig. 9), maxilla[79] (allotransplants survived up to 105 days following transplantation), and composite hemiface/nose/lower lip/premaxilla models[80–82] (long-term survival of the allotransplants was 180 days following transplantation). These models tested the activity of complex allografts under different protocols and the growth potential of the maxillary and mandible components, including teeth, over the course of long-term survival.[72–82]

### Penile Allotransplantation Model

To study immunologic and functional aspects of penile allograft transplantation, an experimental model of allogeneic penis transplantation was developed (long-term survival of the allotransplants was 200 days following transplantation).[79,83]

## THE FUTURE: PRESERVATION PROTOCOL AND BANKING

In 2006, Imhof et al. cryopreserved whole ovaries using a controlled-rate freezing system, and the thawed ovaries were returned to the contralateral orthotopic site with microsurgical vascular anastomosis. One sheep conceived after spontaneous intercourse and delivered a healthy lamb 545 days after transplantation. They concluded that microvascular anastomosis of whole ovaries and orthotopic transplantation after cryopreser-

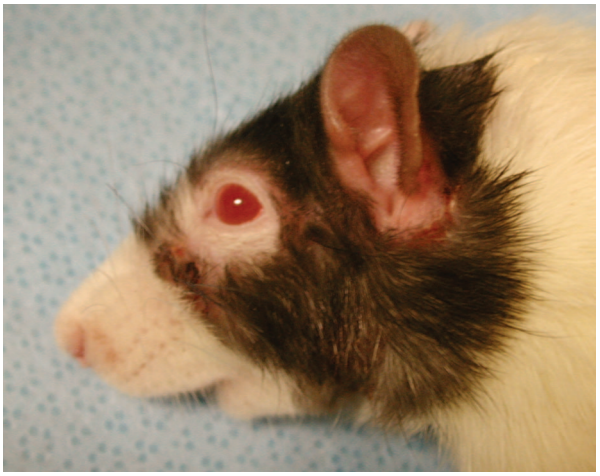


**Fig. 8.** Hemifacial allograft transplantations were performed between fully allogeneic ACI donors and Lewis recipients. Late postoperative view (day 150) with no signs of rejection under a low maintenance dose of cyclosporine A.

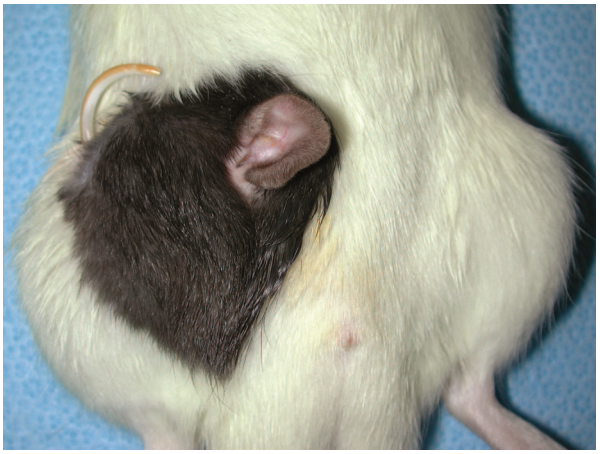


**Fig. 9.** Hemiface/mandible/tongue allotransplantation model. This photograph shows the appearance of the hemiface/mandible/tongue allograft transplant at day 100 following transplantation (Lewis–Brown Norway to Lewis rats).



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vation is a technically feasible and promising procedure in ovarian tissue banking.[84] In the experimental study we performed on sheep, we concluded that as cryopreservation protocols improve, ovarian autotransplantation with vascular anastomosis may prove to be superior to current ovarian tissue banking and grafting techniques.[85]

These studies are giving great promise for future cryopreservation studies. There is no doubt that composite tissue allotransplantation has a great future in plastic and reconstructive surgery.

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