

Experimental Murine and Primate Models for Dissection of the Immunosuppressive Potential of Photochemotherapy in Autoimmune Disease and Transplantation

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This paper reviews the results achieved in murine and primate models of autoimmune disease and transplantation. These studies have attempted to clarify the nature and specificity of the response induced by reinfusion of phototreated immunoactive lymphocytes.

Results obtained in murine lupus have demonstrated that some of the disease features related to the abnormal proliferation of inducer T cells can be inhibited both prophylactically and therapeutically by exposure to photoinactivated autoimmune splenocytes. Radiolabeling studies performed in normal syngeneic mice have shown that, if immunoactive cells are phototreated and injected, their recirculation pattern is altered, and increased sequestration in the spleen, bone marrow, and kidney is noted. These studies suggest that reinfused, phototreated, antigen-activated lymphocytes may localize in sites where they are available for induction of immune responses. Primate cardiac xenotransplantation models have demonstrated that reinfusion of phototreated autologous leukocytes, administered with cyclosporine A and steroids, mediates enhanced specific suppression of both the cellular and humoral host response to foreign tissue.

Taken as a whole, the experimental models suggest that photopheresis may provide a means of inducing specific suppression of immunoactive T cells. This form of therapy may have a role as an immunosuppressive agent in both autoimmune disease and transplantation.

The dramatic clinical response achieved in erythrodermic patients with the leukemic form of cutaneous T-cell lymphoma (CTCL), through reinfusion of photoinactivated autologous lymphocytes, suggested that photopheresis therapy induced a host response that exceeded the results predicted for simple tumor cytotoxicity [1]. Clearance of skin lesions as well as reductions in circulating malignant T cells indicated that this response was specific for the abnormal cell type. In addition, retention of the delayed type of hypersensitivity and the absence of infectious complications provided evidence that generalized immune competence was spared and only active T-cell proliferations were effected. The contention that these results might be explained by induction of an autoregulatory host response which recognized phototreated effector T-cell populations and specifically suppressed them may be addressed in animal model systems where syngeneic populations are available for experimentation. The results achieved in these models could then be used to predict those conditions where photopheresis might invoke a beneficial clinical response. Animal models would also provide insights into the nature of the mechanism(s) induced in the host after reinfusion of autologous lymphocytes treated with psoralen and ultraviolet A light.

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Abbreviations: CTCL: cutaneous T-cell lymphoma ds: double-stranded UVA: ultraviolet A light

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MURINE MODELS OF SYSTEMIC LUPUS ERYTHEMATOSUS

The MRL/l mouse model of systemic lupus erythematosus was chosen to evaluate the effects of reinfusion of phototreated autoimmune lymphocytes because many of the features of this disease are directly related to an unregulated proliferation of abnormal benign inducer T cells [2]. Therapies that affect T cells such as neonatal thymectomy [3], injection of monoclonal antibodies directed against the pan T-cell antigen, Thy1 [4], or the inducer T-cell marker, L3T4 [5], and whole-body or total-lymphoid irradiation [6] have been successful in affecting the course of the autoimmune process in the MRL/l mouse model. The genome of the MRL/l mouse contains the *lpr* mutation, which in the homozygous state results in early onset of autoimmune disease with massive lymphadenopathy, and splenomegaly due to hyperproliferation of phenotypically abnormal, benign inducer T cells [2]. These T cells mediate polyclonal B-cell stimulation, resulting in excess antibody production [7]. Some of these antibodies are autoreactive in nature and recognize single- and double-stranded (ds) DNA [8]. Successful therapeutic intervention in this model can be monitored by the effect on survival, lymphoid organomegaly, T-cell hyperproliferation, and anti-DNA antibody production. In addition, the abnormal T cells rapidly lose the capacity to respond to the T-cell mitogen, concanavalin A [9]. Retention of the normal blastogenic response to this mitogen would be consistent with down-regulation of the abnormal T-cell hyperproliferation.

The first protocol pursued in this system involved the prophylactic treatment of young mice (six weeks old), prior to the onset of autoimmune disease, with cells obtained from old, actively diseased mice (17 to 21 weeks old). The goal of these studies was to determine whether it was possible to inhibit some of the features of the autoimmune disease by exposing the recipient to phototreated autoimmune cells at a time when a relatively intact immune system was present [10]. Recipient mice received biweekly intravenous injections of phototreated cells from autoimmune donors. Littermate controls were untreated and monitored in parallel. Mice were sacrificed at weekly intervals to evaluate lymphoid organomegaly, lymphocyte phenotype and function, and serum anti-ds DNA antibody titers.

The results obtained demonstrated that prophylactic reinfusion of phototreated autoimmune splenocytes resulted in significantly improved survival, inhibition of splenic and lymph node hyperplasia, depletion of the abnormal Thy1, LYT1 T-cell population, and reduction of the autoantibody titer to DNA. In addition, the proliferative response to concanavalin A was maintained for a prolonged period in treated mice (Table 1). Therefore, the T-cell-related features of autoimmune disease in this model were suppressed by exposure to phototreated autoimmune effector cells. These results parallel those found in other systems where T-cell-directed therapies were used to treat MRL/l mice [3–6]. The results suggest that treated mice recognize the T-cell hyperproliferation as abnormal and can suppress this cell type if it is inactivated and presented by the immune system at an early stage of the disease process.

In addition to the phototherapy group, a set of mice received injections of unmodified autoimmune splenocytes, and another group of mice received biweekly treatments with photoinactivated splenocytes that had been disrupted by repeated freezing and thawing. Recipients of unmodified autoimmune splenocytes demonstrated a partial response to therapy. While their survival was not improved, lymph

TABLE 1
Effects of Prophylactic Infusion of Photoinactivated Autoimmune Splenocytes on Murine Lupus

Therapy	Survival 50% (weeks)	LN ^a Wt (g)	SP Wt (g)	Phenotype		Anti-DNA AB	Mitogen-Sp	
				THY1	LYT1		Con A	LPS
Photo-Tx Autoimmune Splenocytes	26	.53	.37	15 ^b	12	1,436 cpm	inc	dec
Un-Tx Autoimmune Splenocytes	20	.63	.37	66	14	ND	dec	dec
Un-Tx Controls	23	1.18	.52	227	87	10,709 cpm	dec	inc

^aAbbreviations are as follows: LN, lymph node; SP, spleen; Wt, weight; AB, antibody; Con A, concanavalin A; LPS, lipopolysaccharide; Photo-Tx, Photoinactivation treatment; inc, increased response; dec, decreased response; Un-Tx, untreated; ND, not done.

^bAbsolute number of reactive cells $\times 10^6$

node hyperplasia was significantly decreased but not to the extent noted in the recipients of phototreated autoimmune splenocytes. Splenic hyperproliferation was reduced in unmodified autoimmune cell recipients when older treated mice were examined (19 to 34 weeks old), while younger treated mice demonstrated only a marginal decrease in spleen size. Thyl, LYT1 lymphocytes were depleted in the spleens of these mice, but to a lesser extent than that observed in phototreated recipients. The proliferative response to concanavalin A was not improved in the mice treated with unmodified autoimmune splenocytes (Table 1). The group of mice that received lysed phototreated cells died rapidly from fulminant autoimmune disease.

These two control groups indicate that intact splenocytes are necessary but not sufficient for induction of a successful host response to the autoimmune process. The use of psoralen and ultraviolet A light (UVA) to inactivate the infused autoimmune cells apparently significantly enhances a partial host response to the autoimmune process and renders the recipient capable of down-regulating the abnormal T-cell hyperproliferation. While this protocol was designed to induce an autoregulatory immune response prior to the onset of autoimmune disease, the treatment remained effective during the period when active disease is normally expressed. A subsequent protocol was initiated to determine whether mice that already had established disease could be treated and some features of the disease process inhibited or reversed.

In order to ascertain whether active disease can be suppressed, treatment was begun in a group of MRL/l mice at nine weeks of age, a time when active disease commences [11]. These mice were treated weekly and monitored in parallel with untreated controls to assess survival, lymphoid hyperproliferation, anti-DNA antibody titers, and proliferative response to the mitogens lipopolysaccharide and concanavalin A. Survival, probably due to an inability to reverse established kidney disease, was not improved (Table 2). Lymph node hyperplasia was inhibited, while splenic enlargement was not significantly decreased. The majority of treated mice tested had decreased levels of anti-ds DNA antibody. Lymph node cells from treated mice retained the capacity to respond to both lipopolysaccharide and concanavalin A. These results demonstrate

TABLE 2
Effects of Therapeutic Infusion of Photoinactivated Autoimmune Splenocytes on Murine Lupus

Therapy	Survival 50% (weeks)	LN ^a Wt(g)	SP Wt(g)	Anti-DNA AB	Mitogen-LN	
					Con A	LPS
Photo-Tx Autoimmune Splenocytes	20	.44	.49	8/13 dec ^b	inc	inc
UN-Tx Controls	20	.98	.57	2/10 dec	dec	dec

^aAbbreviations: Refer to Table 1.

^bAnti-DNA antibody titer decreased (\geq one standard deviation) below the control mean in 8 of 13 treated mice as determined in an ELISA assay.

that it is possible to inhibit some features of the autoimmune process even when active disease has been initiated. Clearly this protocol is less efficient than prevention of disease onset, probably due to the presence of a less competent immune system in actively diseased mice. In spite of the abnormal T-cell proliferation, it was possible to reduce lymph node hyperplasia and to maintain a residual normal lymphoid population, as demonstrated by the capacity of these cells to respond to mitogens. The inhibition of anti-DNA autoantibody also probably relates to the suppression of the abnormal T-cell population which promotes unrestrained B-cell antibody synthesis. Therefore, in both a prophylactic and a therapeutic model of murine lupus; reinfusion of phototreated effector cells has resulted in down-regulation of the T-cell-mediated features of autoimmune disease and retention of a more normal immune status. These studies also demonstrate that, in order to be effective, the treatment requires reinfusion of intact lymphocytes treated with psoralen and UVA and a relatively competent immune system in the recipient.

Little is known about the fate of the reinfused phototreated cells or their sites of sequestration in the recipient. To determine whether lymphocytes treated with psoralen and ultraviolet A are retained in the recipient and if their recirculation kinetics are altered, a protocol was established to investigate the localization sites and residence time of both resting and antigen-primed phototreated lymphocytes in normal murine recipients.

RADIOLABELING STUDIES OF PHOTOTREATED ANTIGEN-PRIMED AND RESTING LYMPHOCYTES IN A NORMAL MOUSE MODEL

These studies were designed to determine whether phototreatment alters the capacity of reinfused lymphocytes to enter and be retained in various organ systems [12]. Cells treated with psoralen and UVA have been shown to die gradually *in vitro*, probably due to cross-linking of DNA molecules [13]. Reinfusion of dead or damaged cells should lead to rapid clearance and absence of sequestration in normal localization sites. In addition to resting lymphocytes, the radiolabeling distribution of antigen-primed cells was studied. Cells that are antigen-activated may serve as the primary target population that induces a host response after reinfusion. Also, the recirculation kinetics of antigen-primed cells may differ from the resting lymphocyte pattern.

Normal syngeneic age-matched mice were used as donors and recipients of

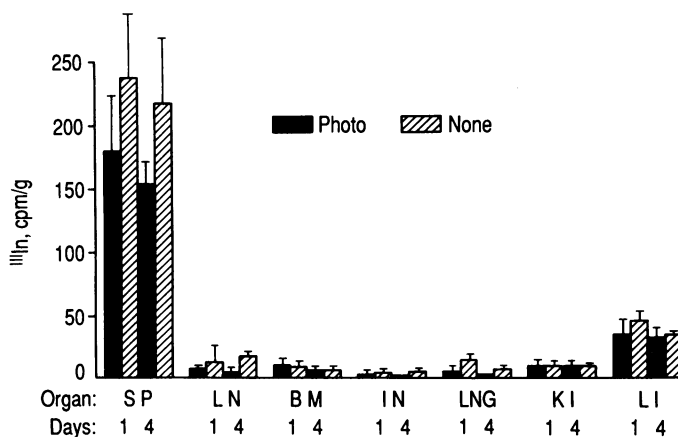


FIG. 1. The distribution of radioisotope in cpm/g is depicted in organs obtained from mice receiving injections of resting splenocytes treated with psoralen and UVA (Photo ■) or non-treated (None ▨) on days 1 and 4. The cpm/g of ^{111}In were less than 4 in the thymus, blood, heart, and skin and are not presented. **In**, indium; **SP**, spleen; **LN**, lymph node; **BM**, bone marrow; **IN**, intestine; **LNG**, lung; **KI**, kidney; **LI**, liver; **Photo**, photo-treated.

splenocytes for radiolabeling. Resting splenocytes were radiolabeled directly with ^{111}In or phototreated prior to labeling. Approximately 20×10^6 cells were intravenously injected and pairs of mice sacrificed at 24-hour intervals. A second group of mice received splenocytes from mice that had been primed on two occasions with sheep red blood cells. One set of antigen-primed splenocytes was photoinactivated prior to radiolabeling, while the remaining cells were radiolabeled directly. These mice were studied in a comparable fashion to the recipients of non-immune splenocytes.

The results obtained in recipients of non-immune splenocytes demonstrate that substantial numbers of radiolabeled cells persist in the recipient irrespective of whether they have been photoinactivated (Fig. 1). Phototreatment of non-immune cells, however, decreases the accumulation of these cells in the spleen, lymph nodes, thymus, blood, heart, intestine, and lung. Similar levels of non-treated and photoinactivated cells were found in the bone marrow, skin, kidney, and liver. Therefore, phototreatment of non-immune cells did not result in rapid clearance from the recipient, and substantial numbers of cells could be identified at seven days post-infusion in organs where non-treated cells were localized. Non-immune cells do not appear to alter their recirculation kinetics in response to phototreatment, and no increase in sequestration was found compared to the normal pattern.

Antigen-activation resulted in altered localization in some organ systems (Fig. 2). Non-treated, antigen-activated cells were found at lower levels in the spleen, blood, liver, and lung when compared to non-immune cells. In bone marrow, thymus, heart, skin, intestine, and kidney, antigen-primed splenocytes showed a level of sequestration comparable to non-immune cells. When antigen-primed cells were phototreated, an altered pattern from that observed in non-treated, antigen-activated splenocytes was identified in some organs. Significantly increased numbers of phototreated antigen-activated lymphocytes were found in the spleen, bone marrow, and kidney. Levels of radiolabeled cells comparable to those found in untreated antigen-activated recipients

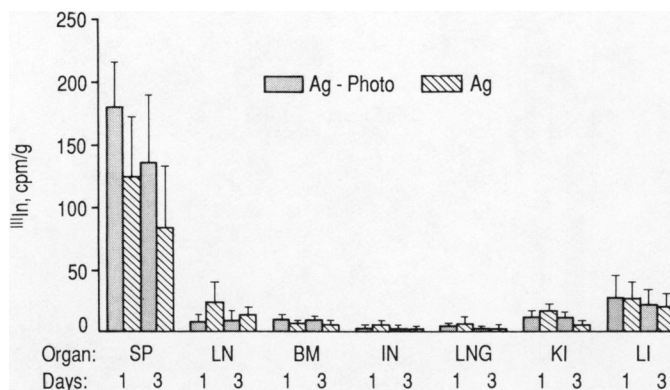


FIG. 2. The distribution of radioisotope in cpm/g is depicted in organs obtained from mice receiving injections of antigen-primed splenocytes treated with psoralen and UVA (Ag-Photo □) or antigen-primed only (Ag ▨) on days 1 and 3. The cpm/g of ^{111}In were less than 5 in the thymus, blood, heart, and skin and are not presented. In, indium; SP, spleen; LN, lymph node; BM, bone marrow; IN, intestine; LNG, lung; KI, kidney; LI, liver; Ag-Photo, antigen-primed and phototreated; Ag, antigen-primed only.

were present in the thymus, blood, heart, skin, lung, and liver. Twenty-four hours post-infusion, significantly fewer phototreated, antigen-primed splenocytes were present in the lymph nodes and intestine of recipient animals.

These results demonstrate that phototreatment does not alter the recirculation kinetics of resting lymphocytes and does not result in rapid clearance of these cells from the recipient. In addition, an altered pattern of sequestration of phototreated antigen-activated lymphocytes was found with increased localization of these cells in the spleen and bone marrow. The persistence of phototreated antigen-primed cells in these organs may play a role in the promotion of a host response to the reinfused immunoreactive lymphocytes. Kidney accumulation of phototreated cells may reflect the primary site of clearance of dying phototreated cells. The results support the contention that reinfusion of autologous immunoreactive lymphocytes treated with psoralen and UVA changes the distribution of these cells in the body and may focus these cells in sites where immunologic recognition can be achieved.

In addition to murine models, where lymphocyte activation in one syngeneic donor is used to treat another recipient, autologous reinfusion systems were investigated where the response to a known antigenic stimulus could be monitored. A primate cardiac xenograft transplantation model was studied, and the vigorous immune response to a trans-species graft was monitored.

PRIMATE CARDIAC XENOGRAFT MODEL

In humans, allotransplantation of donor organs has been successfully developed through the use of cyclosporine A, steroids, and other immunosuppressive agents. An acute shortage of donor organs has made the search for alternative organ sources imperative. Primates are closely related to man and clearly would offer the best source for procurement of foreign tissue. While suppression of the response to alloantigen is primarily cellular in origin, transplantation of tissue from a different species results in

TABLE 3
Effect of Reinfusion of Phototreated Autologous Lymphocytes
on Cardiac Xenograft Survival

Tx ^a	n	Survival	MLC	Antibody	AMLR
Photo Cyclo and Steroids	6	38 ± 18	Specific Suppression vs. donor	5/6 dec	3/6
Cyclo and Steroids	5	26 ± 16	Non-specific Suppression	5/6 inc	1/6

^aAbbreviations are as follows: Tx, treatment; n, number of animals; MLC, mixed leukocyte culture; AMLR, autologous mixed lymphocyte reaction; Photo, photochemotherapy; dec, decreased formation of cytotoxic antibody; Cyclo, cyclosporine A; inc, increased formation of cytotoxic antibody.

rapid rejection due to the formation of anti-donor antibodies [14]. The addition of photochemotherapy to conventional immunosuppressives was explored in a primate model of cardiac xenograft transplantation [14,15].

Baboons were heterotopically transplanted with cardiac grafts from cynomolgus monkeys. The animals were started on cyclosporine A and steroids two days prior to transplantation, and photopheresis was begun three days post-transplant and administered twice a week thereafter. Control baboons did not receive photopheresis but were treated with cyclosporine A and steroids. The animals were monitored for graft survival, response to the donor in mixed lymphocyte culture, and the production of anti-donor lymphocytotoxic antibodies.

The results demonstrated that photochemotherapy increased graft survival, specifically suppressed the mixed leukocyte culture response to the donor, resulted in an increased response to self in some animals, and suppressed the formation of anti-donor antibodies (Table 3). In addition, biopsy-proven rejection episodes were reversed in two photochemotherapy animals, while cyclosporine-treated animals demonstrated pathology consistent with progressive rejection. Control animals did develop inhibition of the mixed leukocyte culture response to the donor, but this suppression was nonspecific, affecting the response to unrelated allo- and xenoantigens, as well as the response to the donor. No induction of an autologous response to self was noted in controls, except in one animal who had a pre-existent increased response in autologous mixed leukocyte culture. Cytotoxic anti-donor antibody formation was not inhibited in control animals, and levels of antibody exceeding 30 percent cytotoxicity led to rapid graft loss.

These studies demonstrate that the vigorous immune response to xenoantigens can be suppressed by photopheresis given in a synergistic combination with cyclosporine A and steroids. Photopheresis renders the nonspecific suppression, induced by cyclosporine, specific for the cells responding to the donor xenoantigens. This procedure permits unrelated immune responses to be preserved intact. The prolongation of graft retention in phototreated animals probably relates to the inhibition of anti-donor antibody formation induced by photochemotherapy. This finding may reflect the capacity of photochemotherapy to develop a regulatory response in the host, which suppresses the activated effector T cells that promote B-cell antibody production. The duration of suppression mediated by photochemotherapy must be fairly long-lived, since the graft is continually in place and constantly provokes an anti-donor response, while phototherapy is only given twice weekly. Eventually, some T cells escape immune

surveillance, and cumulative cellular and humoral damage results in graft destruction. Perhaps the addition of other forms of immunosuppression such as monoclonal antibody therapy to photopheresis and cyclosporine will result in even greater prolongation of trans-species engraftment.

The animal model systems have clarified some features of the mechanism by which photopheresis induces a host response, although many questions remain to be answered. The major conclusions that can be drawn from the current model systems are:

1. Phototherapy targets T-cell-directed processes.

This conclusion was suggested by the results achieved during the therapy of the inducer T-cell malignancy cutaneous T-cell lymphoma and was confirmed in the murine lupus model where many of the features of the autoimmune process are directly related to an unregulated proliferation of benign inducer T lymphocytes. Treatment with psoralen and UVA inactivated effector cells of autoimmune disease resulted in prophylactic and therapeutic amelioration of the T-cell-related disease features. Moreover, in the transplantation model, T-cell-directed cellular rejection and anti-donor antibody formation were suppressed when photochemotherapy was added to conventional immunosuppressive regimens.

2. The suppression induced by photochemotherapy is specific for the immunoreactive cell type.

In the clinical trial of photopheresis, generalized immunocompetence was preserved as demonstrated by the absence of infectious complications and the retention of skin test responses. This observation was confirmed in the xenograft transplantation model, where animals with a xenograft in place were suppressed to the donor xenoantigen while maintaining the capacity to respond to other unrelated allo- and xenoantigens. This selective suppression was achieved even though the animals were receiving cyclosporine A, which rendered control animals nonspecifically suppressed to all histocompatibility challenges.

3. Reinfusion of the phototreated cells results in recirculation of the photoinactivated cells and their sequestration in sites where immune responses may be engendered.

CTCL patients demonstrated large populations of antigen-negative cells recirculating 24 to 48 hours post-reinfusion of the treated pheresis. This finding suggested either that phototreated cells that lacked expression of cell surface membrane antigens were recirculating or that large populations of null cells had been released into the peripheral blood. In the radiolabeling studies, the results demonstrate that phototreated cells do recirculate for a prolonged period of time and are sequestered in organ systems. Phototreated antigen-activated lymphocytes demonstrate altered recirculation patterns with increased numbers of cells localized in the spleen and bone marrow of the recipient. Both the spleen and the bone marrow could serve as sites for induction of autoregulatory cell populations, which could suppress the immunoreactive cell population.

4. An intact immune system is required for induction of a host response to reinfused phototreated cells.

If photopheresis induces a host response to the reinfused photoinactivated lymphocytes, an immunocompetent recipient is required. In the autoimmune

mouse model, more efficacious results were achieved with prolonged survival and pronounced inhibition of lymphoid organomegaly when younger mice without active disease were treated prophylactically. Although some features of the autoimmune process could be treated in actively diseased mice, established kidney disease could not be remedied, and survival was not improved. These results support the argument that the capacity to mount an immunoregulatory response depends on the presence of a relatively intact immune system.

5. Intact cells or membranes and psoralen plus UVA are required for induction of an effective host response.

The results in the lupus model demonstrate that reinfusion of untreated cells results in a partial response to therapy. Improved survival and extensive suppression of lymphoproliferation are present only when phototreated autoimmune splenocytes are infused. Lysed phototreated cells are not effective in this protocol. Therefore, this form of therapy appears to require reinfusion of whole cells or intact cell membranes treated by photoinactivation to achieve a maximum response.

6. Conditions that are related to T-cell dysfunction should respond to photochemotherapy.

This contention is borne out by the results achieved in the MRL/l mouse model where T-cell-related autoimmune disease is ameliorated by reinfusion of phototreated effector cells and in the transplantation model where reinfusion of autologous phototreated lymphocytes suppresses xenograft rejection. These results suggest that beneficial clinical responses may be achieved by photochemotherapy in some autoimmune diseases and as an adjunct immunosuppressive agent in transplantation.

Further studies are required in both animal models and clinical trials to answer many remaining questions. The direct effect of photopheresis on B-cell-mediated diseases is being studied in patients with B-cell chronic lymphocytic leukemia and in discordant xenograft protocols where preformed antibodies to xenoantigens preclude graft survival. Other mechanisms not considered in these protocols may play a significant role in phototherapeutic regimens. Macrophages are relatively spared by this treatment and their role in induction of a host response may be significant. Release of lymphokines by dying phototreated cells may also function to promote autoregulatory responses. Natural killer cells and cytotoxic T cells may promote the host response that down-regulates the immunoactive cell type. The results of current protocols and future studies will not only extend the clinical arsenal by adding a new immunosuppressive modality but will also further our understanding of immunoregulatory responses.

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