

Immunomodulatory oligonucleotide IMT504: Effects on mesenchymal stem cells as a first-in-class immunoprotective/immunoregenerative therapy

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Abstract

The immune responses of humans and animals to insults (*i.e.*, infections, traumas, tumoral transformation and radiation) are based on an intricate network of cells and chemical messengers. Abnormally high inflammation immediately after insult or abnormally prolonged pro-inflammatory stimuli bringing about chronic inflammation can lead to life-threatening or severely debilitating diseases. Mesenchymal stem cell (MSC) transplant has proved to be an effective therapy in preclinical

studies which evaluated a vast diversity of inflammatory conditions. MSCs lead to resolution of inflammation, preparation for regeneration and actual regeneration, and then ultimate return to normal baseline or homeostasis. However, in clinical trials of transplanted MSCs, the expectations of great medical benefit have not yet been fulfilled. As a practical alternative to MSC transplant, a synthetic drug with the capacity to boost endogenous MSC expansion and/or activation may also be effective. Regarding this, IMT504, the prototype of a major class of immunomodulatory oligonucleotides, induces *in vivo* expansion of MSCs, resulting in a marked improvement in preclinical models of neuropathic pain, osteoporosis, diabetes and sepsis. IMT504 is easily manufactured and has an excellent preclinical safety record. In the small number of patients studied thus far, IMT504 has been well-tolerated, even at very high dosage. Further clinical investigation is necessary to demonstrate the utility of IMT504 for resolution of inflammation and regeneration in a broad array of human diseases that would likely benefit from an immunoprotective/immunoregenerative therapy.

Key words: Immunohomeostasis; Immunoprotection; Immunoregeneration; Inflammation; Mesenchymal stem cells; IMT504

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Core tip: Mesenchymal stem cell (MSC) transplant has been demonstrated to be an effective therapy in pre-clinical studies evaluating a vast diversity of inflammatory conditions. However, in clinical trials of transplanted MSCs, the expectations of great medical benefit have not yet been fulfilled. In this regard, IMT504, the prototype of a major class of immunomodulatory oligonucleotides, induces *in vivo* expansion of MSCs, resulting in a marked improvement in preclinical models of neuropathic pain, osteoporosis, diabetes and sepsis. IMT504 is easily manufactured and has an excellent preclinical safety record. Further clinical investigation is necessary to demonstrate the utility of IMT504 for resolution of inflammation and regeneration in a broad array of human diseases that are likely to benefit from an immunoprotective/immunoregenerative therapy.

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INTRODUCTION

Homeostasis (from the Greek: Homeo, meaning

unchanging + stasis, meaning standing), is a concept that goes back to the old Greek philosophers who believed that harmony was a fundamental attribute of life and health. Empedocles (495-435 BC) hypothesized that all material comprised elements that were in active opposition or association, and that equilibrium was a necessary condition for subsistence of living entities. Thereafter, Hippocrates (460-375 BC) stated that healthiness is the tuneful equilibrium of the components of the body, and disease is the disorganized relationship of these components^[1,2]. Lately, Claude Bernard (1813-1878) specified that "All of the vital mechanisms, however varied they may be, always have one goal: To maintain the uniformity of the conditions of life in the internal environment (*milieu intérieur*)"^[3]. Finally, Cannon^[4] (1871-1945) expanded Claude Bernard's idea of constancy of the "*milieu intérieur*", naming his theory "homeostasis".

According to Cannon, homeostasis was a number of coordinated changes in the internal environment, leading to the preservation of physiological parameters within defined limits. These parameters encompassed temperature, pH, blood pressure and many others. Furthermore, in Cannon's view, homeostasis constancy requires communication among intelligent sensors able to identify unacceptable deviations. This concept of homeostasis is the most widely accepted nowadays, owing to its simplicity and physiologic rationale.

The immune system contributes to homeostasis by protecting the organism from an invasion by foreign organisms, such as bacteria, fungus, virus and parasites, and by participating in the defense of the organism against tissue damage caused by trauma, cancer or metabolic disorders such as diabetes. The immune response is biphasic, with the first phase represented by the inflammatory reaction, which aims for the prompt elimination of the causes of body aggression. Inflammatory signals include cytokines, chemokines, biogenic amines and eicosanoids that induce changes in diverse processes ranging from alterations in local vascular responses to abnormal rise in body temperature. Thus, acute inflammatory signals are antagonists of the normal homeostatic signals^[5]. The second phase of the immune response aims to restore the normal homeostatic parameters. This phase includes the clearing of debris from the "battlefield" created by invading pathogens and phagocytic cells, and then the reconstitution of tissue integrity and normal function.

In order to proceed from the initial inflammatory phase to the reconstitution phase, a switch command needs to be turned on. Failure to make this switch results in chronic inflammation and consequently in diseases such as autoimmunity (*i.e.*, diabetes, multiple sclerosis, lupus erythematosus) and neurodegenerative diseases (*i.e.*, Alzheimer's disease). However, termination of acute inflammation too early presents the risk of inadequate clearance of pathogenic microorganisms that can result in chronic infection. Therefore, gaining an understanding of the nature of the switching mechanism that connects

the first and second phase of the immune response is important for the finding of new efficient treatments.

Over the last few years, numerous studies have identified mesenchymal stem cells (MSCs) as the essential elements in this switching mechanism^[6], since transplant of autologous MSCs expanded *in vitro* or even allogenic MSCs results in significant salutary effects in animal models representing various inflammatory diseases^[7-9]. On the other hand, in 2007, we discovered that treatment of rats with a novel class of immunomodulatory oligonucleotides (ODNs) (PyNTTTGT ODNs) lacking CpG motifs, induces MSC expansion in bone marrow and blood, thus markedly increasing the therapeutic potential of the autologous MSC pool during pathologic conditions^[10]. This discovery greatly advances the development of defined, easy-to-produce and fully-controllable pharmaceuticals for treatment of inflammatory diseases. Such an exciting prospect as the one suggested by these studies prompted us to review the relevant information in the field of immunoprotection and immunoregeneration mediated by MSCs or ODNs of the PyNTTTGT class.

MSCS AND IMMUNOMODULATION

MSCs are non-embryonic multipotent cells characterized by the capability to differentiate into mesodermal cell, for instance osteoblasts, chondroblasts and adipocytes^[11,12]. MSCs are resident of bone marrow, adipose tissue, umbilical cord blood and may other tissues^[13-15]. These cells do not express class I or class II major histocompatibility complexes, thereby permitting adoptive transfer of MSCs between hosts without inducing acute rejection.

In addition to their progenitor cell properties, phenotypical plastic MSCs are able to interrelate with constituents of the immune system, exhibiting anti-inflammatory or pro-inflammatory properties depending on the milieu composition^[16-18]. In general, MSCs adopt a pro-inflammatory phenotype (MSC₁) during early microbial invasion or trauma, when the concentration of pro-inflammatory cytokines in the milieu is relatively low. Some important effects of MSC₁ at the damaged body site are stabilization of a pro-inflammatory classic phenotype (M₁) in resident macrophages and activation of antimicrobial properties of neutrophils^[19-23].

As inflammation proceeds, pro-inflammatory cytokines accumulate up to a critical level that switches differentiation of MSCs to an anti-inflammatory phenotype (MSC₂). Abundant information has been published on the relationship between MSC₂ and resolution of the inflammatory setting, and tissue protection and repair^[24-34]. Some of the well-known anti-inflammatory effects mediated by MSC₂ are skewing macrophages to the M2 immunosuppressive alternative phenotype^[35-41], promoting T cells to T regulatory (T_{reg}) cell differentiation^[42-48], skewing monocyte-derived dendritic cells to a regulatory phenotype^[49-54], inhibiting neutrophil influx and respiratory burst while maintaining

or even increasing its phagocytic capacity^[55-59], inhibiting mast cell degranulation^[60-62], and inhibiting pro-inflammatory activities of T cells^[63-72], natural killer (NK) cells^[73-79] and B cells^[80-84]. Furthermore, throughout the numerous reports describing the regulatory role of MSCs attenuating (at some point) inflammation, several intercellular molecular signals have consistently emerged as relevant. For example, the cytokines interferon-gamma (IFN- γ), interleukin (IL-6) and tumor necrosis factor-alpha (TNF- α), and also stimulation of the toll-like receptor (TLR)3 and TLR4 have been proposed as main signals for switching MSC differentiation to its anti-inflammatory and pro-resolving differentiation stage^[85].

Once differentiated into the anti-inflammatory and pro-resolving phenotype MSC₂, MSC communication with other cells is mediated by molecular signals such as prostaglandin E₂ (PGE₂), indoleamine 2,3-dioxygenase (IDO), TNF-inducible gene 6 protein (TSG-6), hepatic growth factor (HGF) and transforming growth factor-beta 1 (TGF- β 1). PGE₂ is a bioactive lipid with early and late effects in the setting of inflammation. In the early stages, PGE₂ stimulates vasodilatation, relocation and activation of macrophages, mast cells and neutrophils. Later on, PGE₂ promotes differentiation of macrophages and monocytoïd dendritic cells to an anti-inflammatory phenotype that suppresses NK cell and neutrophil inflammatory function and mast cell degranulation^[86]. Variances in sensitivity, desensitization and activation of different signaling pathways among several PGE₂ receptors accounts for this adaptable pattern of responses at different stages of the immune response^[87]. TGF- β 1 also presents biphasic activities, since its strong chemoattractive properties brings about a rapid incoming of T cells, granulocytes and macrophages that can contribute to inflammation but can also exert a potent anti-inflammatory response by constraining the synthesis of inflammatory cytokines and stimulating differentiation of naïve T cells to T_{reg} cells^[88]. IDO is an intracellular enzyme that catabolizes the production of kynurenine from tryptophan. Induction of IDO in the inflammatory setting results in arrest and functional anergy of CD8+ T cells, inhibition of differentiation of T helper (Th) cells to Th₁₇ cells and activation of differentiation to T_{reg} cells^[89]. TSG-6 is an anti-inflammatory protein secreted by MSCs in response to inflammatory cytokines (*i.e.*, IL-1 and TNF- α) that mediates suppression of dendritic cell maturation and function^[90]. HGF is a morphogenic and growth factor secreted by MSCs that also has anti-inflammatory activity by inhibition of the production of pro-inflammatory cytokines and by stimulation of macrophage differentiation to the M2 phenotype^[91].

Figure 1 displays a highly simplified representation of interactions between MSCs and other cells of the immune system during the anti-inflammatory phase of the immune defensive response. In addition, anti-inflammatory MSCs directly or indirectly interact with resident cells at the site of inflammation, for example with oligodendrocytes in the central nervous system,

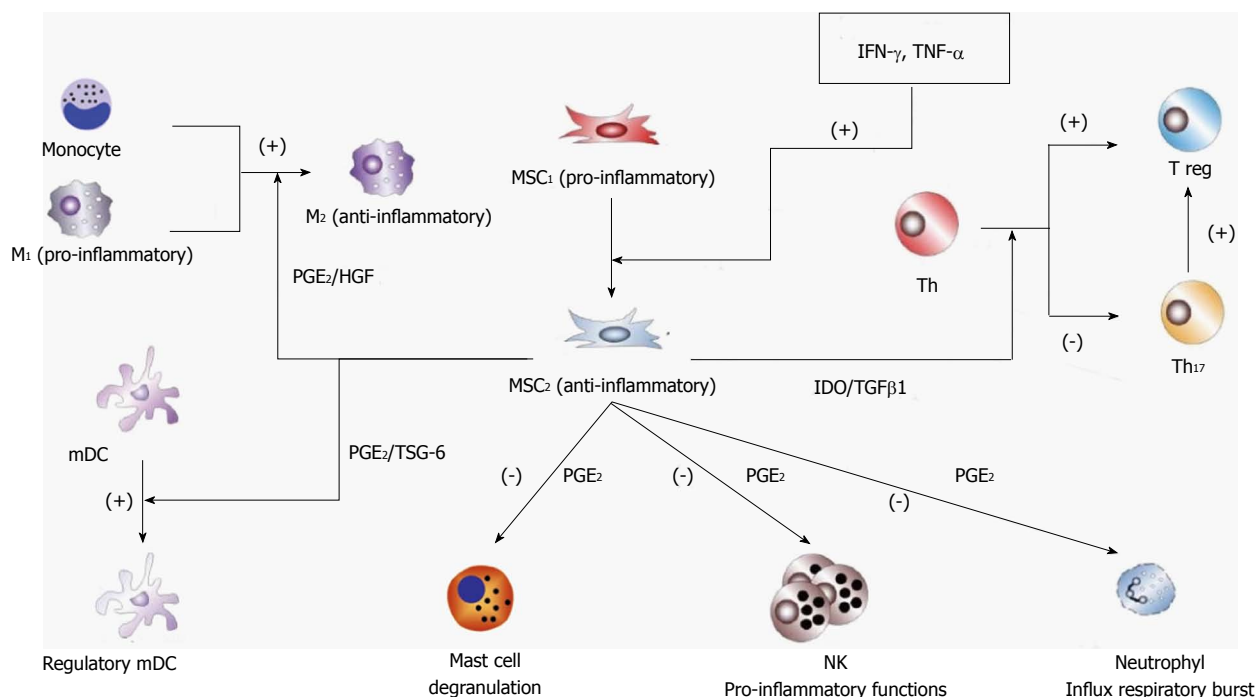


Figure 1 Mesenchymal stem cell immunosuppressive regulatory effects. MSCs are polarized to an immunosuppressive stage (MSC2) by a high relative concentration of pro-inflammatory cytokines such as IFN- γ and TNF- α . MSC2 induce macrophage polarization of monocytes and pro-inflammatory macrophages (M1) to the immunosuppressive stage M2 by secreting immunomodulatory mediators such as PGE2 and HGF. MSC2 also induce differentiation of Th and Th17 to T regulatory cells (Treg) by secretion of TGF- β 1 and indoleamine 2,3-dioxygenase (IDO). Furthermore, MSC2 induce differentiation of mDCs to a regulatory anti-inflammatory stage (mDCreg), inhibit mast cell degranulation, inhibit NK cell pro-inflammatory functions and suppresses neutrophil respiratory burst. MSC2-derived PGE2 contributes to all of these effects. Other cytokines that have been implicated in at least some of the MSC2 immune-suppressive effects are IL-6 and GM-CSF^[6]. MSC: Mesenchymal stem cell; IFN- γ : Interferon-gamma; TNF- α : Tumor necrosis factor-alpha; PGE2: Prostaglandin E2; Th: T helper; HGF: Hepatic growth factor; TGF- β 1: Transforming growth factor-beta 1; mDCs: Monocyte-derived dendritic cells; NK: Natural killer; IL-6: Interleukin-6; GM-CSF: Granulocyte macrophage-colony stimulating factor.

with osteoblasts and osteoclasts in bones, with beta cells in pancreas, etc. Therefore, the ability to respond under such diverse circumstances requires a highly adaptable cell, such as MSCs, in order to orchestrate the appropriate response.

PROSPECTIVE THERAPEUTIC USE OF MSC TRANSPLANT

The central role of MSCs in maintaining tissue homeostasis serves as the basis for their therapeutic application in many diverse inflammatory disorders. A large number of reported studies representing a wide spectrum of diseases reinforce this expectation. For example, MSC transplant has proven to be beneficial in preclinical as well as clinical studies of heart disease^[92-105], renal disease^[106-142], lung disease^[143-159], liver disease^[160-175], neural system disease^[176-204], bone damage^[205-227], skin wound healing^[228-244], autoimmune disease^[245-265], infectious diseases and sepsis^[266-287], allergies and asthma^[288-306], graft vs host disease^[307-325] and diabetes^[326].

Despite the current enthusiasm about the broad potential clinical use of MSC transplant, some concerns have been growing about some potential issues as follows.

Economic

MSC-based treatments might be expensive if founded on autologous cells because of the need to take a biopsy for each patient, grow the cells *in vitro*, and perform the quality testing previously to the use of MSC for treatment. Furthermore, it is not sure that this process would produce enough cells as needed or if these cells would retain their phenotypical and functional characteristics after subculture. Convenient substitutes of autologous MSCs are allogeneic MSCs because they do not present immunologically significant surface molecules and in consequence do not provoke significant immune rejection to cell transplantation. Therefore, allogeneic MSC can be multiplied, aliquoted and stored beforehand and used when needed for treatment. Still, several regulatory and safety issues concerning allogeneic MSCs should be resolved as discussed below.

Reproducibility

Consistent results with allogeneic MSC therapies are possible if the different cell batches are constant within certain prefixed limits. Nevertheless, each allogeneic MSC batch is originated from a different donor. This fact results in substantial variation among the cell batches excluding establishment of a master cell bank. Furthermore, the starting material (*i.e.*, bone marrow

aspirate) consists in several cell types, and current techniques to isolate MSCs can rarely result in a pure cell preparation. This can be solved deriving the batch from a single cell; a fact that implies a long growth process that could result in undesirable random mutations.

Safety issues

MSC prepared from human tissues might hold retroelements, retroviruses and other viruses, and many other pathogens. A handful of these pathogens can be detected using current assays. Microbial contaminants may also upset therapeutic potency of MSCs. In addition, the use of fetal calf serum during cell growing culture raises concern regarding transmission of prion-associated diseases.

Rationality of MSC treatment to stimulate tissue repair rest on the hypothesis that endogenous repair prompted by MSC expansion, activation and relocation from the patient's own MSCs reservoirs is deficient in numerous pathological conditions. A reasonable alternative to cell infusion could be the use of a synthetic medicine aimed to stimulate expansion, activation and relocation of the patient endogenous stem cells, as long as the disease does not permanently altered these endogenous cells. Development of a medicine like this may solve most, of the above-stated difficulties connected with therapeutic applications of MSC transplant.

In this regard, our research group has pursued study for several years on the properties of a major class of immunostimulatory ODNs with the capacity to stimulate *in vitro* and *in vivo* MSC expansion. Preclinical studies indicate that these synthetic drugs are safe and competent in the treatment of several of the disorders that are responsive to MSC transplant. General properties of the prototype of these ODNs, named IMT504, will be briefly described in the following sections, with special emphasis on the ability of IMT504 to promulgate endogenous recruitment of MSCs for regenerative medicine.

IMMUNOMODULATORY OLIGONUCLEOTIDE IMT504 AND INFLAMMATORY DISEASE

Oligonucleotides with regulatory activities on the immune system may be categorized into two major classes: (1) CpG ODNs, that include at least one CpG dinucleotide^[327]; and (2) PyNTTTTGT ODNs, that include at least one PyNTTTTGT octanucleotide in (Py: Pyrimidine; N: Adenine, Cytosine, Thymidine or Guanine; T: Thymidine; G: Guanine)^[328]. ODNs of both classes have as target cells B-cells and/or plasmacytoid dendritic cells (PDCs).

The seal of CpG ODNs is their capability to stimulate secretion of IFN- α by PDCs interacting with the TLR9^[329,330], a characteristic that is absent in members of

the PyNTTTTGT class. On the other hand, hallmarks of the PyNTTTTGT class are induction of an efficient release into the milieu of granulocyte macrophage colony-stimulating factor (GM-CSF) by NK and natural killer T (NKT) cells in collaboration with IL-2^[331] and stimulation of MSCs^[10], characteristics that are absent or poorly expressed in CpG ODNs. Interestingly, IFN- α inhibited the GM-CSF secretion stimulated by PyNTTTTGT ODNs, and reciprocally these ODNs inhibit the excretion of IFN- α stimulated by CpG ODNs *via* TLR9 in PDCs^[331]. Therefore, this mutual interference between ODNs of the major classes of immunostimulatory ODNs suggested that they stimulate different and incompatible immune response pathways^[331].

Participation of MSCs in the pathway stimulated by PyNTTTTGT ODNs prompted us to hypothesize that these ODNs may modulate the inflammatory process, thereby stimulating the switch from the pro-inflammatory to the anti-inflammatory reconstructive stage of the immune response. To test this hypothesis, IMT504, the prototype of the PyNTTTTGT ODN class, was assayed as a therapeutic agent in animal models representing diverse medical conditions in which an MSC transplant had proven to be useful. The chosen animal models were of neuropathic pain, osteoporosis, diabetes and sepsis. A brief description of these preclinical studies is provided below.

Neuropathic pain

Neuropathic pain is a chronic, excruciating pain triggered by a injury or disease of the somatosensory system^[332]. Typical symptoms of neuropathic pain include allodynia (an answer to painful stimulation that does not usually provoke discomfort), hyperalgesia (augmented pain induced by stimuli that usually provoke pain), and spontaneous pain^[333]. While pain represents an adaptive response, acting as a protective mechanism that inform an organism of actual or potential tissue injury, neuropathic pain is thought as a maladaptive answer of the nervous system to harm^[334]. MSC transplantation has proven to be effective for the treatment of neuropathic pain in several preclinical studies^[335-342]. In addition, parenteral treatment with IMT504 has been shown to ameliorate neuropathic pain in a rat model of peripheral nerve lesion even when administered several days after nerve injury^[343] (Figure 2).

Osteoporosis

Osteoporosis is a medical condition characterized by decreased bone strength that results in frequent fractures. Mechanistically, osteoporosis results from a pathological increase of the activity rate of osteoclasts vs osteoblasts^[344]. Usually, osteoporosis has been considered an exclusive endocrine disease; however, it is now well established that continuing inflammation plays an important role in the osteoporosis development^[344,345]. Pro-inflammatory cytokines (*e.g.*, IL-6 and TNF- α), stimulate osteoclastogenesis and inhibit

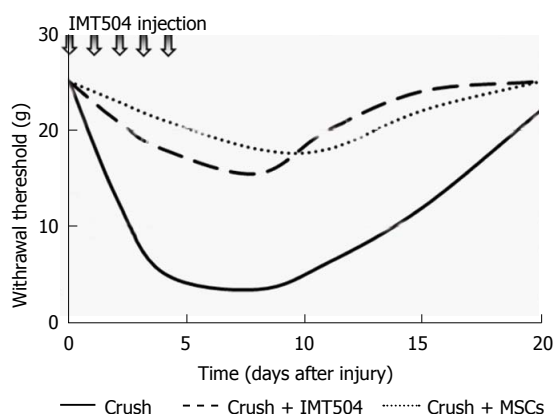


Figure 2 Effect of IMT504 or mesenchymal stem cell treatment on the development of mechanical allodynia in rats. Sciatic nerve crush induced a significant decrease in paw withdrawal threshold to the von Frey filaments. It is noticeable that the administration of either IMT504 or MSCs prevents the development of allodynia. Experimental details are described in Coronel *et al.*^[343]. MSC: Mesenchymal stem cell.

osteoblastogenesis and anti-inflammatory cytokines (e.g., IL-4 and IL-10), inhibit osteoclastogenesis^[344]. There are currently only a few preclinical studies that have been published on the effect of MSC transplant in osteoporotic animals, and results in these reports are encouraging^[346,347]. Furthermore, in a study performed in an ovariectomized rat model of osteoporosis, we observed that parenteral treatment with IMT504 results in a remarkable recovery of the bone structure, as indicated by morphometric characteristics such as trabecular volume, trabecular density, trabecular thickness and trabecular distance in the femur head (Figure 3).

Diabetes

Diabetes is a group of metabolic illnesses characterized by high blood glucose levels and altered metabolism of sugars, fatty acids and proteins because of faults in insulin secretion, activity, or both^[348]. Type 1 diabetes results from deficient insulin production by the pancreas and its cause is unknown. Symptoms are polyuria, polydipsia, continuous hunger, weight loss, visual alterations and fatigue. Type 1 diabetes patients are susceptible to a potentially lethal state of diabetic ketoacidosis.

Type 2 diabetes begins with the fail of cells to properly react to insulin. Symptoms are similar but usually less marked than those of type 1 diabetes. Type 2 diabetes patients rarely results in ketoacidosis^[349].

Although the cause of type 1 diabetes is unknown, contribution of the immune system in pancreas and other organs damage in type 2 diabetes is unquestionable^[350]. The key pathogenic event appears to be damage of pancreatic β cells caused by the attack of autoreactive cytotoxic T cells resulting in chronic inflammation of the pancreatic islets^[351].

In type 2 diabetes, a state of chronic inflammation encompassing innate and adaptive immune responses,

is in general accepted to be the primary alteration^[352]. Since islet inflammation contributes to the loss of functional β cells in both type 1 and type 2 diabetes, anti-inflammatory therapies have emerged as a reasonable option to current treatments. In particular, MSC transplant as a therapy in animal models of type 1 and type 2 diabetes resulted effective^[353-356]. In these studies, improvement of the glucose metabolism and regeneration of pancreatic islets were observed. Furthermore, parenteral treatment with IMT504 also markedly reversed pancreatic damage in a rat model of diabetes induced by one high-dose administration of streptozotocin^[357]. A striking recovery of islet number and structure accompanied by lowering of glucose and rising of insulin concentration reaching normal levels was observed in diabetic animals during and after the treatment (Figure 4). Study of histological markers for pancreatic progenitor cell proliferation and differentiation and for active angiogenesis indicated that stimulation of the remaining resident pancreatic islet cells might be critical for success of the IMT504 treatment.

Sepsis

Sepsis is a syndrome of dysregulated systemic immune responses to an infection or to microbial pathogenic components^[358]. Diabetes mellitus, lymphoproliferative disease, hepatic cirrhosis, extensive burning, severe trauma, use of intravenous or vesicular catheters, prosthesis and treatments with immunosuppressive medicines or intravenous drugs are frequent causes that contribute to acquisition of infections resulting in sepsis.

Stimuli prompting sepsis can be exogenous (*i.e.*, infectious) or endogenous (*i.e.*, severe trauma) resulting in gut hypoperfusion, impaired epithelial barrier function and translocation of luminal bacteria and/or their toxins into the systemic circulation. Pathogen-associated molecular patterns and damage-associated molecular patterns are recognized by pattern recognition receptors. These alarm signals activate systems in charge of keeping homeostasis. However, during sepsis, this system becomes dysregulated, leading to multiple organ damage.

During a first phase of sepsis, oxygen and nitrogen reactive forms accumulate. Some symptoms corresponding to this period include tachycardia, fever and neutrophilia. This is quickly followed by a marked elevation of proinflammatory cytokines and chemokines in plasma as well as the migration of polymorphonuclear leukocytes, monocytes and lymphocytes to affected tissues. Owing to this dramatic presentation, the prevalent and long-time definition for sepsis has been that of an uncontrolled inflammatory response. However, a number of recent observations have led to a redefinition of sepsis^[359], bringing about the idea that in sepsis there exist successive pro-inflammatory and anti-inflammatory (immunosuppressive) periods. Even though some patients die during the first pro-inflam-

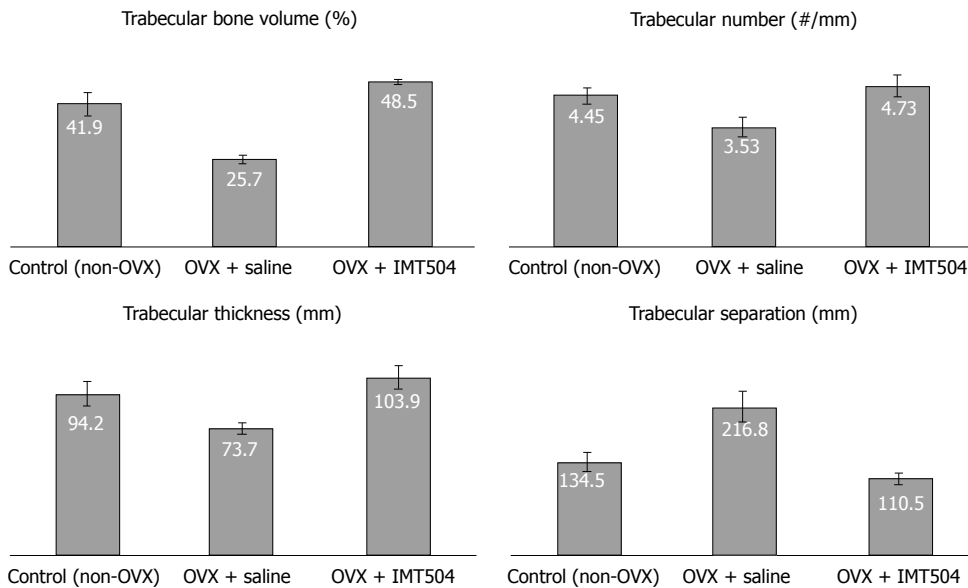


Figure 3 Effect of the IMT504 treatment on bone structure in ovariectomized (osteoporotic) rats. Female Sprague-Dawley 16-wk-old rats underwent ovariectomy (OVX). When animals were 1-year-old, half of them (treated group) received a subcutaneous dose of IMT504 (20 mg/kg per dose in saline) injected daily for 5 successive days. The other half received saline under the same scheme (non-treated group). The treatment was repeated 30 d later. A group of non-OVX rats served as control. Body weight and general health was measured weekly. One month after the last treatment, animals were euthanized and femurs dissected, decalcified and embedded in paraffin. Slides of 0.5- μ m sections of the distal femur were generated using a Leica RM2145 microtome, stained with hematoxylin and eosin, and examined by light microscopy. Digital images were recorded with a Nikon Coolpix 4500 camera at 16.5-fold magnification under a Leica MZ16A stereomicroscope. Three fields in each slide were evaluated, totaling a combined area of 3 mm². Trabecular bone was identified, and its perimeter and area measured. Histomorphometric analysis was performed using the Image Pro-Plus 4.5 software and standard histomorphometric parameters calculated (our unpublished results).

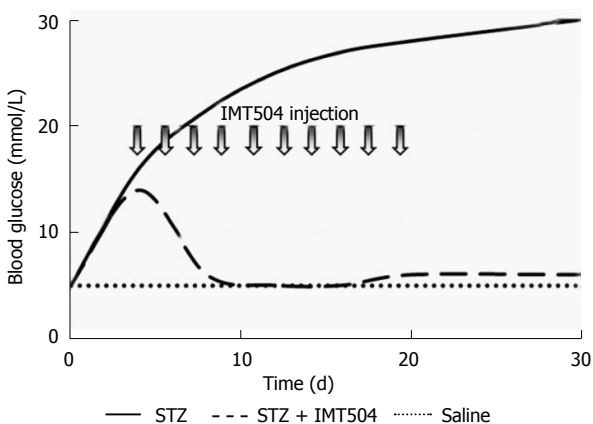


Figure 4 IMT504 treatment induced a marked recovery of the diabetic condition in streptozotocin-treated rats. Arrows indicate IMT504 treatment, which consisted of daily subcutaneous injections containing 4 mg of IMT504 over 10 successive days. Experimental details are described in Bianchi *et al.*^[357]. STZ: Streptozotocin.

matory period, due to septic shock, most patients survive it presently^[360]. The great majority of deaths occur during the immunosuppressive period, which in general starts between the second and third day of sepsis and could persist for several weeks. In spite of antibiotic treatment and strong medical supportive care, many patients cannot eradicate the infection and may acquire secondary intra-hospital infections^[361].

MSC transplant has been protective in preclinical animal models of polymicrobial sepsis^[282,270] as well as

in infections caused by bacterial strains of *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*^[266,284,362]. The protective role of MSCs in sepsis has been mainly attributed to their broad paracrine modulatory properties^[269]. On the other hand, remarkable protection against *Pseudomonas* infection was obtained in neutropenic rats in response to IMT504 treatment^[363]. Protection was 90%-100% using either early or late intervention after infection on par with antibiotic treatment (Figure 5). IMT504 treatment resulted in a marked decrement in serum IL-6 and in bacterial load in organs such as lungs, liver and spleen.

PRACTICAL CONSIDERATIONS REGARDING THE PROSPECTIVE CLINICAL USE OF IMT504 FOR TREATMENT OF INFLAMMATORY DISEASES

IMT504 is a drug with a well-defined formula that is relatively easy to synthesize using a rapid automatic process under GMP conditions and at reasonable cost if large quantities are required. In addition, formulations of IMT504 are not problematic because IMT504 is highly soluble. Additionally, once injected using different routes, IMT504 has a rapid and broad distribution^[364]. Moreover, because IMT504 has good thermal stability, extreme conditions of transport and storage are not

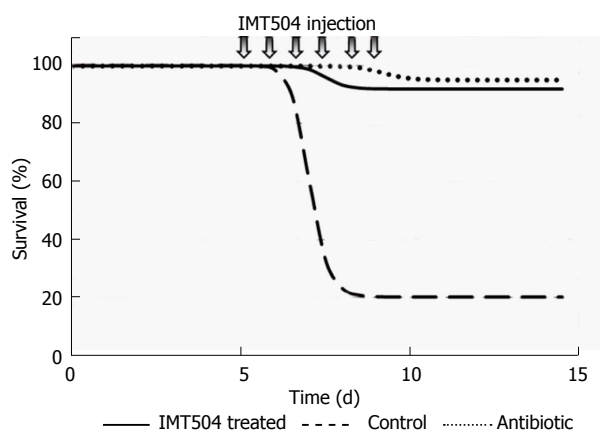


Figure 5 IMT504 protects neutropenic animals from fatal *Pseudomonas aeruginosa* bacteremia and sepsis. Kaplan-Meier survival plot representing IMT504 monotherapy vs antibiotic (cefepime) monotherapy vs control. IMT504 daily doses were started at day 5 after bacterial infection. Arrows indicate IMT504 treatment, which consisted of subcutaneous injections containing 50 g of IMT504 over 5 successive days. Experimental details described in Chahin *et al.*^[363].

necessary. Finally, IMT504 preclinical toxicity studies performed in several animal species, including non-human primates, indicate that IMT504 is a very safe drug with few secondary effects that are well-tolerated and within the therapeutic range of this agent^[364,365].

WHAT DO WE KNOW ABOUT THE MECHANISM OF ACTION OF IMT504 ON THE IMMUNE SYSTEM?

Known direct cell targets of IMT504 are B cells, PDCs, CD56⁺ cells (NK and NKT cells) and MSCs^[10,328,331].

B cells

B cells contribute to the immune response by producing antibodies and stimulating T cell activation^[366]. Besides, B cells can act as professional antigen-presenting cells (APCs) and B cell antigen presentation is essential for specific CD4⁺ T cell expansion, memory development and cytokine secretion^[367,368]. CD80, CD86, and CD40 surface components of B cells are essential for optimal T cell activation^[369]. Furthermore, in inflammation and autoimmunity, B cells exert an immunomodulatory role in part by IL-10 production and secretion^[370]. *In vitro* stimulation of human immature B cells with IMT504 results in cell proliferation, MHC I, MHC II, CD40, CD80 and CD86 cell surface expression, immunoglobulin secretion, and IL-6 and IL-10 secretion^[328]. Furthermore, upon stimulation with IMT504, B cell transcripts for most of the components of the proteasome are significantly augmented (our unpublished results). Most of these effects indicate that IMT504 incubation empowers B cells for competent presentation of antigens to CD4⁺ T cells. In line with this, addition of IMT504 to different vaccines greatly increases their activity^[371-373]. However, the strong secretion of IL-6 and IL-10 induced by

IMT504 suggests that IMT504-activated B cells may also participate in regulation of the immune response.

PDCs

PDCs are dendritic cells specialized in producing type I IFNs when stimulated by nucleic acids through TLRs 7 and 9^[374]. Additionally, PDC stimulation by nucleic acids results in surface expression of MHC I, MHC II, CD40, CD80 and CD86^[375]. Consequently, PDCs can present antigens to CD4⁺ T cells, leading to activation or tolerance depending on the context^[375,376]. PDCs are also involved, by unrestrained IFN type I secretion, in several inflammatory autoimmune diseases such as multiple sclerosis, psoriasis, systemic lupus erythematosus and inflammatory bowel disease^[377]. *In vitro*, stimulation of human immature PDCs with IMT504 also results in surface expression of MHC I, MHC II, CD40, CD80 and CD86^[328]. However, in contrast with CpG ODNs, IMT504 does not induce IFN type I secretion. Furthermore, incubation with IMT504 inhibits PDC IFN type I secretion induced by CpG ODNs^[331]. Interestingly, this inhibition of the IFN type I secretion allows activation of CD56⁺ (NK and NKT) cells by IMT504 in collaboration with IL-2, resulting in strong secretion of IFN- γ , TNF- α and GM-CSF^[331].

CD56⁺ (NK and NKT) cells

NK cells are innate lymphoid cells involved directly in the immune protection through cytotoxicity and cytokine secretion, and indirectly by modulating APCs and T cells^[378]. The cytotoxic activity of NK cells depends on the release of lytic molecules toward target cells. NK cells can stimulate inflammation by excreting cytokines (e.g., IFN- γ and TNF- α); however, they can also limit inflammation and autoimmunity^[379,380].

On the other hand, NKT cells specialized in recognition of lipid antigens presented by an MHC I-like antigen (CD1d). NKT cells also are able to modulate the immune responses involved in inflammation and autoimmunity^[381]. Incubation of human PBMCs with IMT504 results in strong secretion of IFN- γ , TNF- α and GM-CSF, providing that IL-2 is present in the milieu^[331]. IL-2 induces synthesis of the cytokines, and the presence of an ODN is necessary for their efficient secretion. CD56⁺ (NK and NKT) cells are responsible for the cytokine secretion and IFN- α inhibits the process. Induced cytokine secretion depends on two different IMT504 activities: (1) inhibition of the TLR9 dependent IFN- α secretion from PDCs; and (2) activation of a pathway of cytokine secretion presumably similar to the one described by Rao *et al.*^[382]. This last effect does not depend on the nucleotide sequence since ODNs with very diverse compositions were able to stimulate cytokine secretion when acting on purified CD56⁺ cells^[331].

Figure 6 shows a schematic representation of the likely IMT504 effects leading to defensive immune activation as well as resolution of excessive inflammation by MSC expansion and secretion of cytokines necessary

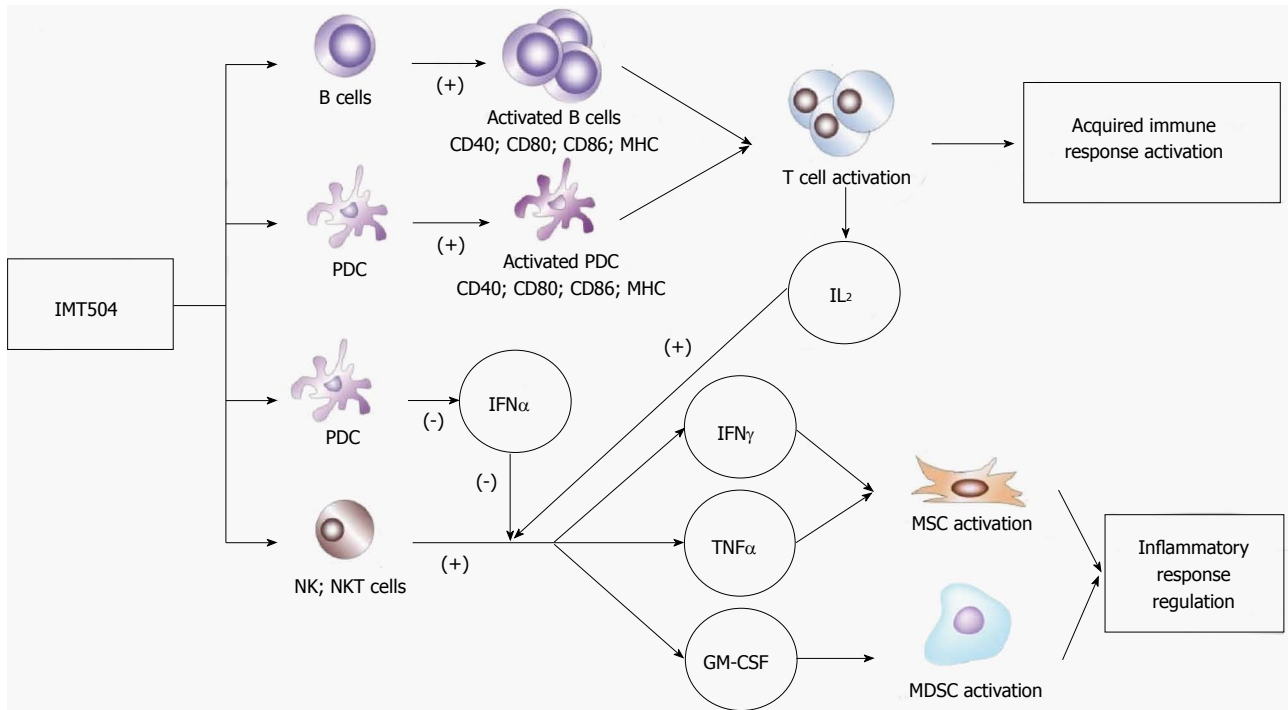


Figure 6 IMT504 effects on the immune system. Primary targets of IMT504 are B lymphocytes (B), PDCs, NK and NKT cells. IMT504 acting on B and PDCs induces a phenotype of antigen presenting cells, which in the presence of an appropriate antigenic stimulus initiates a strong adaptive immune response^[371-373]. On the other hand, IMT504 acting on NK and NKT cells, in collaboration with IL-2, induces the strong secretion of IFN- γ and TNF- α that can induce MSC immunosuppressive properties and of GM-CSF that can activate MDSCs. This immunosuppressive pathway is inhibited by the presence of IFN- α . Reciprocally, IMT504 inhibits IFN- α secretion by PDCs. Therefore, activation of this immunosuppressive pathway depends on the balance between IMT504 activity and activity of IFN- α inducers that are present^[331]. PDCs: Plasmacytoid dendritic cells; NK: Natural killer; NKT: Natural killer T; IL-2: Interleukin-2; IFN- γ : Interferon-gamma; TNF- α : Tumor necrosis factor-alpha; GM-CSF: Granulocyte macrophage colony-stimulating factor; MDSCs: Myeloid-derived suppressor cells.

for MSC differentiation to the MSC₂ anti-inflammatory stage. This scenario is congruent with the results of the above-described IMT504 preclinical assays involving animal models of neuropathic pain, osteoporosis, diabetes and sepsis.

CONCLUSION

The immune homeostatic response of animals to aggression (infections, traumas, tumoral transformation, radiation, *etc.*) is based on an intricate network of cells and chemical messengers. Abnormally high inflammation immediately after aggression or abnormally prolonged pro-inflammatory stimulus bringing about chronic inflammation are associated with life-threatening and severe debilitating diseases^[383]. In both cases, albeit with different urgency, therapeutic intervention to restore homeostasis of the immune system is necessary. Current interventions mainly rest on positive or negative action on a particular element of the immune network abnormally represented in a specific immune disorder. However, given the complexity of the immune network and the general pleiotropism of its components, the effect of such interventions is often poor or even contradictory with the "a priori" rationality^[384,385]. An exception is the transplantation of MSCs, which has demonstrated to be effective in preclinical studies representing a vast array of inflammatory conditions. Unfortunately, results

from clinical trials involving transplantation of MSCs, in general, have not fulfilled expectations. Cell dosing and/or cell preconditioning seem to be critical issues that should be further studied in order to improve human treatments. As an alternative to MSC transplantation, a synthetic drug with the capacity to boost human MSC expansion and/or activation *in vivo* may also be effective, while avoiding many of these problems.

Regarding this, we have reported that IMT504, the prototype of a major class of immunomodulatory ODNs, induces *in vivo* expansion and likely activation of MSCs. This effective endogenous recruitment of MSCs by IMT504 for regenerative medicine results in a marked improvement of animals' chronic suffering as well as acute inflammatory disorders such as neuropathic pain, osteoporosis, diabetes and sepsis. IMT504 can be easily synthesized, purified and mass produced, and has an excellent preclinical safety record. In the small number of patients studied thus far, IMT504 has been well-tolerated, even at very high dosage. Further clinical investigation is necessary to demonstrate the utility of IMT504 for resolution of inflammation and regeneration in a broad array of human diseases that are likely to benefit from immunoprotective/immunoregenerative therapy.

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