20

Stem Cells in Infectious Diseases

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1. Introduction

Stem cells are unspecialized cells found in embryos (blastocyst stage) and in various tissues of adults. They divide mitotically to self renew and can differentiate into different types of cells in appropriate conditions for specific functions. They serve as cell reservoirs for purpose of repair of damaged tissues of the body. Recent research suggests that stem cells especially mesenchymal stem cells have immuno-modulatory characteristics. Due to this property many trials are being conducted with transplantation of MSCs in treating diseases which arise from immunological abuses. These cells have capacity of specific homing and thus can repair infection induced injuries of various organs of body. Evidences suggest that mesenchymal stem cells could on the other hand be a potential target for treatment of tuberculosis.

Even after more than a century of its discovery in 1882 by Robert Koch, *Mycobacterium tuberculosis* (*M. tb*) continues to be one of the leading causes of mortality and morbidity in humans among infectious diseases. One third of global population is latently infected with *M. tb* (World Health Organisation November 2010), and is a cause of around two million deaths each year. The majority of infected individuals remain asymptomatic until there is any perturbation of host immune responses. Currently available vaccine, Bacillus Calmette-Guérin (BCG) is effective only in disseminated TB in young children. On the contrary, its efficacy dramatically varies in adult pulmonary TB depending on ethnicity and geographical locations. Current therapy of TB is very effective and is adopted by internationally recognized Directly Observed Treatment Short course (DOTS) programme. However, this regimen of therapy consists of multiple antibiotics for an extended period of time, and thus incorporates the risk of developing drug resistance. In fact, non-compliance is the central cause for generation of multiple and extensively drug resistant (MDR and XDR) forms of TB (Peter A. Otto *et al*., 2008). Therefore, there is an urgent need for alternative therapeutic targets and newer strategies for treatment of *Mycobacterium tuberculosis* infections.

Considerable efforts have been made to uncover the strategy used by the harbouring tubercular bacilli to induce persistent/latent infection. Only recently, it has been clearly demonstrated that mesenchymal stem cells (MSCs) play a "Janus" like activity and establish a dynamic equilibrium. MSCs position themselves in between harbouring bacilli and host protective T cells. Therefore, MSCs could be a potential therapeutic target for treatment of

latent tuberculosis (Raghuvanshi S. *et al*., 2010). They are recruited at the site of infection and do not allow *M. tb* to spread but at the same time suppress host immune response mounted against the pathogen, thus preventing complete elimination of pathogen from the host (Raghuvanshi S. *et al*., 2010). These results shed a light on possible new ways for treating tuberculosis, which has been a major killer of humans for centuries.

2. Stem cells and various diseases

Due to self renewal and multi-lineage differentiation capabilities, transplantation of stem cells has emerged as a very promising way of treatment of many diseases. Stem cell therapy of different diseases involves the local delivery of stem cells to injured/ infected site or their systemic transfusion. Owing the ability to differentiate into various lineages, stem cells hold therapeutic potential for treatment of many non-infectious and infectious diseases.

2.1 Non-infectious diseases

Mesenchymal stem cells can manipulate host immune responses; they have been used for treating/preventing many diseases which arise because of irregularities of immune system or host responses. Also the infused stem cells are able to differentiate to a particular type of cell after reaching the site in response to local signals. Although this notion have not yet been demonstrated very well. Many reports suggest their use in case of cardiovascular, lung fibrosis, neural and orthopaedic diseases (Barry FP and Murphy JM, 2004; Ortiz LA. *et al*., 2003).

In a study by Teng, YD. *et al*., 2002, have shown improvement in injured spinal cord by transplanting neural stem cell in adult rat. These approaches can also be extended to treat the conditions of stroke and other neurodegenerative diseases (Barry FP. and Murphy JM, 2004). Recently Lin H. *et al*., 2011, reported positive therapeutic use of MSCs in different liver diseases and inherited metabolic disorders. They have shown that cytokines produced from MSCs can attenuate inflammatory injury to the liver and prevent apoptosis of liver cells. Also MSCs helped in regaining the proliferation and function of hepatocytes.

2.1.1 Auto-immune diseases

When immune system of human body recognises its own component as non-self, it starts immune response against it. This leads to auto-immune diseases such as inflammatory bowel disease, arthritis etc. In inflammatory bowel disease which includes ulcerative colitis and Crohn's disease, the intestine become inflamed (Melgar S and Shanahan F, 2010; Siegmund B and Zeitz M, 2011). This is due to immune reaction of person's body towards its own intestinal tissues. In case of arthritis especially in rheumatoid arthritis, there is inflammation of joints due to overt immune responses. This leads to damage of joints which is due to inflammation of joint lining tissues. So, objective of treatments will be suppression of immune responses.

2.1.2 Graft Versus Host Diseases (GVHD)

It is a situation when host immune system rejects transplanted organ or part of it as a non-self. Infiltration of MSCs can suppress host immune response and thus can prevent GVHD

(Le Blanc K, *et al*., 2004; Tse WT, 2003). Prolonged survival of skin graft was observed when MSCs were used (Bartholomew A, *et al*., 2002). So it can reverse the process of rejection and GVHD when used in transplantation (Bobis S., *et al*., 2006; Le Blank K and Ringden O., 2005). GVHD was not observed in case of patients with metachromatic leukodystrophy and Hurler's syndrome after MSCs were infused (Koc, O. N. *et al*., 2002).

In such situations immuno-suppressive effect of MSCs can help in preventing these diseases.

2.2 Infectious diseases

There is growing understanding among scientific community that many of infectious diseases may be cured or controlled using stem cells. Stem cell therapy can also be used in general to fight infections e.g. sepsis, a life threatening condition which arises from spread of an infection throughout the body and body's response to it. Report from Mei SH. *et al*., 2010; suggest that sepsis could be treated successfully by transplanting mesenchymal stem cells to the patient.

2.2.1 Stem cell therapy for treatment of HIV infection

Stem cell therapy for treatment of HIV is under intensive investigation in recent times. Scientists are trying to reconstitute HIV-resistant lymphoid and myeloid system in experimental mice model to combat HIV infections (Holt, N. *et al*., 2010; Steven G Deeks and Joseph M McCune, 2010). Holt, N. *et al*. 2010, engineered human hematopoietic cells to disrupt the CCR5 receptors which are utilized by viruses for their entry. When these engineered cells are transplanted to mice, they confer resistance towards the HIV infections. When CCR5 disrupted stem cells transplanted in a HIV patient, patient remained free of virus for 20 months even in absence of antiretroviral therapies (Hütter G *et al*., 2009).

In a similar kind of approach Kitchen SG. *et al*., 2009; demonstrated that hematopoietic stem cells could be engineered to target HIV infected cells. They generated CD8+ cytotoxic T cell lymphocytes which express transgenic-human anti-HIV T cell receptor. After cloning and transplantation to mice model, these cells were able to kill cells which were infected with HIV and were displaying its antigens.

2.2.2 Stem cell therapy for treatment of malaria

Malaria, which is characterized by invasion of erythrocytes by *Plasmodium*, leads to extreme perturbation of hematopoiesis. Severe destruction of red blood cells causes anaemia, thus posing pressure on bone marrow to meet the requirement of myeloid cells. Scientists from National Institute for Medical Research, UK, have identified an atypical progenitor cells from malaria infected mice which can give rise to a lineage of cells capable of fighting this disease (Belyaev, NN, 2010). Transplantation of these cells into mice with severe malaria helped mice recover from the disease. Other reports also supports stem cell therapy for malaria treatment (Saei, AA. and Ahmadian, S., 2009). Stem cells can also be engineered to produce erythrocytes with modified hemoglobin as its variants are associated with protection from malaria.

Approaches may differ but stem cells are in focus for treatment of many diseases. The current reports from our lab suggest that tuberculosis could be prevented possibly by targeting mesenchymal stem cells.

3. Tuberculosis and its treatment options

Mycobacterium tuberculosis infects humans through aerial route and thus lungs are the primary organ for its infection. Subsequently infection spreads to other organs of body such as spleen and lymph nodes. Recruitment of macrophages and lymphocytes at the site of infection leads to formation of granuloma which is small area of inflammation due to tissue injury or infection and a hallmark of tuberculosis. Many other diseases are also associated with the formation of granulomas such as sarcoidosis, histoplasmosis, syphilis, Crohn's disease etc. Granulomas are formed when immune cells contains a foreign substance after recognition which could not get cleared by body's immune system. They are characterized by presence of macrophages and infectious agent besides other cells and body matrix such as lymphocytes, neutrophils, eosinophils, fibroblasts and collagen.

In case of tuberculosis granulomas are formed at the site of infection where *Mycobacterium tuberculosis* remains as a latent infection. Infection to the macrophages of lungs leads to secretion of several of chemokines which attracts lymphocytes and neutrophils. These cells are able to contain pathogen inside granuloma, thus preventing the spread of bacterium to other parts of body and further inflammation. In other words granulomas are hiding place of bacteria in the infected organs. Final outcome of these interactions and whether it will lead to disease condition or not depends on the strength of host immune response.

Host immune response blocks spread of infection and prevents disease condition but it is not able to completely remove *M. tb* from body. Its persistent infection in a person converts into diseased condition when there is suppression of immunity such as in case of AIIDS. As HIV infection compromises immunity, the person will become highly susceptible to active tuberculosis as latent infection turns into active form (Goletti D, *et al*., 1996). Co-existence of both TB and HIV fuel each other worsening the patient's condition. Immunosuppression in HIV patients occur as a result of decrease in number of $CD4^+$ T cells and leads to progression of TB. One report suggests that the chances of getting TB increases from 4% to 49% when there is decrease in $CD4^+$ T cells from 200 cells/µl to 100 cells/µl (Jones BE *et al*., 1993). On the other hand *Mycobacterium tuberculosis* infection facilitates replication of HIV. This is done by cytokines such as TNF-α and IL-6 secreted from *M. tb* infected macrophages (Havlir DV and Barnes PF 1999; Nakata K, *et al*., 1997). These cytokines creates a microenvironment which are inductive to HIV replication (Goletti D, *et al*. 1996). Thus, both HIV and *M. tb* can shorten the lifespan of patients by working together.

4. Bacillus Calmette–Gue´rin (BCG) and its efficacy

Bacillus Calmette–Gue´rin (BCG) vaccine is prepared from attenuated strain of *Mycobacterium bovis*. This strain has become avirulent due to continuous passages in artificial medium for a long time but still remained antigenic, being used as vaccine to prevent tuberculosis. But its effectiveness is not 100% and does not last longer (Colditz GA *et al*., 1994). At the maximum it can provide protection up to 15 years depending on many factors including geographical conditions. Directly Observed Treatment, Short Course (DOTS) is a world health organisation (WHO) recommended treatment for tuberculosis. It was launched in India in 1997 as a revised national tuberculosis control programme. Before launching the programme, it was tested from 1993-1996. The key components of this programme are as follows-

i. Political commitment to control TB;
ii. Case detection by sputum smear microscopy examination among symptomatic patients;
iii. Patients are given anti- TB drugs under the direct observation of the health care provider/community DOT provider;
iv. Regular, uninterrupted supply of anti-TB drugs; and
v. Systematic recording and reporting system that allows assessment of treatment results of each and every patient and of whole TB control programme.

Treatment of tuberculosis involves- isoniazid, rifampicin, ethambutol, pyrazinamide daily for two months, followed by four months of isoniazid and rifampicin given three times a week. Sometimes one or the other drugs are omitted during treatment depending on the patient's condition. Later in 2006; WHO launched stop TB programme as a multi-dimensional approach to fight this disease at international level and better management of treatment strategies.

5. Mesenchymal stem cells (MSCs) and its role in *M. tb* infection

Discovered by A. J. Friedenstein in 1968 (Friedenstein, AJ. *et al*.,1974) MSCs are a subset of non-haematopoietic pleuripotent cells found in adult bone marrow and are capable of differentiating into adipocytes, fibroblasts and even myoblasts (Ren G. *et al*., 2010). The mesenchymal stem cell name to these cells was given by Caplan. They have very high capacity to proliferate *in vitro* and don't loose proliferation capacity for a long time (Sundin, M. *et al*., 2006). After their discovery and growing understanding of their role in the modulation of host immune response, they have been thought to be an important tool for regenerative medicine and immunotherapy. Although there are no exclusive markers for MSCs, they are characterized by their ability to differentiate into different kinds of cells mentioned above and by the combined surface expressions of $CD29^{+}CD44^{+}Sca\text{-}1^{+}CD45^{-}CD11b^{-}CD11c^{-}Gr\text{-}1^{-}F4/80^{-}MHC\text{-}II^{-}MHC\text{-}I^{low}$ (Ren G. *et al*., 2008 and 2010).

MSCs are immuno-suppressive in nature and they exert their effect only when they are stimulated. Unstimulated MSCs are not capable of performing this effect (Yufang Shi *et al*., 2010). MSCs have been shown to prevent rejection of allogenic skin grafts (Xu G, *et al*. 2007), graft versus host diseases (K. Le Blanc and O. Ringden, 2006), and therefore are helpful in treating auto-immune disorders. They are able to alter function of T cells, B cells, dendritic cells (DCs) and natural killer (NK) cells (Ren G. *et al*., 2010). This is done by cytokines secreted by MSCs and through direct cell-cell contact. MSCs produce number of cytokines, signalling molecules and growth factors which can suppress inflammatory response and may also lead to trophic effects (Caplan AI and Dennis JE. 2006; Lin H. *et al*., 2011). Their regulatory effect on immune system, such as anti-proliferative (Bartholomew A, *et al*., 2002; Di Nicola M *et al*., 2002; Le Blank K *et al*., 2003; Sudres M, *et al*., 2006) and anti-inflammatory roles makes them an important candidate for therapy of many inflammatory diseases (Newman RE *et al*., 2009).

Mesenchymal stem cells have ability to create a microenvironment which helps in engraftment. The expressions of major histocompatibility I (MHC I) molecules are less on these cells and they lack human leukocyte antigen (HLA) class II and costimulatory molecules such as CD40, CD80 and CD86 (Krampera, M. *et al*., 2003). Low level expression

of MSC I can still activate T cells but they become anergic as there is no secondary signals or co-stimulation (Javazon EH. *et al*., 2004; Wong RS. 2011). Also low level expression of MHC I prevent these cells from being destroyed by natural killer cells (Moretta A. *et al*., 2001). They generally do not express MHC II molecules on their surface (Le Blank K. *et al*., 2003) but could be immunogenic in certain circumstances (Le Blank K. *et al*., 2003; Stagg J. *et al*., 2006). The above characteristics help them to be less immunogenic (Herrero C. and Perez-Simon, J. A. 2010) and also have ability of interaction with components of both innate and adaptive immune system. Suppression of T and B cell proliferation and their activation makes them useful for treatment of different infectious and non-infectious diseases such as tuberculosis, graft versus host disease and various auto-immune diseases (Sundin, M. *et al*., 2006). These cells have ability to migrate specifically to the site of injury. This has been shown in many of diseases involving injury of tissues and cartilages.

5.1 Effector molecules of mesenchymal stem cells

The molecular players which perform immunosuppression are mainly nitric oxide (NO), indoleamine 2,3-dioxygenase (IDO) and prostaglandin E2 (PGE2) (Ren G. *et al*., 2008). Three nitric oxide synthases catalyse the synthesis of NO, which by interacting with many receptors and enzymes plays critical role in immune-suppression. It affects the phenotype of T cells and impairs its proliferation and function affecting TCR mediated signalling (Hoffman, RA. *et al*., 2002). MSCs has been shown to express many chemokine receptors such as CCR1, CCR4, CCR5 and CCR10, thus in response to many of the cytokines, they move to desired destination (Von Luttichau *et al*., 2005).

5.2 Host immune response

Both innate and adaptive immunity plays role against *Mycobacterium tuberculosis* infection. Host immune response against *Mycobacterium tuberculosis* is Th1 rather than Th2 mediated as IFN-γ knock out mice fails to mount immune response against its infection (Schroder K *et al*., 2004). Of note, IFN-γ plays suppressive role for Th2 cell differentiation. *M. tb* evades host protective immune responses by modulating various immune mechanisms that includes down regulations of Major Histocompatibility Complex (MHCs), co-stimulatory molecules, and up-regulating production of immune suppressive cytokines viz. TGF-β and IL-10, and prostaglandins. Each of these targets is extensively studied for therapeutic interventions. However, it has been mostly unsuccessful. It is now evident that MSCs confine harbouring bacteria and segregate host protective responses. Cell mediated immunity is required for protection from *M. tb.* But *M. tb* has evolved mechanisms to evade the host immune response and remains as persistent infection inside the granuloma.

5.3 Balance between immune response and disease outcome

After *M. tb* infection, macrophage and lymphocytes are mobilized to the site of infection, resulting in formation of granuloma. Thus cells of innate and adaptive immune system of body surround the pathogen. Recognition of pathogen associated molecular patterns leads to activation of T cells which secrete IFN-γ. Since *M. tb* is an intracellular pathogen, effector T cells plays crucial role in host immunity against this pathogen. To evade the host defence mechanism, pathogen recruits MSCs at the periphery of granuloma (Raghuvanshi S. *et al*.,

2010). Reports from various groups suggest that MSC interferes with antigen presenting cell functionality, block the differentiation of B cells. They also suppress natural killer cell and T cell responses. Both naïve and memory T cell responses were inhibited by MSCs. The suppression is due to cell cycle arrest at G0/G1 stage of T cells (Glennie S. *et al*., 2005). They induce Th2 cells to produce interleukin-4 (IL-4) and also inhibit the production of interferon-γ thus creating an anti-inflammatory state. MSCs also arrest B cells at G0/G1 stage of their cell cycle besides suppressing their differentiation (Corcione, A. *et al*., 2006; Tabera, S. *et al*., 2008) and inhibit immunoglobulin production (Herrero, C. and Perez Simon J. A. 2010). MSCs also hinder functional differentiation of dendritic cells (Jiang XX., *et al*., 2005; Ramasamy R., *et al*., 2007). Besides above mentioned roles there is conflicting reports regarding immune-suppression effect of MSCs in murine models *in vivo* (Muriel Sudres *et al*., 2006).

Pro-inflammatory cytokines induces MSCs to secrete several cytokines/ chemokines (IL-10, TGF-β, IDO and PGE2) and nitric oxide (NO). Together they perform immuno-suppression (Ren G. *at al*., 2008) and also induce regulatory T cells which prevent killing of *M. tb* by cytotoxic T cells (Scott-Browne JP *et al*., 2007). NO inhibits T cell proliferation, production of cytokines, and induce tolerance (Niedbala, W. *et al*., 2006; Ren G. *et al*., 2008). NO diffuses rapidly to the vicinity but its active concentration drops very fast as it is highly unstable (Ren G. *et al*., 2008). It is effective only up to a distance of 100 micrometer (J.R. Lancaster Jr., 1997). To perform immunosuppressive activity, T cells must be held in close proximity to the MSCs. This is done by MSC surface molecules such as intercellular adhesion molecule-1 (ICAM1) and vascular cell adhesion molecule-1 (VCAM1), which are shown to interact with T cells and hold them close to the mesenchymal stem cells (Ren G. *et al*., 2010 and 2011). Thus besides soluble factors secreted from MSCs, cell surface molecules on MSCs also play crucial role in immune suppression against *Mycobacterium tuberculosis* (Xu G, *et al*. 2007; Shi Y. *et al*., 2010).

In mice after infection by *Mycobacterium tuberculosis*, MSCs exclusively infiltrate to infected organs such as lungs and spleen (Raghuvanshi S. *et al*., 2010). They have not been found to the uninfected organs of the infected person. This report suggests that immune suppression by MSC is local and confines to the infection site only. Although MSCs recruited at the site of infection contains pathogen inside granulomas, it also prevents killing of *Mycobacterium tuberculosis* by suppressing the host immunity. These cells intercept immune cells from the pathogen by being there physically and helping to establish equilibrium between host and the pathogen (Figure 1). In other words, *M. tb* rely on MSCs to establish long lasting infection which should be intervened to achieve objective of treating tuberculosis.

6. Issues in therapy with stem cells

Therapy with stem cells have shown hope for treatment of those diseases which otherwise seems to be untreatable. But this approach also has its own risks. Utilization of MSCs for therapeutic use is like a double edged sword putting patient at the danger of cancer. The anti-proliferative effects of these cells are often associated with anti-apoptotic effect also, which may leads to tumour progression, metastasis and drug resistance. So even with vast therapeutic potential of stem cells in various non-infectious and infectious diseases, there

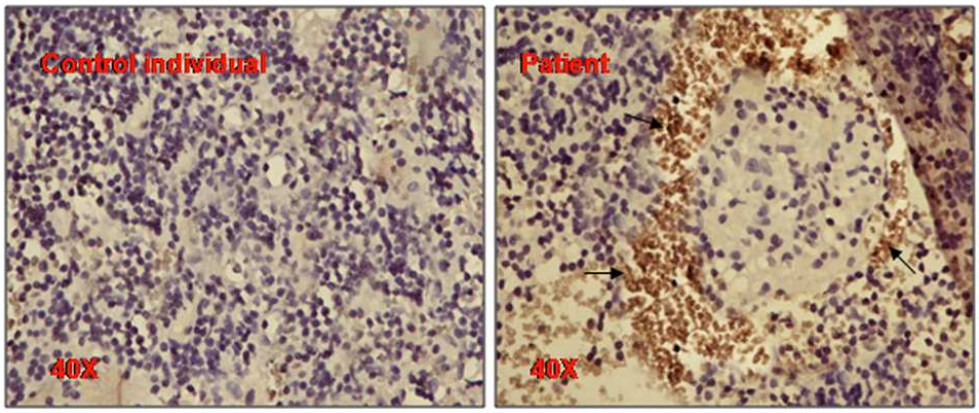

Fig. 1. Immunohistochemical staining for the presence of MSCs (arrows) in granuloma-containing lymph node of patients with tuberculosis. Adapted from Raghuvanshi S. *et al*., PNAS, 2010.

are some issues which have to be addressed before its actual implementation. Some of them are as follows-

i. Reach of the administered stem cell to its desired destination such as injured tissue and infected/affected organ. Also the effect of endogenous population of the stem cells should be considered.
ii. Proper understanding of the host immune response against the administered stem cell.
iii. Dose of the transplanted stem cells. Also being animal product for administration into patients, long term safety issues has to be understood.
iv. Risk to the patient with secondary infections in case of immune suppression of the host by stem cells. Immuno-compromised condition of the patient may lead to infection of fungus, bacteria and viruses. This should be considered while going for stem cell infiltration and should be tested clinically (Sundin, M. *et al*., 2006).
v. Although anti-tumor response of MSCs has been observed, they can also suppress anti-tumor immune response. MSCs can be potentially tumorogenic by direct transformation. So, use of MSCs for therapy of patients with high risk to cancer should be avoided.

Since allogenic MSCs are little immunogenic, the other choice should be administration of autologous MSCs. Clinical applications of autologous MSCs of bone marrow has been successfully shown in case of MDR tuberculosis (Erokhin VV., *et al*., 2008). They have shown that systemic transplantation of the autologous MSCs stopped the bacterial discharge and lung tissue cavities were resolved in tuberculosis patients infected with resistant forms of *Mycobacterium tuberculosis*. Contrary to the role of MSCs in various diseases which have been discussed earlier, where transplantation of these cells is required for treatments of various diseases, report from our lab suggest them as a target for treatment of tuberculosis.

7. Conclusion and future perspectives

Use of stem cells for treatment of many diseases is the area of intensive research these days with many clinical trials undergoing. Mesenchymal stem cells are the main cell type being used due to their longevity and less ethical issues. Still there are many concerns as discussed including their immunogenicity. Suppression of immune system is the other major concern which poses serious threat of other infections to the patients. Studies from our lab using mouse model of tuberculosis suggest role of mesenchymal stem cells in this disease. Besides currently available strategies for treatment of tuberculosis, the probable new target such as MSCs holds promise in the current scenario of MDR and XDR tuberculosis. Targeting MSCs will also wouldn't lead to generation of any new resistance in pathogen as one does not need to target them directly rather manipulate the host immune response. In the coming future we may be able to use MSCs as an immuno-therapeutic target for the treatment of tuberculosis.

8. Acknowledgements

Authors would like to thank Wellcome-DBT India Alliance; Department of Biotechnology, Government of India and Council of Scientific and Industrial Research, Government of India for financial support.

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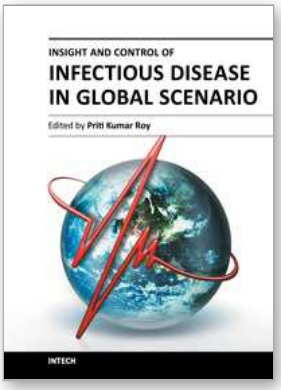

Insight and Control of Infectious Disease in Global Scenario
Edited by Dr. Roy Priti

ISBN 978-953-51-0319-6
Hard cover, 442 pages
Publisher InTech
Published online 21, March, 2012
Published in print edition March, 2012

This book is projected as a preliminary manuscript in Infectious Disease. It is undertaken to cover the foremost basic features of the articles. Infectious Disease and analogous phenomenon have been one of the main imperative postwar accomplishments in the world. The book expects to provide its reader, who does not make believe to be a proficient mathematician, an extensive preamble to the field of infectious disease. It may immeasurably assist the Scientists and Research Scholars for continuing their investigate workings on this discipline. Numerous productive and precise illustrated descriptions with a number of analyses have been included. The book offers a smooth and continuing evolution from the principally disease oriented lessons to a logical advance, providing the researchers with a compact groundwork for upcoming studies in this subject.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Ramesh Chandra Rai, Debapriya Bhattacharya and Gobardhan Das (2012). Stem Cells in Infectious Diseases, Insight and Control of Infectious Disease in Global Scenario, Dr. Roy Priti (Ed.), ISBN: 978-953-51-0319-6, InTech, Available from: http://www.intechopen.com/books/insight-and-control-of-infectious-disease-in-global-scenario/stem-cells-in-infectious-diseases

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