

# Immunobiology of Face Transplantation

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**Abstract:** Fourteen face transplants have been performed worldwide since the procedure was successfully introduced in 2005. Vascularized composite tissue allotransplantation may now be considered a viable option for the repair of complex craniofacial defects, for which the results of autologous reconstruction remain suboptimal. However, the benefits must be balanced against the risks inherent in major surgery and the adverse effects of lifelong immunosuppression. In this article, we review the current practice and areas of controversy in facial vascularized composite tissue allotransplantation with particular respect to the unique immunobiology of this procedure. We also describe promising recent advances in immunotherapy and tolerance induction strategies that may soon reach clinical application.

**Key Words:** Face transplant, composite tissue allotransplant, immune biology, facial allograft

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Face transplantation was introduced to the clinical arena in 2005, by Devauchelle et al<sup>1</sup> in France. This case followed the first successful hand transplant in 1998 and built on many years of pre-clinical research and surgical development in establishing the specialty of vascularized composite tissue allotransplantation (VCA). The dedication and determination of Nobel laureate plastic surgeon, Dr. Joseph Murray, opened the era of clinical organ transplantation; however, 30 years elapsed before plastic surgeons reentered the world of clinical transplantation.<sup>2</sup> On the preclinical front, it was Black et al<sup>3</sup> in 1985, investigating the calcineurin inhibitor cyclosporine A in a rodent limb transplant model, who demonstrated that long-term acceptance of VCA could be achieved across a major histocompatibility barrier.

Today, clinical VCA programs have been developed in a number of countries, including France, China, United States, and Spain. To date, 14 facial allotransplants have been performed, although not all have been reported in the scientific literature. Indications have included burns, ballistic trauma, and reconstruction

after tumor resection, with transplants covering a broad spectrum of size and design, from myocutaneous facial flaps of near-total facial area to complex osteomyocutaneous designs based on Le Fort osteotomies for reconstitution of the midfacial skeleton.<sup>4</sup> Among the many challenges posed by this complex surgery, balancing the need to prevent the rejection of facial tissues, particularly skin and mucosa, against the cumulative risks of lifetime immunosuppressive treatment is paramount and remains a major focus of research.

In this regard, the purpose of this article was to review the current practice and existing controversies in facial VCA with particular respect to the unique immunobiology of this procedure. We will also describe promising recent advances in immunotherapy and tolerance induction strategies that may soon reach clinical application.

## CURRENT PRACTICE

Facial VCA, although still an infrequent procedure, is now a viable option for the reconstruction of complex craniofacial defects. Despite great refinement of autologous techniques, the reconstruction of facial subunits such as the eyelid, lip, and nose frequently yields results suboptimal in both function and form. Furthermore, transplants based on Le Fort osteotomies offer unmatched reconstruction of devastating three-dimensional deformities of the cranio-maxillofacial skeleton, in which satisfactorily “replacing like with like” is virtually impossible using autologous techniques. Osteomyocutaneous facial VCA, therefore, represents the ultimate application of Gillies’ fundamental principle, to “honor that which is normal and return it to normal position.”<sup>5</sup> However, the benefits do not come without cost, and the cases completed to date demonstrate the many significant challenges and concerns associated with facial VCA, including control of infection, prevention of rejection, psychologic adaptation, rehabilitation, cortical integration, and ethical practice.<sup>6</sup>

Considerable variation in indication, total surface area of facial and scalp skin transplanted, and tissue types included (ie, skin-muscle only versus osteomyocutaneous VCA) make direct comparison between cases in the literature difficult. However, there have been similarities in the immunosuppressive regimens used. Most notably, all patients have been maintained on triple-therapy regimens of tacrolimus, mycophenolate mofetil, and prednisolone, after induction with antithymocyte globulin. These immunosuppression protocols have proven effective, with no reported cases of rejection in patients compliant with treatment, although acute rejection episodes requiring treatment with intravenous and/or oral steroid regimens have occurred in all patients.<sup>4</sup>

In addition to the triple-therapy approach, derived from experience in solid organ transplantation, some centers have used novel adjuvant therapies to address the perceived heightened challenge of skin transplantation or perhaps reduce the overall requirement for immunosuppression. Devauchelle and Dubernard, citing the improved survival of organ transplants in some recipients of donor hematopoietic stem cells,<sup>20,21</sup> included donor bone marrow infusion in the regimen for the first case. However, there was no significant evidence of benefit, and the doses and levels of immunosuppression were not reduced. This patient also developed significant

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tacrolimus-induced nephrotoxicity, requiring conversion to sirolimus, highlighting the potential benefits of reducing the long-term requirement for such agents.<sup>8</sup>

Extracorporeal photopheresis, which has been found successful as a supportive treatment in solid organ acute rejection, was introduced to face transplantation by Hivelin et al<sup>9</sup> and Lantieri et al,<sup>10</sup> and this has been used in their series of 4 cases to date. Although the mechanism of extracorporeal photopheresis has not been fully elucidated, it has been found beneficial in other areas of transplantation and has been used successfully after face transplantation to reverse rejection crises triggered by viral infection—a scenario in which escalation of immunosuppression could be detrimental.

## AREAS OF CONTROVERSY

Not surprisingly in such a novel field, a number of controversies relevant to the immunobiology of facial VCA exist, mainly relating to the risks of lifelong immunosuppression, and significant debate surrounds strategies for reducing this immunosuppressive burden versus the potential impact of reduced intensity regimens on long-term transplant function (ie, chronic rejection).

### Chronic Rejection

Chronic rejection is an incompletely understood phenomenon, frequently encountered in renal transplantation, which results in vasculopathy, gradual fibrosis and loss of function late after transplantation, despite levels of immunosuppressive drugs sufficient to prevent acute graft rejection. Chronic rejection is a significant problem in cardiac transplantation as well, with cardiac allograft vasculopathy a major cause of heart transplant loss. The prevailing hypotheses concerning the etiology of chronic rejection include subclinical alloreactivity of host-versus-graft that results in detrimental vascular pathology and graft loss.

Discussion of chronic rejection in VCA refers to vasculopathy characterized by neointimal hyperplasia, progressive vascular occlusion, and, ultimately, allotransplant loss. However, because of the short follow-up times so far available for facial VCA, it is not yet clear whether vasculopathy will manifest in a clinically relevant manner and what impact chronic rejection may have in facial transplantation. Progressive vasculopathy after facial transplantation has not been reported; however, in hand allotransplant experience, Breidenbach and Kaufman have reported a patient who developed rapid neointimal hyperplasia between 3 and 6 months after transplant, necessitating amputation of the progressively ischemic transplanted hand. They subsequently introduced a sophisticated ultrasound technique for monitoring transplant vasculopathy, and although this technology remains experimental and is not yet ready for clinical application, they have observed varying degrees of neointimal hyperplasia in other patients, in the absence of clinical problems, and the long-term course of these patients will be followed up with interest.<sup>11</sup> It must be emphasized, however, that a number of these patients were on experimental immunosuppressive regimens designed to significantly reduce the level of maintenance immunosuppression. As described previously, most face transplant recipients to date are maintained on multiagent regimens, based on standard “triple-therapy” (tacrolimus, mycophenolate mofetil, corticosteroid) protocols adapted from solid organ transplantation. Because of the similarity of the regimens, relevant comparison may be made to a number of other hand allotransplantation centers including those in Innsbruck and Poland, where all patients are maintained on triple therapy, with no reports of clinical or arteriographic evidence of vasculopathy in patients as far out as 10 years after transplant.<sup>12</sup> Long-term follow-up will be required to characterize the incidence and clinical manifestations of chronic rejection in facial transplantation

and to evaluate the effect of current and novel immunosuppressive regimens in this regard. In addition, further preclinical study will enhance our understanding of these phenomena in models currently under development at a number of centers.

### Opportunistic Infection With Cytomegalovirus

A second controversy related to the unique immunobiology of facial transplantation involves the recipient's susceptibility to opportunistic infection. Face transplant recipients, in common with recipients of solid organ transplants, are vulnerable to a wide variety of opportunistic viral pathogens—most commonly the cytomegalovirus (CMV). Despite appropriate prophylaxis, CMV viremia occurs at a rate of approximately 5% in the lowest-risk patients (donor seronegative/recipient seronegative) and approaches 50% in high-risk patients (donor seropositive/recipient seronegative). More importantly, the development of asymptomatic CMV infection during the first 100 days after transplant has been identified as an independent risk factor for mortality in transplant patients. Therefore, efforts to avoid the donor seropositive/recipient seronegative mismatch, reduce donor-related CMV transmission, and prevent disease progression could significantly improve long-term outcomes in facial transplantation, as such efforts have in solid organ transplantation.<sup>13</sup> It is therefore critical that centers performing facial transplant be fully aware of the current strategies and guidelines for universal CMV prophylaxis and therapy.

### Presensitization and Indolent Infectious Agents in Burn Patients

In the recent report of Lantieri et al<sup>10</sup> on a series of face transplants, it is noteworthy that 1 of 5 potential recipients recruited to the trial never underwent transplantation. Pretransplant screening for panel-reactive antibodies showed high levels, and despite desensitization treatment, these levels remained elevated to an extent that a suitable donor could not be identified. The patient was therefore removed from the waiting list. This patient had experienced electrical burns and, during initial treatment, had received cadaveric skin allografts. This scenario is not uncommon in burn patients, many of whom may require multiple cadaveric skin grafts to provide temporary coverage in the acute phase of burn treatment. Thus, it is likely that this exposure to alloantigen may have resulted in cross-sensitization to antigens of subsequent potential facial allotransplant donors. Transplantation under this circumstance could result in hyperacute rejection.<sup>14</sup> Although this complication has yet to be observed in clinical practice, the implications of hyperacute rejection of a facial transplant would be serious, so the discretion demonstrated by Lantieri et al and their patient was likely warranted.

Burn patients present additional challenges in facial transplantation because induction of systemic immunosuppression may allow indolent, resistant bacteria, which colonized the wound during the acute burn to reemerge in a clinically significant manner. This phenomenon has been suggested as potentially causative in the fatal infection observed in 1 of the 2 facial transplant mortalities so far reported in the literature. A strain of *Pseudomonas* identical in its resistance profile to that previously isolated during the patient's acute burn phase was implicated in a destructive soft tissue infection of the concomitantly transplanted hands and face. This required multiple debridements, during one of which the patient experienced cardiorespiratory arrest subsequent to airway obstruction. Despite resuscitation and intensive care, the patient ultimately died 2 months after transplant.<sup>15</sup> Despite the devastating nature of this complication, it must be appreciated that there is no precedent for these clinical situations. Only by honest reporting of complications, as exemplified in this case by Lantieri's group, will other centers be able to learn from these clinical outcomes and potentially avoid similar morbidity and mortality.

## Concomitant Face and Hand Transplantation

This same case, the first of concomitant face and hand transplantation, also highlighted some particular concerns regarding concomitant composite tissue allotransplants, not least the technical and logistical challenges involved. Recent studies have quantified the surface area of skin incorporated in concomitant face and upper extremity transplantation and hypothesized a potential correlation between transplanted skin area, as a measure of antigenic load, and the recipient immune response.<sup>16,17</sup> It is worth noting that Lantieri et al<sup>10</sup> used the same immunosuppressive regimen in this case, as in their series of face transplants without concomitant hands, and that there was no evidence of rejection at post mortem. However, this issue warrants further investigation and concomitant transplantation of the face and hands or other tissues will undoubtedly remain a challenging and contentious area.

## Pediatric Facial VCA

Although no cases of facial transplantation in pediatric patients have thus far been reported, the potential of this technique to offer high-quality single-stage reconstruction to children with complex congenital craniofacial defects has been proposed.<sup>18</sup> Pediatric facial transplantation will require the most rigorous assessment of risk-benefit ratio because of the potential impact of immunosuppression on growth and development, and the prolonged functional life span required of these transplants. In this setting, acceptance of facial transplantation as a reconstructive option will most likely require development of a robust tolerance induction strategy.

## RECENT ADVANCES IN IMMUNOTHERAPY IN VCA

In facial transplantation, as in all areas of transplant surgery, the benefits of the procedure must be balanced against the risks of lifelong immunosuppression, which may include infection, nephrotoxicity, diabetes, and malignancy. The benefits of facial transplantation must not be underestimated, however; and the potential of this procedure has been well demonstrated by the short- and medium-term outcomes of the cases to date.<sup>4</sup> Substantial improvement of this risk-benefit ratio could be achieved by reduction in the toxicity of, or requirement for, conventional long-term immunosuppression or by induction of donor-specific immunologic tolerance.

In formulating the immunosuppressive protocol for the first human face transplant, Devauchelle et al<sup>1</sup> recognized the potential of donor bone marrow infusion to mitigate the immune response against the transplant. This approach has been shown to induce tolerance in animal models (as reviewed by Sykes and Sachs<sup>19</sup>), and clinical trials in organ transplantation have reported improved graft survival without chronic rejection.<sup>20,21</sup> Although there has been little evidence of efficacy reported in the case of Devauchelle et al, with the patient remaining on triple-therapy immunosuppression, the Pittsburgh Hand Transplant Program has recently reported positive early results from their experience with donor bone marrow infusion and reduced intensity immunosuppression. Immunosuppression with alemtuzumab and tacrolimus, followed by bone marrow infusion at day 15, and maintenance with oral tacrolimus, has permitted acceptance of hand transplants in 2 patients. A rejection crisis in 1 patient was successfully treated with topical tacrolimus and clobetasol; the other remains rejection free.<sup>22</sup> Long-term follow-up will be required to assess the safety and efficacy of this regimen as well as the rate and severity of chronic rejection. Nevertheless, these early results represent a substantial reduction in immunosuppressive burden when compared with conventional triple therapy and point to the potential for similar regimens in facial VCA.

Induction of tolerance not only offers the potential for facial transplantation free from lifelong immunosuppression but also

avoids chronic rejection. Such tolerance has long been the goal of transplant surgeons, but it is viewed as particularly significant in VCA, where ethical concerns remain regarding the risks of immunosuppression in the treatment of conditions, which, in contrast to organ transplants, are not directly life threatening.<sup>23</sup>

Induction of donor-specific tolerance across major histocompatibility complex barriers reached clinical application for organ transplantation with the recent study of Kawai et al.<sup>7</sup> In this study, patients underwent conditioning with cyclophosphamide, anti-CD2 monoclonal antibody, thymic irradiation, and cyclosporine A before receiving a combined bone marrow and kidney transplant from HLA haplotype mismatched, living related donors. Immunosuppression was initially maintained with oral cyclosporine A, which was tapered during a period of several months and successfully discontinued in 4 of 5 patients.<sup>7</sup> These patients demonstrated transient lymphohematopoietic mixed chimerism and have maintained stable renal function without immunosuppression to date. Importantly, they showed no evidence of chronic rejection, either clinically or histologically, during follow-up periods of 3 to 5 years.

Donor and recipient HLA may be significantly more disparate in facial transplantation than in living donor renal transplantation. However, it is noteworthy that Devauchelle's initial case was performed across a comparable single haplotype HLA mismatch,<sup>1</sup> and thus, progress in the field of organ transplantation should not be discounted when considering future strategies in VCA.

This progress applies to the transplantation of the skin component of the VCA as well, which remains a significant challenge and the focus of considerable research effort.<sup>24</sup> Work in our laboratory, using an MHC-defined miniature swine model of VCA, has demonstrated reliable induction of tolerance of musculoskeletal tissues across both single haplotype and full class I and class II MHC mismatches. Recipients were conditioned with CD3<sup>+</sup> T-cell-depleting immunotoxin and received either donor bone marrow or cytokine-mobilized hematopoietic stem cells collected by leukapheresis from peripheral blood, under cover of a 30-day course of cyclosporine A. Although skin tolerance was not achieved with this protocol, prolonged skin survival to between 35 and 50 days was observed. Stable mixed chimerism was not found to be necessary for tolerance of musculoskeletal tissues.<sup>25</sup>

In a further development of this model, we have demonstrated robust, long-term tolerance of vascularized skin transplants across an MHC mismatch, having previously achieved stable mixed chimerism by a nonmyeloablative conditioning regimen and donor hematopoietic stem cell infusion.<sup>26</sup>

Graft-versus-host disease (GVHD) is common after hematopoietic stem cell transplantation and could be expected to complicate tolerance induction strategies based on mixed chimerism. Encouragingly, the incidence of GVHD in chimeras on this protocol has been minimal, with only 1 mild, nonprogressive case observed.<sup>27</sup>

The achievement of skin tolerance in a large animal preclinical model, without significant toxicity or GVHD, represents an important milestone in the immunobiology of VCA, but direct clinical application of this protocol is precluded by the need for donor preconditioning. To be applicable to facial transplantation, a tolerance induction protocol must commence after the decision to harvest the facial graft from a heart-beating, brain-dead donor and avoid any unnecessary delay of, or interference with, the work of the organ retrieval team. Work continues on developing this protocol to better meet the demands of clinical VCA.

Tolerance induction for VCA through the establishment of mixed chimerism seems to require engraftment of donor hematopoietic stem cells in the recipient bone marrow compartment. These engrafted stem cells are thought to provide a persisting source of donor cells to maintain stable peripheral blood chimerism, facilitating the development of both central and peripheral tolerance.

Central tolerance results from clonal deletion of donor reactive T cells during development in the thymus, whereas peripheral tolerance is mediated by the development of T regulatory cells, capable of suppressing donor reactive T cells that escape intrathymic deletion.

Although other approaches to tolerance induction, focusing on peripheral mechanisms, have been shown to be effective in preclinical and clinical studies of kidney transplantation<sup>7,28</sup> and have resulted in tolerance of skin in a humanized murine model,<sup>29</sup> the establishment of stable, mixed chimerism remains the only strategy to have achieved tolerance of skin in a preclinical large animal model. Recent studies have identified potential adjuncts to this approach, including cotransplantation with mesenchymal stem cells,<sup>30</sup> or T regulatory cells,<sup>31</sup> with the potential to enhance the survival of composite tissue transplants while minimizing the toxicity of the conditioning regimen. Further work will be required for these techniques to reach clinical applicability, but initial reports are encouraging.

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