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Recent Advancement of MMP Inhibitors

Ajay K Chaudhary* and Anita H Nadkarni

Department of Immunohematology, National Institute of Immunohematology, KEM Hospital Campus, Parel, Mumbai, India

Matrix metalloproteinase (MMPs) are a family of zinc dependent endopeptidases that play a significant role in cancer as well as in numerous other diseases [1]. It degrades the extracellular matrix (ECM) components and controlled remodeling of ECM is essential for invasion, metastasis and growth of various malignant tumors [2]. Collagen based matrix metalloproteinase (MMP) inhibitors were the first generation of MMP inhibitors. MMP inhibitors block or inactivate the functional activity of various MMPs. These enzymes have the capability to degrade all the components of connective tissue. It is well known that the expression of MMPs is elevated in many pathological conditions and many metabolic disorders.

Last three decades many researcher & pharmaceutical companies developed exogenous MMP inhibitors (MMPIs) such as Batimastat (BB-94, angiogenic inhibitors) and Marimastat (BB2516, anti-neoplastic drug) , MAG-182 (Prostate Cancer MMP inhibitors), AZD-8955 (Arthritis & Cancer; MMP and aggrecanase inhibitors) etc., used as anticancer drugs [3]. More than 50 MMPIs were investigated and used in clinical trials. Preclinical studies indicated that they had strong anticancer potential to treat many cancers. Unfortunately, all preclinical data indicates that clinical trial has failed. There are various enlightenments for these clinical failure such as BB-94 was the first MMPI that went into clinical trials in 1994, while it reached Phase-III clinical trial, whether it was never marketed because it couldn't be administered orally and also when BB-94 injection were delivered into peritoneum, it caused peritonitis (inflammation of the peritoneum). Unfortunately, many of them has been failure in the clinical trial, although plenty of clinical trials with various synthetic MMP inhibitors for the treatment of different malignancies were disappointing but many recent scientific data specify that the use of selective inhibitors might lead to new therapies option for severe & critical chronic inflammatory diseases. The reasons is behind this failure are complexity of the MMP biology, metabolic activity and its toxicity level.

MMP have been linked to many cancers such as breast, prostate, ovarian, oral, colorectal, lung and cervical. Now day's synthetic MMP inhibitors are being discovered for the use in cancer prevention and treatment because of their demonstrated anti-metastatic and anti-angiogenic properties. It is well known that most of the breast cancer leads to bone metastasis. Cell-cell and cell-matrix interactions, growth factors release and bioactive of the various cytokines and removal of large amounts of bone matrix are the important requirements for the development of bone metastasis in breast cancer patients. MMPs play an important role in all of these processes, using BB-94 or GM6001 synthetic MMP inhibitors decrease and prevent bone metastasis in mice [4]. Roshe 28-2653, a new synthetic matrix metalloproteinase inhibitor reduces tumor growth and prolongs survival in a prostate cancer standard rat model [5].

The new next generation of MMPs inhibitors strategies can be based on selectively targeting membrane bound MMPs with specific antibodies of the specific type of cancer. Because the progression of cancer involves the several proteolytic functions, in which, it has been well documented that the membrane bound MMPs play an essential role. Tumor microenvironment changes enhanced the proliferation of the cancer cells, invasiveness. In this situation many MMPs have participated to inhibit the functional activity of the drug target response.

As I mentioned earlier, the MMPs inhibitors (MMPIs) have portentous novel class of various anticancer agents [6] that are presently considering intensive clinical assessment and evaluation in several diseases. Various MMPs inhibitor compounds are efficaciously improved and move positively towards clinical trials and being considered & finally assessed clinical trials in conclusive randomized manner for the multifactorial targeted therapy of the different cancer. The outcomes of these clinical trials studies, which should be available in the enthusiastic treatment option coming near future. Further, significant biological areas being examined including the development of additional specific MMP inhibitors, the modification of MMPs inhibitors design for clinical trial, and also the developmental treatment policies and strategies that syndicate MMP inhibitors with biologic agents. In conclusion, the targets of the specific MMPs may signify an attractive drug development and it may use for the cancer treatment.

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***Corresponding author:** Ajay K Chaudhary, Department of Immunohematology, National Institute of Immunohematology, KEM Hospital Campus, Parel, Mumbai, India, Tel: +91-022-24138518; E-mail: ajaygenome@gmail.com / Ajay.Chaudhary@RoswellPark.org

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