Novel targeted drug delivery systems to minimize systemic immunosuppression in vascularized composite allotransplantation

Adriano Taddeo, Catherine Tsai, Esther Vögelin, and Robert Rieben

Purpose of review
The long-term adverse effects of immunosuppressive treatment, the high rate of acute rejection and the development of chronic rejection are the main factors preventing a wider clinical application of vascularized composite allotransplantation (VCA). Targeted immunosuppression using innovative drug delivery systems (DDS) may help to overcome these hurdles, increasing therapeutic efficacy while reducing systemic toxicity. This review provides a summary of the recently developed strategies for targeted delivery of immunosuppressive drugs in VCA.

Recent findings
Currently, several innovative strategies for targeted immunosuppression have been designed based on the anatomy and function of the target organ. Site-specific DDS have been developed both for directly accessible organs (i.e. skin, eye and lung) and internal organs (i.e. lymph nodes, liver, nervous system, etc.). In preclinical models, DDS designed for sustained, ‘on demand,’ or ‘on cue’ drug release has been shown to promote VCA survival while reducing systemic toxicity. These findings suggest that targeted delivery could increase patient compliance and potentially decrease toxicity in VCA recipients.

Summary
Targeted immunosuppression in VCA represents a promising approach for improving patient compliance and graft survival while reducing off-target toxicity, intensity and frequency of acute rejection episodes and risk of chronic rejection.

Keywords
drug delivery system, immunosuppression, immunosuppression toxicity, vascularized composite allotransplantation

INTRODUCTION
Vascularized composite allotransplantation (VCA) is an increasingly performed reconstructive procedure to restore the appearance, anatomy and function in patients suffering major tissue loss and not candidates for conventional reconstruction [1–3]. The success achieved in upper extremity and face transplantation has fueled a rapid expansion of the VCA field and a host of other types of VCA being performed around the world, including transplantation of abdominal wall, bone and joint, laryngotrachea, uterus, penis, tongue, ear, scalp and lower extremity [4].

Long-term adverse effects, however, of immunosuppressive treatment (IST) are the main factors preventing a wider clinical application of VCA. Chronic immunosuppression using this protocol is associated with diabetes mellitus, nephrotoxicity, osteonecrosis, leukopenia, hypertension, hyperlipidemia, opportunistic infections, higher cancer risk as well as psychological sequelae and increased financial burden [3,5]. Moreover, a high rate of acute rejection, with 88% of the patients experiencing at least one episode in the first posttransplant year [6*], and development of chronic rejection [7] leading to
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KEY POINTS

- Targeted drug delivery systems can increase the therapeutic index in VCA.
- Implantable and nanocarrier-based drug delivery systems have shown promising results for site-specific immunosuppression in skin, eye, lung and lymph nodes.
- On demand, inflammatory-responsive hydrogels represent a promising therapeutic approach for the treatment of inflammatory diseases and VCA rejection.
- Sustained site-specific immunosuppression can reduce side effects increasing patient compliance.
- Validation of targeted immunosuppression: exploration in large animal models is urgently required.

graft vasculopathy and often to graft loss, are others major problems in VCA management that strongly decrease the risk-to-benefit ratio of this procedure.

Several strategies have been investigated to boost the therapeutic index of immunosuppression (i.e. increasing efficacy and reducing toxicity). Among them, the development of drug delivery systems (DDS) has been relentlessly investigated and a plethora of DDS have been described for controlled drug release, enhanced bioavailability and selective organ targeting [8,9]. Due to its accessibility, VCA offers unique opportunities for site-specific delivery of immunosuppressive medications directly to the graft [10]. The rationale for such site-specific, transplant-targeted IST is to reduce systemic exposure and global collateral or end-organ adverse effects. Moreover, site-specific treatment may be used to increase patient compliance. Finally, because of the high availability of immunosuppressive drug where needed, targeted IST can reduce the number of systemic drugs required for desired efficacy, as well as the dose and frequency of IST.

In this review, we will summarize recently developed strategies for targeted delivery of immunosuppressive drugs. We will start by describing DDS developed for inflammatory diseases and solid organ transplantation (SOT) and will then focus on DDS developed specifically for targeted delivery in VCA.

TARGETED IMMUNOSUPPRESSION IN SOLID ORGAN TRANSPLANTATION AND INFLAMMATORY DISEASES

Several DDS for delivery of IST have been described in the fields of inflammatory disease and transplantation. An overview is presented in Tables 1 and 2.

Readers are directed to recent reviews that comprehensively describe the different strategies for drug delivery [54–56].

Strategies for targeted delivery should always be designed based on the anatomy and function of the target organ. Indeed, organs such as the skin, the eye or the lung offer unique opportunities for targeted delivery (e.g. topical administration, eye drops, inhalation of aerosolized medication). Conversely, visceral organs such as the liver, lymph nodes and kidney require DDS containing specific targeting moieties capable of directing the DDS to the target organ after systemic application.

Site-specific administration of IST has a long history in the management of inflammatory skin disease [57]. Considering that the skin represents the primary target in VCA rejection [58], DDS developed for targeted IST delivery in the skin are of outstanding interest to the VCA community. Several topical formulations of calcineurin inhibitors have been described so far and include Food and Drug Administration (FDA)-approved commercial formulations such as tacrolimus ointment, pimecrolimus cream and clobetasol propionate cream [10]. Recently, innovative nanocarrier-based topical formulations of tacrolimus have been developed with the aim to increase skin penetration while reducing systemic exposure. Topical application of a liposomal tacrolimus formulation has been shown to increase drug availability in the skin and delay skin allograft rejection in a mouse model [11]. In addition, smart DDS that are able to respond to the tissue environment have been described for IST delivery into the skin. Thermoresponsive nanogels loaded with tacrolimus [37,38] or pH-sensitive dexamethasone-loaded nanoparticles [16**] are only some of the examples showing improved skin penetration and efficacy.

Similar to the skin, the eye and the lung offer the possibility to use topical application for targeted delivery of immunosuppressive drugs. Topical instillation of eye drops, intravitreal delivery methods and periocular routes of drug delivery are some of the described routes for targeted delivery of medications directly to the eye [41*]. Moreover, intraocular implantable DDS for targeted delivery of dexamethasone [59,60] and other corticosteroids [41*] as well as tacrolimus [42] have been developed and are used in a wide range of chronic ocular inflammatory diseases to deliver drugs in a sustained fashion. Aerosolized calcineurin inhibitors have been developed and their efficacy has been tested in clinical trials. Although these formulations failed to show efficacy in disease-free survival or overall mortality, high concentration of the drug was observed in the lung with minimal systemic
### Table 1. Targeted immunosuppression using nanoparticles and microparticles in solid organ transplantations and inflammatory diseases

<table>
<thead>
<tr>
<th>DDS description</th>
<th>Target organ (mechanism)</th>
<th>Immuno-suppressive drug</th>
<th>Testing model</th>
<th>DDS administration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposome</td>
<td>Skin (site-specific administration)</td>
<td>Tacrolimus</td>
<td>Mouse skin allograft</td>
<td>Topical application</td>
<td>[11]</td>
</tr>
<tr>
<td>Neutral multilamellar liposomes</td>
<td>Skin (site-specific administration)</td>
<td>Tacrolimus</td>
<td>Rat allergic contact dermatitis</td>
<td>Topical application</td>
<td>[12]</td>
</tr>
<tr>
<td>Methoxy-PEG-dihexyl substituted PLA micelles</td>
<td>Skin (site-specific administration and improved deposition)</td>
<td>Tacrolimus</td>
<td>In-vitro human skin</td>
<td>Topical application</td>
<td>[13]</td>
</tr>
<tr>
<td>Transferrinomes</td>
<td>Skin (site-specific administration)</td>
<td>Tacrolimus</td>
<td>Mouse atopic dermatitis</td>
<td>Topical application</td>
<td>[14]</td>
</tr>
<tr>
<td>Rhodolipid-based nanoparticles</td>
<td>Skin (site-specific administration)</td>
<td>Dexamethasone or Tacrolimus</td>
<td>In-vitro human skin</td>
<td>Topical application</td>
<td>[15]</td>
</tr>
<tr>
<td>pH-sensitive nanoparticles (various formulation)</td>
<td>Skin (site-specific administration)</td>
<td>Dexamethasone</td>
<td>In-vitro evaluation</td>
<td>In solution</td>
<td>[16**]</td>
</tr>
<tr>
<td>Liposomes containing bile salts</td>
<td>Eye (site-specific administration)</td>
<td>Tacrolimus</td>
<td>Naive rabbit cornea</td>
<td>Eye instillation</td>
<td>[17]</td>
</tr>
<tr>
<td>Eudragit P-4135F nanoparticles</td>
<td>Intestine (sensitivity to luminal pH during intestinal passage)</td>
<td>Tacrolimus</td>
<td>Porcine small bowel transplantation</td>
<td>Oral administration</td>
<td>[33]</td>
</tr>
<tr>
<td>PEG-PE-amine and N-palmitoyl homocysteine micelles</td>
<td>Endothelial cells (using cyclic Arginine-Glycine-Aspartate, cRGD moieties to target αvβ3 integrin)</td>
<td>Rapamycin</td>
<td>In-vitro and ex-vivo EC culture</td>
<td>In-vitro culture</td>
<td>[36]</td>
</tr>
</tbody>
</table>

**PEG, poly(ethylene glycol); PLC, poly(D,L-lactide-co-e-caprolactone); PLGA, poly(lactide-co-glycolide); PPS, poly(propylene sulfide).**
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Table 2. Targeted immunosuppression using controlled delivery systems and special formulations in solid organ transplantations and inflammatory diseases

<table>
<thead>
<tr>
<th>DDS description</th>
<th>Target organ (mechanism)</th>
<th>Immuno-suppressive drug</th>
<th>Testing model</th>
<th>DDS administration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyglycerol-based thermoresponsive nanogels</td>
<td>Skin (site-specific administration)</td>
<td>Dexamethasone or Tacrolimus</td>
<td>In-vitro human skin</td>
<td>Topical application</td>
<td>[37,38]</td>
</tr>
<tr>
<td>PLC microfilms</td>
<td>Eye (site-specific administration)</td>
<td>Prednisolone acetate or Tacrolimus</td>
<td>Rat corneal transplantation Mouse allergic conjunctivitis</td>
<td>Subconjunctival implanted</td>
<td>[39,40]</td>
</tr>
<tr>
<td>Intravitreal implants (various formulations)</td>
<td>Eye (site-specific administration)</td>
<td>Corticosteroids</td>
<td>In clinical use</td>
<td>Intravitreal implant</td>
<td>[41]</td>
</tr>
<tr>
<td>PLGA scleral plug</td>
<td>Eye (site-specific administration)</td>
<td>Tacrolimus</td>
<td>Rabbit uveitis</td>
<td>Intravitreal implant</td>
<td>[42]</td>
</tr>
<tr>
<td>Propylene glycol suspension</td>
<td>Lung (site-specific administration)</td>
<td>Cyclosporine</td>
<td>Human clinical trial</td>
<td>Inhalation</td>
<td>[43,44,45]</td>
</tr>
<tr>
<td>3D-macroporous polydimethylsiloxane (PDMS) scaffold</td>
<td>Pancreatic islets (site-specific administration)</td>
<td>Dexamethasone</td>
<td>Diabetic mouse model</td>
<td>Seeding of the islets on the scaffold</td>
<td>[46]</td>
</tr>
<tr>
<td>Fibroin gel reservoirs containing solubilized, particulated, and PLGA-microspheres-encapsulated drug</td>
<td>Peripheral nerve (site-specific administration)</td>
<td>Tacrolimus</td>
<td>In-vitro neurite extension</td>
<td>In-vitro culture</td>
<td>[47]</td>
</tr>
<tr>
<td>Electrosyn polye[ster urethane] urea and tacrolimus elastomeric matrix (PEUU-Tac)</td>
<td>Central nervous system (site-specific administration)</td>
<td>Tacrolimus</td>
<td>Rat acute central nervous system ischemia</td>
<td>Wrapped and sutured around the nerve injury</td>
<td>[48**]</td>
</tr>
<tr>
<td>Ascorbyl palmitate inflammation-targeting hydrogel</td>
<td>Inflammation (negative surface charge to facilitate adhesion to the positively charged inflamed colon epithelium)</td>
<td>Dexamethasone</td>
<td>Mouse colitis models</td>
<td>Rectal administration</td>
<td>[49]</td>
</tr>
<tr>
<td>Triglycerol monostearate inflammation-responsive hydrogel</td>
<td>Joint (site-specific administration)</td>
<td>Triamcinolone acetonide</td>
<td>Mouse inflammatory arthritis</td>
<td>Intra-articular injection</td>
<td>[50**]</td>
</tr>
<tr>
<td>Ointment and cream</td>
<td>Skin (site-specific administration)</td>
<td>Tacrolimus or Triamcinolone</td>
<td>Clinical use</td>
<td>Topical application</td>
<td>[10]</td>
</tr>
<tr>
<td>Inhalation solution</td>
<td>Lung (site-specific administration)</td>
<td>Tacrolimus</td>
<td>Rat lung allograft</td>
<td>Inhalation</td>
<td>[51]</td>
</tr>
<tr>
<td>Nanostructured aggregates</td>
<td>Lung (site-specific administration)</td>
<td>Tacrolimus</td>
<td>Rat lung allograft</td>
<td>Inhalation</td>
<td>[52]</td>
</tr>
<tr>
<td>Solutions and ointment</td>
<td>Eye (site-specific administration)</td>
<td>Tacrolimus or Cyclosporine</td>
<td>Clinical</td>
<td>Topical application</td>
<td>[53]</td>
</tr>
</tbody>
</table>

PEG, poly(ethylene glycol); PLC, poly(ε-caprolactone); PLGA, poly(lactide-co-glycolide); PPS, poly(propylene sulfide).

exposure [43–45]. Furthermore, encouraging results have been obtained in preclinical models for the prevention of acute lung rejection using inhalation [51] of nanostructured aggregates [52] of tacrolimus. Although DDS specifically designed for IST targeting the eye and lung may have limited applications in upper extremity and face transplantations, these studies have shown that site-specific immunosuppression is an effective method to control allograft rejection providing new means and ideas for the generation of innovative DDS in other VCA procedures.

Draining lymph nodes are the main site of immune activation after transplantation. Therefore, many studies have focused on delivering IST directly to the lymphatic system and to the draining lymph node [61**]. Passive accumulation of nanoparticles or microparticles into the lymph node after systemic administration (i.e. subcutaneous, intravenous or intraperitoneal injections) has been reported by several groups [24,25,62]. Shirali et al. [24] developed poly-lactide-co-glycolide (PLGA) nanoparticles loaded with mycophenolic acid (MPA) that
accumulated into the lymph node prolonging murine skin allograft survival without detectable toxicity. Dane et al. [26] demonstrated that encapsulated tacrolimus and rapamycin inside micelles drain to the lymph nodes following intradermal injection and promote allograft survival in an allogeneic skin transplantation model. In order to improve the trafficking of nanoparticles to lymph nodes, Azzi et al. [28] designed microparticles containing tacrolimus coated with an anti-MECA-79 antibody for specific delivery to lymph node. Treatment using these microparticles achieved prolongation of heart allograft survival with low circulating levels of tacrolimus. At present, to the best of our knowledge, none of these targeted IST delivery modalities to the lymphatic system have been investigated in VCA models.

Site-specific delivery of tacrolimus has also been investigated as a means to provide protective and regenerative benefits to neurons. Fibrin hydrogel reservoirs containing solubilized, particulate or PLGA microsphere-encapsulated tacrolimus could be utilized for enhancing peripheral nerve regeneration as shown by in-vitro dorsal root ganglion neurite extension assays [47]. The beneficial effect of locally delivered tacrolimus has recently been confirmed in vivo. A biodegradable and elastic matrix of poly(ester urethane) urea (PEUU)-loaded tacrolimus wrapped around the nerve injury was shown to decrease astrogliosis and increase axon growth signaling pathways, confirming the potential of site-specific delivery of tacrolimus to improve nerve repair while minimizing adverse side effects [48**]. The beneficial effect of locally delivered tacrolimus on nerve regeneration may contribute to the process of neural repair after VCA. As functional recovery is one of the most important determinants of clinical success in VCA, more studies are warranted to investigate this intriguing possibility.

‘Smart’ materials that can respond to environmental stimuli such as biological signals, pathological abnormalities or exogenous signals are appealing therapeutic platforms for targeted IST delivery [63]. Considering that inflammation is a driving force for many chronic diseases, inflammation-responsive hydrogels represent an ideal candidate for such a material. It has been demonstrated that ascorbyl palmitate hydrogels loaded with dexamethasone have preferential adhesion to inflamed epithelial surfaces and result in a significant reduction of inflammation with lower drug serum concentrations in murine colitis models [49]. More recently, the same group reported the development of a triglycerol monostearate hydrogel loaded with triamcinolone acetonide, demonstrating inflammation-dependent disassembly and reduction of arthritis activity in a mouse model [50**]. These reports confirm that inflammation-responsive hydrogels are promising next-generation DDS for the treatment of inflammatory diseases and transplant rejection.

**TARGETED IMMUNOSUPPRESSION IN VASCULARIZED COMPOSITE ALLOTRANSPLANTATION**

VCA is still a young field in transplantation. After an initial phase in which the experience gained in SOT was the driving force for improving outcomes in VCA patients, researchers have started to develop VCA-specific strategies to address specific problems presented by composite grafts. Immunosuppression obviously represents one of the most pressing issues in VCA [64]. Consequently, the field has started to develop approaches for targeted IST (Fig. 1) using the argument that these highly visible grafts allow easy monitoring of rejection episodes and provide the ideal setting for the use of site-specific immunosuppression [65].

Data generated in rodent models suggest that topical tacrolimus [66,67] and clobetasol [67], can prolong survival without systemic levels of immunosuppressive drugs. Tacrolimus and clobetasol ointments are already used clinically in episodes of acute rejection [66]. A topical formulation of MPA with high local but low systemic exposure in patients has recently been reported, further expanding the options for topical application of IST in VCA [68]. A drawback of using ointments and creams in the clinical setting is the twice-daily application that demands high patient compliance. Moreover, the skin penetration of ointments is limited and there are no commercially available topical formulations of widely used drugs such as rapamycin [10]. Therefore, although topical applications can be helpful in the immediate treatment of acute rejection episodes, their use as an alternative to systemic immunosuppression is unlikely.

Recently, our group reported that an intra-graft injection of high-dose tacrolimus may induce long-term survival with half of the treatment group of rats reaching 200 days’ survival without signs of rejection [69]. Intra-graft tacrolimus application immediately after transplantation increased tissue drug availability, promoting the establishment of transient donor-cell chimerism and thus long-term graft acceptance. Recently, the beneficial effect of peri-transplant high-dose tacrolimus for VCA survival have also been reported in a swine model [70].

In an earlier work, our group reported the use of an innovative DDS to achieve long-term (>100 days) VCA survival with reduced systemic exposure
We demonstrated that triglycerol monostearate (TGMS), an agent generally recognized as well tolerated by the FDA, could self-assemble into hydrogels and disassemble in response to proteolytic enzymes that are overexpressed during inflammation, providing 'on-demand' drug release. Building upon this study, we recently investigated the long-term outcomes and the immunological and toxicological impacts of this approach. Our data showed that periodic TGMS loaded with tacrolimus (TGMA-TAC) injections (every 70 days) promoted long-term graft survival up to 280 days. Systemic drug exposure was significantly reduced and TGMS-TAC-treated rats showed decreased toxicity compared with systemic tacrolimus-treated rats, the latter group showing increased creatinine, increased blood urea nitrogen levels, appearance of opportunistic infections and aggressive tumors. These results clearly show the advantages of our 'on-demand' release system for the reduction of immunosuppression toxicity.

However, while providing better recipient outcomes, TGMS-TAC treatment resulted in inferior graft outcomes with TGMS-TAC-treated rats experiencing at least one rejection episode. Therefore, further studies are warranted to understand if these rejections are because of low intra-graft tacrolimus levels, and if they can be avoided by increasing frequency or dose of the 'on-demand' DDS.

The Pittsburg group recently developed a biodegradable disk containing tacrolimus-loaded microspheres for sustained regional immunosuppression in VCA. As the disk slowly degrades, tacrolimus-laden microspheres are released to act in solution or are actively broken down and phagocytosed by macrophages. The published results showed sustained tacrolimus release from the disk with steady systemic levels and significant accumulation of tacrolimus in the groin lymph nodes. A single injection of the tacrolimus disk in hind limb-transplanted rats promoted allograft survival for more than 180 days. Moreover, as compared with TGMS-
TAC, burst release of tacrolimus was reduced in animals injected with the tacrolimus disk. However, long-term graft outcomes and the toxicity profile of this sustained-release DDS were not explored.

The same group has recently presented an abstract describing the development of a DDS drug that not only provides sustained IST release but also ‘on-cue’ triggered drug release upon ultrasound stimulation (USS) [74]. The study reported that alginate gels loaded with tacrolimus, rapamycin or both, released the immunosuppressive drug in response to USS. When used in vivo in a rat model of hind limb transplantation, alginate gels promoted long-term allograft survival (>100 days) in rats receiving tacrolimus-containing gels. However, although concentration in allograft tissue was higher than in the blood and the contralateral limb, sustained drug release occurred from alginate gels in the absence of ultrasound, prompting the authors to devote further efforts to optimizing the on-cue drug release.

The potential of locally delivered immunosuppression to promote VCA survival has also led us to investigate whether the administration of immunosuppressive drugs directly into the graft may reduce potential side effects as well as directly influence the magnitude and nature of an allogeneic immune response. We have designed an in-situ forming implant (ISFI) loaded with the immunoregulatory drug rapamycin [75]. A single injection of the rapamycin-loaded ISFI (Rapa-ISFI) in close proximity to the transplant prolonged VCA survival up to 100 days. Importantly, rats treated with Rapa-ISFI had significantly higher levels of multilineage chimerism and Treg in peripheral blood and transplanted skin compared with untreated rats. This study demonstrates that targeted IST delivery can be used not only to promote less toxic immunosuppressive protocols and patient compliance but also to favor the reprogramming of the local response toward regulatory function.

**LIMITATIONS AND FUTURE PERSPECTIVES**

All these preclinical experiments confirm that site-specific immunosuppression is a feasible and promising approach in VCA. However, thus far the success of this therapeutic approach has been proven only in rodent models. Targeted IST therapies need to be validated in large animal models that generate solid preclinical data in order to substantiate the notion that targeted immunosuppression has real advantages in VCA. Evaluation of long-term graft and toxicity outcomes should be the main focus. Moreover, in order to determine the right dose of local immunosuppression needed, more efforts should be devoted to building a graft-specific ‘therapeutic window’ rather than relying on systemic drug levels.

On the other hand, multidrug immunosuppressive protocols are currently used in human patients to guarantee an effective level of immunosuppression. Therefore, localized immunosuppression should further evolve to include multiple drugs to control graft rejection. Eventually, combined use of minimized systemic immunosuppression and targeted immunosuppression might be envisaged to balance graft and toxicity outcomes.

Importantly, despite promising results, limitations associated with implantable DDS such as foreign body reaction, pro-inflammatory microenvironment promoted by the biomaterials, activation of the complement system and immunogenicity, particularly following consecutive implantations, should be carefully evaluated in specifically designed studies.

**CONCLUSION**

Targeted immunosuppression in VCA represents a promising new approach for improving patient compliance and graft survival while reducing off-target toxicity, intensity and frequency of acute rejection episodes and risk of chronic rejection. More studies are needed to generate solid preclinical data on the modalities of application, drug-distribution, toxicity profile and immunological parameters of DDS-based approaches. Such studies will foster the development of effective delivery platforms, paving the way for the design of clinical trials in VCA patients.

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**Conflicts of interest**

There are no conflicts of interest.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

● of special interest

●● of outstanding interest


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