DOWNLOAD PDF X.33. SELECTIVE MMP INHIBITORS BMS 275291, BAY12-9566, MARIMASTAT, PRINOMASTAT.

Chapter 1 : Novel therapies for lung cancer | tien hoang - calendrierdelascience.com

These include drugs inhibiting matrix breakdown, the matrix metalloproteinase inhibitors (MMPIs), such as marimastat, prinomastat, BMS, BAY, and neovastat drugs that block endothelial cell signaling via vascular endothelial growth factor (VEGF) and its receptor (VEGFR) including rhuMAb VEGF, SU, SU, ZD, CP, and.

Description The present invention relates to solid pharmaceutical compositions and, in particular, the use of substantially water insoluble therapeutically active agents for local delivery for preventing or treating disease. The present invention more specifically relates to solid matrix metalloproteinase MMP inhibitor compositions and their use in preventing scarring. The present invention also relates to specific MMP inhibitor solid dosage forms. Therapeutic agents that are substantially water insoluble are generally delivered to the human or animal body in a suitable solvent, such as DMSO, etc. However, by delivering the therapeutic agent in a solution, the agent is usually administered systemically. If such a solution is administered locally, it generally only remains at the site of administration for a short period of time i. It is desirable to deliver therapeutic agents locally so that only the relevant part of the body is exposed to the agent. It is also important that any therapeutically active agent delivered to the body has a suitable dissolution profile enabling a therapeutically effective concentration of the active agent to be achieved for a sufficiently prolonged period of time to allow treatment. Numerous multicomponent and complicated drug formulations have been developed in an effort to resolve these issues; however, such formulations can be expensive, physically and chemically sensitive and labile, and specific to the therapeutically active agent being delivered. One preferred aspect of the present invention concerns preventing or treating tissue scarring. The processes involved in scarring can play a part in treatment failure in a variety of situations. Furthermore, scarring appears to play a part in treatment failure in virtually every blinding disease in the world today. A very good example of the importance of healing and scarring in the eye is what happens after glaucoma surgery to create a fistula to reduce the pressure in the eye. The final eye pressure determines the success of the operation and is dependent on the healing and scarring process. The wound healing process that occurs in the eye after trabeculectomy starts after the initial conjunctival incision. Plasma proteins and blood cells are released in the wound area and a fibrin clot is formed. Neutrophils and macrophages are recruited at the wound area and degrade the clot by expressing several enzymes and MMPs such as MMP-8 and -9 among them. Activation and migration of fibroblasts to the wound site also takes place. The fibroblasts in normal unwounded tissues are quiescent undifferentiated mesenchymal cells known as fibrocytes. After their activation, these fibroblasts produce large amounts of extracellular matrix ECM molecules such as collagens, glucosaminoglucans and elastin. Moreover, comparison between normal and healing conjunctiva has shown that the MMP-1 and TIMP-1 were located only in the healing subconjunctival tissue. Neither molecule was found in normal subconjunctival tissue nor in the conjunctival epithelium. Based on these results, a possible role for MMPs in post-operative subconjunctival scarring has been proposed. After continuous remodeling of the granulation tissue and apoptosis of myofibroblasts, dense collagenous subconjunctival scar tissue is formed. Extended subconjunctival fibrosis and the contraction of the tissue is the end result. This causes loss of function of the bleb with subsequent increase of intraocular pressure IOP. Solutions of antimetabolites such as mitomycin C MMC and 5-fluorouracil 5-FU have been shown to be effective in reducing the scarring after trabeculectomy Dahlmann et al. Many studies have been published by the inventors that describe the increase of the functioning period of the outflow channel in the bleb. Results indicate that a single five minute application of a 5-FU or mitomycin C solution during surgery reduces the healing response and decreases scar formation. It is thought this is mainly due to suppression of fibroblast proliferation, prolonging the bleb survival Doyle et al. Unfortunately, severe complications often occur after treatments with these metabolites. The bleb often leaks and there other side effects including hypotony, endophthalmitis and excessive ocular cell apoptosis that can cause irreversible vision loss. Hence safer and more effective agents are needed to reduce scarring and to control healing after GFS. Since MMPs take part in

several pathological conditions, it is important to identify selective inhibitors that can be used therapeutically to control MMP activity in defined ways. These are hydroxamic acid derivatives that bind reversibly to the zinc in the active site of MMPs. MMPs play a significant role in wound contraction Daniels et al. Both in vitro and in vivo studies have been performed in order to test the effect of MMP inhibitors in contraction models. Observations revealed inhibition of the contraction of the gels with the application of all the three MMP inhibitors in a dose-dependent manner and Ilomastat was observed to be the most effective. The tested MMP inhibitors were also found to have a non toxic and reversible effect and zymography results indicated significant reduction of the proteolytic activity of the detected MMP bands after the application of the MMP inhibitors. It was also shown that Ilomastat inhibited collagen production from fibroblasts in a dose-dependent manner. This was an important finding, as excessive collagen production and deposition at the incision area is mainly responsible for the bleb failure Cordeiro et al. Histological findings showed that reduction of scar tissue formation in the Ilomastat treatment group occurred with decreased cellularity compared to the control group. There was also decreased cell apoptosis that is known from other studies to be associated to MMC , decreased myofibroblasts in the wound area possibly because of an inhibitory effect of Ilomastat in fibroblast migration and a large bleb area compared to control group. Importantly, this study showed that the morphology of the subconjunctival tissue was normal in the Ilomastat group but hypocellular in the MMC group. The clinical use of Ilomastat for post surgical wound management may have advantages over the currently used cytotoxic antimetabolites. Ilomastat displays specific MMP inhibition and blocks the activation of fibroblasts. No reports of toxicity have been published, so it is possible that Ilomastat will be better tolerated for post-operative GFS treatment than the antimetabolites. Currently, a single administration of MMC is used during trabeculectomy beneath the scleral flap. Multiple, repetitive injections of an antimetabolite is not a viable choice due to toxicity associated with the drug, and to the discomfort and risk of infection to the patient caused by multiple injections. It is also not possible to continuously infuse the agent. There is a need to develop a continuous prolonged drug release system that can be placed in the subconjunctival space after trabeculectomy. Ilomastat is known to inhibit in vitro contraction in collagen I gels in a dose dependent manner in concentrations ranging from nM Daniels et al. While this preliminary work established the favourable pharmacological effects of Ilomastat, the therapeutic concentration could only be achieved with injections that had been prepared from aqueous-DMSO solutions. DMSO has not been approved for ocular human use. There is a need for a method of localised delivery of a substantially water insoluble therapeutically active agent for treating or preventing a disease. There is also a particular need for an agent that has suitable anti-scarring activity, low toxicity when implanted in the human or animal body, the active agent has low toxicity both locally and systemically, and an optimal dissolution profile for providing long term anti-scarring activity. The present invention overcomes at least some of the problems associated with the prior art methods. In accordance with a first aspect of the invention, there is provided a solid, implantable dosage form comprising a therapeutically active agent in solid form, optionally with one or more pharmaceutically acceptable excipients, wherein the one or more excipients, when present, do not lead to a significant delay or prolongation of the release of active agent, as compared to an equivalent dosage form containing no excipients when tested in vitro. The dosage form of the first aspect is based on the surprising finding that it is possible to implant relatively simple solid dosage forms at selected sites in vivo and these dosage forms provide a steady release of active agent, without the need for complex sustained release formulations in which the release profile is controlled primarily by the excipients. The comparison in dissolution rates between excipient-containing and excipient-free dosage forms may be conducted using any suitable dissolution apparatus providing a flow of media which mimics the flow of in vivo media following tissue implantation, such as the flow-though rig described herein. The dissolution should be conducted at around 37 deg C. The dosage form is preferably suitable for the localised prevention or treatment of a disease. It is possible that the dosage form of the first aspect may be implanted for the systemic delivery of an active agent. In a preferred embodiment, the dosage form is suitable for ocular, periocular or intraocular

implantation. For example, the dosage form may be suitable for implantation in the subconjunctival space. In preferred embodiments, the dosage form is sterilised. Such treatment enables the dosage form to be safely implanted in a wider range of sites in vivo. Depending on the solubility of the active agent concerned, and the flow of aqueous biological media through the tissue into which implantation is to be made both of which may readily be determined , non-sink conditions can generally be achieved. Because the tissue is non-sink, it does not matter, as far as drug release is concerned, if the dosage form has excipient or not. Without excipient, the dosage form is more simple because only the active needs to dissolve. Indeed, in many instances, the only reason to use an excipient is to ensure the dosage forms are compliant with manufacturing specifications; in general, excipient use is primarily for processing considerations in fabricating the dosage form. In the vast majority of active agents of usefulness according to the invention, excipient use is not required to aid dissolution or release characteristics. In certain embodiments, the dosage form is prepared by compression. In particular instances, the dosage form is a tablet. Surprisingly, it has been found that a number of active agents, hitherto known to be formulated in solid dosage forms in which the majority of the dosage form comprises a variety of excipients, can be formulated as implantable tablets with little or no excipient content. This allows the dosage forms to be efficiently prepared using existing tableting apparatus, and also provides advantageous results in terms of dissolution profile of the dosage forms so prepared. In some embodiments, the dosage form has a volume of between 0. Such limits allow the dosage form to be implanted in a wider variety of sites in vivo. In particular embodiments, the dosage form is substantially free of excipients. It is a surprising finding that a variety of active agents can be formed into solid unit dosage forms, such as compressed dosage forms e. In preferred embodiments, the active agent is substantially water insoluble. Such insolubility enhances the sustained release of active agent in the dosage forms of the invention. In general, the therapeutically active agent can be any suitable agent that is a solid at ambient temperature and which can be formulated into a solid unit dosage form. Such a limitation can readily be assessed by the skilled formulator. The therapeutically active agent may be a naturally occurring agent or a synthetic agent. In may instances, the active agent will be at least partially crystalline. Preferably the therapeutically active agent is a synthetic chemical compound. For MMP inhibitors and other receptor antagonists or enzyme inhibitors , agents with low Ki values, i. For example, ilomastat has a Ki of 0. An advantage of the present invention is that relatively low solubility compounds can be successfully delivered by means of the described dosage form. Equally, in traditional formulation approaches to solid active agents, solubility and tissue permebaility characteristics of the active are key considerations. In the implantable dosage forms of the present invention, and the related methods and uses, the need for permeation through a mucosal membrane e. This allows the invention to have a very wide applicability. Preferred agents include MMP inhibitors and other anti-scarring agents, steroids, antibiotics, anticancer agents, antibody molecules and anti-inflammatory agents. Suitable steroids include corticosteroids, such as dexamethasone, hyrdocortisone, prednisolone, triamcinolone and methylprednisolone. Suitable antibiotics include any of the generally used antibiotics, including beta-lactam antibiotics, e. Suitable anti-cancer agents include SFU, paclitaxel and chlorambucil. Any antibody molecule may be used. Preferably the antibody molecules are lyophilised antibody molecules.

Chapter 2 : Angiogenesis-Review | RAKESH R SOMANI - calendrierdelascience.com

Several MMP inhibitors are in various developmental stages for different symptoms, mostly in cancer and rheumatoid arthritis. Compounds tested in clinical trials as MMP inhibitors include marimastat, 69, tanomastat (Bay), 70, prinomastat (AG), 71, and batimastat,

What is claimed is: A method of reducing neurological damage following trauma to nervous tissue in a mammal, said method comprising inhibiting activity or expression of a matrix metalloproteinase in said mammal before, during, or after said trauma. The method of claim 1, wherein said method comprises administering to said mammal a matrix metalloproteinase inhibitor MMPI during or after said trauma. The method of claim 2, wherein said matrix metalloproteinase inhibitor MMPI is selected from the group consisting of a 4-biarylbutyric acid derivative, a 5-biarylpentanoic acid derivative, Fenbufen, peptide MMPIs, a hydroxamic acid, a tricyclic butyric acid derivative, a biphenyl butyric acid derivative, a heterocyclic substituted phenyl butyric acid derivative, a sulfonamide derivative, a succinamide MMP inhibitor, a sulfonated amino acid derivatives, and a neutralizing anti-MMP antibody. The method of claim 2, wherein said MMPI is provided in a unit dosage form at a concentration sufficient to inhibit neurological damage following trauma to nervous tissue in said mammal. The method of claim 2, wherein said trauma is selected from the group consisting of ischemia, spinal cord injury, cranial injury, physical trauma to the head or spinal cord; a brain concussion; ischemic stroke caused by thrombosis or embolism; cerebral hemorrhage, general circulatory failure, circulatory disruption caused by cardiac arrest, hemodynamic shock caused by loss of blood due to injury or hemorrhage elsewhere in the body; vasculatory damage caused by vascular disease, bacterial infection, viral infection, fungal infection, cerebral or spinal tumors, glial cell swelling, hypoxic injury to the brain caused by respiratory disruption, and post-operative brain injury or stress. The method of claim 2, wherein said trauma is spinal cord injury. The method of claim 2, wherein said mammal is a human. The method of claim 2, wherein said mammal is a non-human mammal. The method of claim 2, wherein said mammal is a human afflicted with or following a stroke. The method of claim 2, wherein said mammal is a human afflicted with a spinal cord injury. The method of claim 2, wherein said administering is for up to 5 days following said trauma. The method of claim 1, wherein said method comprises administering to said mammal an agent that inhibits expression of a matrix metalloproteinase, with the proviso that said agent is not a glucocorticoid. The method of claim 14, wherein the agent is not methylprednisolone. The method of claim 16, wherein said trauma is spinal cord injury. The method of claim 16, wherein said trauma is brain injury. The method of claim 16, wherein said trauma is motor nerve injury. The method of claim 16, wherein said trauma is sensory nerve injury. The method of claim 1 or 14 , wherein said method comprises administering to said mammal a MMP-9 inhibitor and a prophylactically or therapeutically effective amount of one or more anti-inflammatory agents during or after said trauma. The method of claim 22, wherein at least one anti-inflammatory agent is a non-steroidal anti-inflammatory drug. The method of claim 23, wherein the non-steriodal anti-inflammatory drug is aspirin, ibuprofen, diclofenac, nabumetone, naproxen, or ketoproten. The method of claim 1 or 24 , wherein said method comprises administering to said mammal a matrix metalloproteinase inhibitor MMPI and a prophylactically or therapeutically effective amount of one or more anti-convulsive agents during or after said trauma. A method of reducing abnormal vascular permeability associated with spinal cord injury, said method comprising administering to a mammal in need thereof a matrix metalloproteinase inhibitor MMPI in an amount sufficient to reduce abnormal vascular permeability associate with or following said spinal cord injury. The method of claim 27, wherein said matrix metalloproteinase inhibitor MMPI is selected from the group consisting of a 4-biarylbutyric acid derivative, a 5-biarylpentanoic acid derivative, Fenbufen, peptide MMPIs, a hydroxamic acid, a tricyclic butyric acid derivative, a biphenyl butyric acid derivative, a heterocyclic substituted phenyl butyric acid derivative, a sulfonamide derivative, a succinarmide MMP inhibitor, a sulfonated amino acid derivatives, and a neutralizing

anti-MMP antibody. The method of claim 27, wherein said MMPI is provided in a unit dosage form at a concentration sufficient to inhibit abnormal vascular permeability following spinal cord injury. The method of claim 27, wherein said mammal is a human. The method of claim 27, wherein said mammal is a non-human mammal. The method of claim 27, wherein said mammal is a human afflicted with or following a stroke. The method of claim 27, wherein said mammal is a human afflicted with a spinal cord injury. The method of claim 16, wherein said spinal cord injury comprises motor nerve injury. The method of claim 16, wherein said spinal cord injury comprises sensory nerve injury. The method of claim 27 or 14 , wherein said method comprises administering to said mammal a MMP-9 inhibitor and a prophylactically or therapeutically effective amount of one or more anti-inflammatory agents during or after said trauma. The method of claim 27 or 24 , wherein said method comprises administering to said mammal a matrix metalloproteinase inhibitor MMPI and a prophylactically or therapeutically effective amount of one or more anti-convulsive agents during or after said trauma. A method of improving recovery of neurological function following injury to neurological tissue, said method comprising administering to a mammal in need thereof a matrix metalloproteinase inhibitor MMPI in an amount sufficient to improve recovery of neurological function following said injury. The method of claim 45, wherein said injury is spinal cord injury. The method of claim 46, wherein said recovery comprises recovery of locomotor function. The method of claim 45, wherein said matrix metalloproteinase inhibitor MMPI is selected from the group consisting of a 4-biarylbutyric acid derivative, a 5-biarylpentanoic acid derivative, Fenbufen, peptide MMPIs, a hydroxamic acid, a tricyclic butyric acid derivative, a biphenyl butyric acid derivative, a heterocyclic substituted phenyl butyric acid derivative, a sulfonamide derivative, a succinamide MMP inhibitor, a sulfonated amino acid derivatives, and a neutralizing anti-MMP antibody. The method of claim 49, wherein said MMPI is provided in a unit dosage form at a concentration sufficient to promote recovery of locomotor function following spinal cord injury. The method of claim 45, wherein said injury can comprise an injury selected from the group consisting of ischemia, spinal cord injury, cranial injury, physical trauma to the head or spinal cord; a brain concussion; ischemic stroke caused by thrombosis or embolism; cerebral hemorrhage, general circulatory failure, circulatory disruption caused by cardiac arrest, hemodynamic shock caused by loss of blood due to injury or hemorrhage elsewhere in the body; vasculatory damage caused by vascular disease, bacterial infection, viral infection, fungal infection, cerebral or spinal tumors, glial cell swelling, hypoxic injury to the brain caused by respiratory disruption, and post-operative brain injury or stress. The method of claim 45, wherein said mammal is a human. The method of claim 45, wherein said mammal is a non-human mammal. The method of claim 45, wherein said mammal is a human afflicted with or following a stroke. The method of claim 45, wherein said mammal is a human afflicted with a spinal cord injury. The method of claim 45 or 14 , wherein said method comprises administering to said mammal a MMP-9 inhibitor and a prophylactically or therapeutically effective amount of one or more anti-inflammatory agents during or after said trauma. The method of claim 45 or 24 , wherein said method comprises administering to said mammal a matrix metalloproteinase inhibitor MMPI and a prophylactically or therapeutically effective amount of one or more anti-convulsive agents during or after said trauma. A kit for reducing neurological damage following trauma to nervous tissue in a mammal, said kit comprising: The kit of claim 68, wherein said matrix metalloproteinase inhibitor MMPI is selected from the group consisting of a 4-biarylbutyric acid derivative, a 5-biarylpentanoic acid derivative, Fenbufen, peptide MMPIs, a hydroxamic acid, a tricyclic butyric acid derivative, a biphenyl butyric acid derivative, a heterocyclic substituted phenyl butyric acid derivative, a sulfonamide derivative, a succinamide MMP inhibitor, a sulfonated amino acid derivatives, and a neutralizing anti-MMP antibody. The kit of claim 68, wherein said MMPI is provided in a unit dosage form at a concentration sufficient to inhibit secondary neurological damage following said trauma. The kit of claim 68, wherein said trauma is selected from the group consisting of ischemia, spinal cord injury, cranial injury, physical trauma to the head or spinal cord; a brain concussion; ischemic stroke caused by thrombosis or embolism; cerebral hemorrhage, general circulatory failure, circulatory disruption caused by cardiac arrest, hemodynarmic shock caused by loss of blood due to injury or hemorrhage elsewhere in the

body; vasculatory damage caused by vascular disease, bacterial infection, viral infection, fungal infection, cerebral or spinal tumors, glial cell swelling, hypoxic injury to the brain caused by respiratory disruption, and post-operative brain injury or stress. The kit of claim 68, wherein said trauma is spinal cord injury. The kit of claim 68, wherein said mammal is a human. The kit of claim 68, wherein said mammal is a non-human mammal. The kit of claim 68, wherein said mammal is a human afflicted with or following a stroke. The kit of claim 68, wherein said mammal is a human afflicted with a spinal cord injury. In a mammal diagnosed as having or as at risk from secondary neurological damage, an exogenously applied inhibitor of a matrix metalloproteinase activity or expression. The mammal of claim 79, wherein said mammal is not diagnosed as having a cancer. The mammal of claim 79, wherein said inhibitor is an inhibitor of MMP-9 expression or activity. The Government of the United States of America may have certain rights in this invention. Motor vehicle accidents are the leading cause of spinal cord injury, followed by acts of violence, falls, and sports. The majority of injuries occur at the mid-cervical and upper thoracic regions of the spinal cord and lead to extremely debilitating conditions. Such injuries are incomplete. However, such patients can still recover substantial function as a result of the axons that are spared at the injury site. The central part of the spinal cord, i. Generally a rim of white matter containing myelinated axons is preserved. Following the initial injury, a series of degenerative processes which promote tissue damage beyond the original site of injury are initiated. This is referred to as secondary injury. Methylprednisolone is a potent free radical scavenger which may also serve to reduce inflammation of the central nervous system. Methylprednisolone is administered to the patient in high doses e. Unfortunately, prolonged administration of glucocorticoids has adverse systemic effects e. Methods of use of matrix metalloproteinase inhibitors for such applications are provided. The method involves inhibiting activity or expression of a matrix metalloproteinase e. MMP-9 in said mammal before, during, or after said trauma. The method can comprise administering to the mammal e. In certain embodiments, teh matrix metalloproteinase inhibitor MMPI includes one or more of the following: In certain embodiments, the MMPI s are provided in unit dosage form s at a concentration sufficient to inhibit neurological damage following trauma to nervous tissue in the mammal. Various neurological traumas include, but are not limited to ischemia, spinal cord injury, cranial injury, physical trauma to the head or spinal cord; a brain concussion; ischemic stroke caused by thrombosis or embolism; cerebral hemorrhage, general circulatory failure, circulatory disruption caused by cardiac arrest, hemodynamic shock caused by loss of blood due to injury or hemorrhage elsewhere in the body; vasculatory damage caused by vascular disease, bacterial infection, viral infection, fungal infection, cerebral or spinal tumors, glial cell swelling, hypoxic injury to the brain caused by respiratory disruption, and post-operative brain injury or stress. In certain embodiments, the trauma comprises a brain injury. In certain embodiments, the agent is not a glucocorticoid. In certain embodiments, the agent is not methylprednisolone. The method involves comprising administering to a mammal in need thereof an inhibitor of matrix metalloporteinsase expression or activity in an amount sufficient to reduce abnormal vascular permeability associate with or following the spinal cord injury. In certain embodiments, the method comprises administering one or more matrix metalloproteinase inhibitor s MMPI s e. The MMPI can be provided in a unit dosage form, e. The method involves comprising administering to a mammal in need thereof an inhibitor of a matrix metalloproteinase expression or activity in an amount sufficient to improve recovery of neurological function following said injury. In certain embodiments, the injury comprises a spinal cord injury. In certain embodiments, the injury comprises a brain injury. In certain embodiments, the injury comprises a motor nerve injury. In certain embodiments, the injury comprises a sensory nerve injury. In certain embodiments, the MMPI s are provided in a unit dosage form at a concentration sufficient to promote recovery of locomotor function following spinal cord injury. MMP-9 expression or activity and a prophylactically or therapeutically effective amount of one or more anti-inflammatory agents during or after the trauma. In certain embodiments, the anti-inflammatory agent is a non-steroidal anti-inflammatory drug e. In various embodiments, the method can comprise administering to the mammal an inhibitor of MMP e. MMP-9 expression or activity and a prophylactically or therapeutically effective amount of one or more

anti-convulsive agents e. The kit can include an inhibitor of matrix metalloproteinase expression or activity e. In certain embodiments, the kit comprises one or more matrix metalloproteinase inhibitor s MMPI s is selected from the group consisting of a 4-biarylbutyric acid derivative, a 5-biarylpentanoic acid derivative, Fenbufen, peptide MMPIs, a hydroxamic acid, a tricyclic butyric acid derivative, a biphenyl butyric acid derivative, a heterocyclic substituted phenyl butyric acid derivative, a sulfonamide derivative, a succinamide MMP inhibitor, a sulfonated amino acid derivatives, and a neutralizing anti-MMP antibody. The MMPI s can be provided in a unit dosage form at a concentration sufficient to inhibit secondary neurological damage following said trauma. In certain embodiments, the trauma is a spinal cord injury. The inhibitor can be a specific inhibitor of MMP The mammal can be a human e. The mammal is preferably a mammal not diagnosed as having a cancer.

Chapter 3 : Proteinases in the joint: clinical relevance of proteinases in joint destruction

This generation comprises of BAY, prinomastat (AG), BMS and CGSA. The latter agent was aborted as a result of limited efficacy and musculoskeletal side effects in phase I clinical trials [64].

Find articles by R. Bhanushali Find articles by U. This article has been cited by other articles in PMC. Abstract Recent advances in cancer research highlighted the importance of target-specific drug discovery. In view of these advances, the most important mechanism in tumour growth is its ability to stimulate the formation of blood capillaries around itself called tumour-driven angiogenesis. Hence targeting the angiogenesis, inhibits the growth of blood vessels around it and responsible for death of the tumour due to starvation and accumulation of toxic waste. The therapy, thus, indirectly cytotoxic to the tumour cells by targeting newly developing blood vessels. In this review, we summarised the various antiangiogenic agents with their clinical uses and current status. Angiogenesis, cancer, inhibitors of angiogenesis, small molecules Angiogenesis is the phenomenon of formation of new blood capillaries from existing small blood vessels. It usually accounts for normal physiological and pathological changes involved in normal functioning of body, like development of endometrium during menstrual cycle or during wound healing. A tumour consists of a group of cancerous cell, which are bodies own cells but have lost their ability to divide in controlled fashion. For their growth they require oxygen and nutrients, this demand can be fulfilled by the angiogenesis. Hence, it was hypothesised that angiogenesis is a factor enabling malignant tumour growth in cancer. These growth factors penetrate into surrounding tissue and stimulate the endothelial cells of the parent blood vessels to release proteases. This enzyme responsible for digestion of basement membrane present on the same cells and allows movement of these endothelial cells from their original place and allows the cells to migrate in the direction of secretion of growth factor to form a sprout. This sprout then forms a loop followed by formation of full-fledged vessel after maturation. In this way a nonvascular tumour gets converted in to highly vascularised tumour. Effects of growth factors: As shown in fig. When they encounter endothelial cells, they bind with specific receptors know as receptor tyrosine kinase RTK present on the endothelial cells. This binding causes the receptor to undergo autophosphorylation, which stimulates Mitogen-activated protein kinases MAPK pathway. This pathway causes the secretion of proteases, like matrix metalloproteinases MMPs. This group of enzymes is responsible for the degradation of the basement membrane present on the endothelial cells of blood vessel and making them to migrate towards the stimulus.

Chapter 4 : Recent advances in MMP inhibitor design - [PDF Document]

These include marimastat, BAY- , CGSA, prinomastat (AG), BMS and metastat (COL-3). These drugs are all in different stages of clinical development, ranging from phase I to III.

The combinations of the invention also advantageously act as modulators of inflammation mediators. The co-existence of abnormalities of MMP enzymes and inflammation in many diseases make these characteristics advantageous. Compounds for treatment of heart failure Field of the Invention The present invention relates to a compound comprising a tetracycline, and an associated molecule that is capable of releasing nitric oxide NO. Also disclosed are methods for the preparation of such compounds, and their use in treating or preventing heart failure, optionally heart failure caused by or associated with diastolic dysfunction. Background to the Invention The prevalence of heart failure HF is increasing in the developed world and the cost of providing medical care for an expanding HF population imposes an increasingly heavy burden on healthcare systems throughout the world. Most commonly, HF is associated with impaired left ventricular LV systolic function. Heart failure HF with preserved ejection fraction HFpEF is predominantly caused by hypertension, is often preceded by asymptomatic left ventricular diastolic dysfunction ALVDD and has few defined therapies. The predominant aetiological cause of DHF is myocardial fibrosis as a result of long standing hypertension and metabolic abnormalities associated with diabetes and obesity. The rising prevalence of metabolic disease due to the obesity and diabetic epidemics means that DHF is a major public health problem. In many of these patients, diastolic dysfunction caused by hypertensive heart disease HHD is implicated as a major contributor, if not a primary cause. There are no proven, life-saving therapies for treating DHF. Many of the well-established drug therapies for systolic heart failure have been directed at DHF without success. The diagnosis of DHF can present a challenge in routine clinical practice. The major limitation in the diagnosis of DHF is the identification of diastolic dysfunction DD , which at present is predominantly reliant on Doppler echocardiographic studies. Echocardiography has been used for many years to provide structural correlates to the clinical picture of HF. It can also measure multiple clinically important parameters of cardiac function, including hemodynamic status and LVEF, volumes and mass. These conditions result in an upward displacement of the diastolic pressure-volume relationship with increased end-diastolic, left atrial and pulmo-capillary wedge pressure leading to symptoms of pulmonary congestion. Data indicate that the underlying pathophysiology in diastolic dysfunction and DHF is related to myocardial interstitial disease. Collagen is a stable protein and its balanced turnover is estimated to be days. Alteration of collagen turnover by various mechanisms can lead to adverse accumulation of collagen in the myocardial interstitium leading to fibrosis, increased tissue stiffness, reduced myocardial compliance and impaired diastolic function. The successful neurohumoral-based approach to pharmacotherapy in HF with systolic dysfunction has not resulted in similarly impressive results in HFpEF, implicating additional pathophysiological signals. Changes in the extracellular matrix ECM , known as myocardial remodeling, are central abnormalities in many patients with HFpEF and are characterized by inflammation, increased ECM turnover and myocardial fibrosis. MMPs in particular have been found to play an important role in both inflammation and fibrosis. MMP-2 and MMP-9 knockout models are associated with reduced aortic elastin degradation and protection from pressure overload hypertrophy, fibrosis and dysfunction. Despite the emerging awareness of the potential role of collagen metabolism in the pathogenesis of diastolic HF there are as yet no effective therapies for this form of HF. Pharmacological modulation of MMPs may present an opportunity. However, all MMP synthetic inhibitors developed to date have either been ineffective or demonstrated dose- and duration-dependent drug-related side-effects, most which were musculoskeletal- related. Despite some promising animal studies of MMP inhibitors showing attenuation of cardiovascular remodeling in chronic pressure-overload models, the approach of direct inhibition of MMP enzymes has proven too toxic or ineffective in the clinic. As well as classic inflammatory diseases such as rheumatoid arthritis, hay fever, periodontitis, inflammation plays an

important role in the development and progression of diabetes and a variety of cardiovascular conditions, most notably coronary atherosclerosis and congestive heart failure. The term "Diabetic cardiomyopathy" was coined 4 decades ago and describes a "silent, stiffening" of the heart tissue which can lead to heart failure. There are no symptoms until heart failure occurs. It is present in half of people with diabetes and is more prevalent than well- recognised "silent pumping problem" which has good treatment available. This silent stiffening of the heart is linked to overweight, diabetes, high blood pressure and there are no specific therapies. Over the past 20 years, basic and human research has shown that enzymes in the heart called matrix metallproteinases or MMPs are involved in the stiffening process. They also affect large and small blood vessels and cause eye and kidney damage in diabetes. Increased urinary excretion of MMP-9 in patients supports a role for MMP-9 dysregulation in diabetic renal dysfunction Thrailkill et al. Aortic and coronary arteries of diabetic patients taken at autopsy had higher expression of MMP-9 compared to non-diabetics and were correlated with HbA1c as well as apoptosis lshibashi et al. Elevated MMP-9 has also been associated with arterial stiffness in patients with diabetes Chung et al. Furthermore, human genetic polymorphisms associated with MMP-9 elevation support a role for this enzyme in the pathophysiology of vascular disease. In age and sex matched controls, patients with type 2 diabetes without and with microangiopathy, T allele frequencies were Similarly, in a cohort of asymptomatic hypertensive patients, the T polymorphism is associated with increased T allele frequency, higher plasma MMP-9 and evidence of increased hypertension and vascular stiffness, measured by pulse wave velocity Zhou et al. Inflammation is also involved in the development and progression of some cancers e. IL-1 beta induces COX-2, which causes brain levels of prostaglandin PG E2 to rise, thus activating the thermoregulatory center for fever production. In the periphery, IL-1 beta activates IL-1 receptors on the endothelium, resulting in expression of adhesion molecules and chemokines, which facilitate the emigration of neutrophils into the tissue spaces. IL-4 is a TH2 type anti-inflammatory and profibrosis cytokine that stimulates and amplifies the inflammatory response by activation of the synthesis of types I and II collagen by fibroblasts and the promotion of the progression of fibrosis. IL-4 stimulates inflammatory responses, activates collagen synthesis, promotes fibrosis progression, and inhibits the production of inflammatory cytokines. Recent studies have shown that pro-inflammatory cytokines play a significant contributory role in the pathogenesis of acute heart failure. The purpose of this study was to determine whether the serum IL-8 concentration in patients with acute myocardial infarction AMI , who were undergoing percutaneous coronary intervention PCI was related to the subsequent presence or absence of heart failure. During their subsequent stay in the coronary care unit, their maximum degree of heart failure was recorded. By multivariante analysis a higher level of IL-8 was a significant predictor of heart failure after PCI. Tetracyclines, commonly known for their broad-spectrum antimicrobial properties, have been characterized as pleiotropic immunomodulatory agents. In human studies, sub-antimicrobial doses of the tetracycline, doxycycline, have exerted potentially beneficial effects on inflammation that could promote plaque stability in an effort to prevent acute coronary syndrome, as doxycycline therapy has been shown to lead to a powerful reduction of aneurysmal wall neutrophil and cytotoxic T-cell count; two cell types considered crucial for the process of aneurysm formation. Attempts have been made to attenuate MMP expression to inhibit aortic abdominal aneurysm formation using doxycycline, thereby reducing the need for surgery. However, in several animal and human studies, the efficacy of MMP inhibition with doxycycline has been questioned. It prompted our group to create analogues of doxycycline that target over-expression of inducible MMP-9 rather than direct enzyme inhibition as a more effective and safer approach. MMP-9 levels in tumor tissue as well as serum, plasma, and urine are significantly elevated in patients with breast cancer. Studies indicate that urinary MMP-9 and ADAM12, in addition to being predictive markers for breast cancer, may also prove useful as noninvasive breast cancer risk assessment tools. Several independent studies have used circulating MMP-9 activity to predict metastatic spread of disease as well as to monitor patient response to primary and adjuvant therapy and to evaluate outcome. MMPs may also be useful in predicting therapeutic efficacy. Plasma MMP-9 levels decrease after the surgical removal of primary breast tumors and a progressive decrease in plasma MMP-9 was observed in

patients who responded well to adjuvant therapy. Importantly, in all patients who suffered a relapse of disease there was a gradual increase of plasma MMP-9 activity 1 to 8 months before the clinical diagnosis of recurrence. Serum and tissue levels of MMP-9 are significantly higher in patients with pancreatic ductal adenocarcinoma than in patients with chronic pancreatitis and healthy controls. Each urinary MMP species was detected at significantly higher rates in urine from patients with cancer as compared with controls. The difference in detection of MMP species in the urine of the two types of cancers studied may serve as a tumor-specific fingerprint that can indicate both the presence of a tumor as well as its location. Increased levels of MMP-9 and MMP-2 in urine correlate with increased expression of these proteases in bladder tumor tissue as well. Urinary MMP-9 levels when combined with telomerase analysis of exfoliated cells from voided urine could also increase the sensitivity of cytology, a commonly used method for bladder cancer detection and monitoring. Enhanced MMP-9 staining in primary tumors was found to be an independent marker of poor prognosis in a study with T3-T4 node-negative patients. Plasma MMP-2 and MMP-9 levels were significantly elevated in patients with colorectal cancer and those with adenomatous polyps, and significant reduction in both were observed after tumor resections, suggesting their potential as markers for therapeutic efficacy. These MMPs may not be prognostic markers for tumor recurrence, however, since plasma proMMP-2 and -9 activities did not correlate with disease relapse after surgery. Tutton and colleagues investigated whether plasma MMP-2 and MMP-9 levels could be used as a surrogate for tumour expression in colorectal cancer patients and they found significant correlations between plasma levels and tumor pre- and post-op. MMP-9 activity in tissue extracts was significantly increased in advanced ovarian cancers International Federation of Gynecology and Obstetrics stage III compared with benign tumors and was found to be an independent prognosticator of poor survival. In another study of invasive epithelial ovarian cancer, high stromal expressions of MMP-9 and were significantly correlated with cancer progression and were independent prognostic markers. Tissue MMPs have also been shown to distinguish different histotypes of ovarian cancer, which is a significant finding given that different histotypes have different prognoses. For example, strong MMP-9 levels in cancer cells were associated with longer survival whereas strong stromal MMP-9 was associated with shorter survival, suggesting a dual role for MMP-9 during ovarian cancer progression. MMP-2, -9, , and expression in tissue or serum have been positively correlated with Gleason score in prostate cancer. Analysis of MMP-2 and -9 levels in radical prostatectomy specimens revealed these two as significant predictors of cancer recurrence. These two enzymes may also be markers of therapeutic efficacy, since both the levels and activities of plasma MMP-2 and -9 decreased significantly in metastatic patients after therapy. In addition, increased urinary MMP-9 activity has been shown to distinguish between prostate and other types of cancer e. MMPs can also be combined with other markers to increase their predictive capability. For example, the mRNA ratio of gelatinases to E-cadherin in biopsy samples independently predicted prostate cancer stage. Both latent and activated forms of MMP-2 and MMP-9 have been detected in the cerebrospinal fluid of patients with brain tumors. Importantly, these studies showed that the upregulation of MMP-2 and -9 in the source tumor tissue was also reflected in CSF as well as in urine of these patients. This proteolytic activity is also required for a cancer cell to invade a nearby blood vessel intravasation and then extravasate at a distant location and invade the distant tissue in order to seed a new metastatic site. MMPs play complex and sometimes conflicting roles in regulating angiogenesis. Studies have also demonstrated that MMPs are involved in the angiogenic switch, one of the earliest stages of tumor growth and progression. It has been shown that MMP-9 can be a regulator of the angiogenic switch in a pancreatic tumor model, further confirming the pro- angiogenic role of MMPs. These findings strongly suggest that MMP activity is critical, not only to the initiation of angiogenesis, but to the maintenance of the growing vascular bed, which in turn supports tumor growth and metastasis. MMP activity can, however, result in the production of negative regulators of angiogenesis as well. ECM degradation products display unique biologic properties that can trigger a variety of cellular signals. MMPs have also been implicated in the epithelial to mesenchymal transition EMT , a hallmark of cancer progression to metastasis. Activation of growth factors and cleavage of

adhesion molecules are some of the proposed mechanisms underlying MMP-induced EMT. Recent studies point to an emerging role for MMPs in modulating aspects of immunity and inflammation during tumorigenesis. A variety of cytokines, cytokine receptors, and chemokines have been found to undergo MMP-mediated cleavage. In breast cancer, MMP-9 expression is upregulated in tumor-associated stromal cells including neutrophils, macrophages, and lymphocytes and may play a role in tumor-associated inflammation. Several members of the MMP and ADAM family can regulate cellular proliferation by modulating the bioavailability of growth factors or cell-surface receptors. There are known clinical benefits of MMP inhibition in cancer management for example Neovastat AstraZeneca is currently under evaluation in phase II renal cell carcinoma. Furthermore, there may be problems with potent, broad spectrum, MMP inhibition. For example, there are some data suggesting that tumour progression is inversely proportional to MMP Recent developments in anti-cancer agents targeting the matrix metalloproteinases have been reviewed Li, et al.

DOWNLOAD PDF X.33. SELECTIVE MMP INHIBITORS BMS 275291, BAY12-9566, MARIMASTAT, PRINOMASTAT.

Chapter 5 : USA1 - Solid compositions - Google Patents

Prinomastat, a more selective nonpeptidomimetic MMPI, topenia in the BAY arm (P.A. Cyrus, personal based MMPIs such as marimastat, BMS causes.

Multiple tyrosine kinase inhibitors. Conclusion Angiogenesis is an important and necessary phenomenon in tissue growth or in wound healing. However, cancerous cells stimulate the formation of vasculature around itself called as tumour-driven angiogenesis for the purpose of its survival and growth. This tumour-driven angiogenesis is stimulated by the abnormal activation of RTK by interaction of growth factors with the tyrosine kinase receptor. Inhibitors of angiogenesis thus, help in blocking progression, growth and development of the tumour and can be a class of anticancer agents. The antiangiogenic agents have advantages over conventional anticancer therapy like, the therapy does not directly targeting the tumour but inhibits the development of blood vessels and thus, indirectly cytotoxic, development of multikinase inhibitors can result in better antiangiogenic agents. Better results have been observed when used in combination with other anticancer agents. Furthermore, these agents are not cytotoxic to normal somatic cells. However, they have also suffered from few disadvantages which includes the inhibition of the initial phase of tumour growth, interference with the wound healing and menstrual cycle, involves huge research cost and the therapy cost is high. Rather than designing the selective inhibitors of RTK, multiple TKIs can be better candidate for antiangiogenic drug discovery. As the possibility of developing resistance due to selective inhibitors will be less and if developed antiangiogenic effect will be due to the inhibition of other RTKs as well. N Engl J Med ; What is the evidence that tumours are angiogenesis dependent? J Natl Cancer Inst ; Regulators and clinical applications. Antiangiogenic therapeutic drugs for treatment of human cancer. J Cancer Mol ;4: Ferrara N, Kerbel RS. Angiogenesis as a therapeutic target. Development trends for monoclonal antibody cancer therapeutics. Nat Rev Drug Discov ;6: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. Bevacizumab, a humanized antiangiogenic monoclonal antibody for the treatment of colorectal cancer. J Clin Pharm Ther ; Sandler A, Herbst R. Blocking the epidermal growth factor and vascular endothelial growth factor pathways. Clin Cancer Res ; Cetuximab for the treatment of colorectal cancer. FDA drug approval summary: Messersmith WA, Hidalgo M. Panitumumab, a monoclonal anti epidermal growth factor receptor antibody in colorectal cancer: Another one or the one? Current developments and future perspectives. Eur J Biochem ; Results of single and repeat dose studies of the oral matrix metalloproteinase inhibitor marimastat in healthy male volunteers. Br J Clin Pharmacol ; Hidalgo M, Eckhardt SG. Development of matrix metalloproteinase inhibitors in cancer therapy. Broad antitumour and antiangiogenic activities of AG, a potent and selective MMP inhibitor undergoing advanced oncology clinical trials. Ann N Y Acad Sci ; Marked antiangiogenic and antitumour efficacy of AG in chemoresistant human non-small cell lung cancer tumours: Single agent and combination chemotherapy studies. Clin Cancer Res ;5: Inhibition of tumour promoter activity toward mouse fibroblasts and their in vitro transformation by tissue inhibitor of metalloproteinases-1 TIMP Host TIMP-1 overexpression confers resistance to experimental brain metastasis of a fibrosarcoma cell line. Tetracyclines inhibit connective tissue breakdown by multiple non-antimicrobial mechanisms. Adv Dent Res ; Matrix metalloproteinases and their inhibition in periodontal treatment. Curr Opin Periodontol ;3: Tetracyclines inhibit tissue collagenase activity. A new mechanism in the treatment of periodontal disease. J Periodontal Res ; Proc Am Soc Clin Oncol ; The tetracycline analogs minocycline and doxycycline inhibit angiogenesis in vitro by a non-metalloproteinase-dependent mechanism. Cancer Chemother Pharmacol ; Marimastat in recurrent colorectal cancer: Exploratory evaluation of biological activity by measurement of carcinoembryonic antigen. Br J Cancer ; Phase III study of matrix metalloproteinase inhibitor prinomastat in non-small-cell lung cancer. J Clin Oncol ; A randomized phase II trial of the matrix metalloproteinase inhibitor BMS in hormone-refractory prostate cancer patients with bone metastases. Invest New Drugs ; An orally active, selective epidermal growth factor receptor tyrosine kinase

inhibitor targeted to the treatment of cancer. Bioorg Med Chem Lett ; Gefitinib ZD Iressa tablets. Design and structure-activity relationship of a new class of potent VEGF receptor tyrosine kinase inhibitors. J Med Chem ; New anilinophthalazines as potent and orally well absorbed inhibitors of the VEGF receptor tyrosine kinases useful as antagonists of tumour-driven angiogenesis. Efficacy and toxicity of the angiogenesis inhibitor SU as a single agent in patients with advanced renal cell carcinoma, melanoma, and soft tissue sarcoma. Clin Cancer Res ;9: Sunitinib in patients with metastatic renal cell carcinoma. Preclinical activity of ABT, a multitargeted receptor tyrosine kinase inhibitor. Mol Cancer Ther ;5: AMG , an oral, multikinase inhibitor that selectively targets vascular endothelial growth factor, platelet-derived growth factor, and kit receptors, potently inhibits angiogenesis and induces regression in tumour xenografts. Current status and future directions. Lessons from phase III trials with bevacizumab and vatalanib in the treatment of advanced colorectal cancer. Sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumours and advanced renal cell carcinoma. Sorafenib for the treatment of unresectable hepatocellular carcinoma. About the Journal The Indian Journal of Pharmacy was started in as "a quarterly journal devoted to the Science and practice of Pharmacy in all its branches". Schroff, Head of the Department of Pharmaceutics. Benaras Hindu University, Benaras.

DOWNLOAD PDF X.33. SELECTIVE MMP INHIBITORS BMS 275291, BAY12-9566, MARIMASTAT, PRINOMASTAT.

Chapter 6 : WOA1 - Compounds for treatment of heart failure - Google Patents

The expression of matrix metalloproteinases (MMPs) is often associated with invasiveness or grade of tumours. Increased blood levels of MMP proteins, including MMP-1, MMP-2, MMP-3 and MMP-9 have been detected in various types of cancers. With the exception of one study, MMPs in serum and plasma have.

Download as PowerPoint Slide Figure 3. An estimate of overall survival in patients with NSCLC treated with bexarotene in combination with cisplatin and vinorelbine. Reprinted with permission from the American Society of Clinical Oncology. J Clin Oncol ; The safety of bexarotene in combination with carboplatin and paclitaxel has also been investigated in previously untreated patients with advanced stage IIIB with malignant effusion or stage IV NSCLC [71]. Because hypertriglyceridemia was expected, patients also received antilipid therapy before or on the same day that bexarotene treatment began. An additional 24 patients have been treated in this multicenter study, and the data are currently being analyzed. A total of 52 patients who had demonstrated stable or responsive disease after prior chemotherapy were eligible for the trial. The median TTP increased from 8 weeks for patients treated with placebo to However, this trial was prematurely terminated because of slow accrual and, therefore, was insufficiently powered to detect statistical differences among the treatment groups. Nevertheless, these results are suggestive of a benefit for bexarotene over placebo in maintenance therapy. Dose-dependent dry skin, headache, and asthenia were the most common bexarotene-related toxicities. However, these were mild to moderate and were manageable. All patients treated with bexarotene also receive antilipid therapy concomitantly or on the same day of bexarotene therapy. Similar to the other phase III trial, patients receiving bexarotene are initiating antilipid therapy before or on the study drug start date. Both studies are ongoing as the primary efficacy parameter is survival. Management of Treatment-Related Adverse Events The use of retinoids that bind to the RARs is associated with significant and often dose-limiting skin toxicity dry, peeling, or flaking skin , mucocutaneous toxicity eye dryness, conjunctivitis , hypercalcemia, and headache [39 , 42]. These toxicities have dramatically slowed the clinical application of this class of agents [73]. In contrast, rexinoids are not associated with hypercalcemia and are associated with only mild to moderate skin toxicity. Another adverse event associated with both retinoid and rexinoid therapy is hyperlipidemia with elevations in both triglycerides and cholesterol. However, these two classes of agents appear to affect lipoprotein homeostasis in different ways. In an analysis of patients treated with ATRA, 9-cis-RA, and bexarotene in phase I or II clinical studies, triglyceride levels were elevated in patients who received higher doses of 9-cis-RA [74 , 75]. Cholesterol elevations in these patients were associated with significantly higher calculated levels of low-density lipoprotein cholesterol. In contrast, patients treated with bexarotene experienced increases in total cholesterol and low-density lipoprotein cholesterol without significant changes in high-density lipoprotein cholesterol and apolipoprotein A1. These data suggest that treatment with the selective RXR ligand bexarotene causes alterations primarily in cholesterol metabolism, whereas treatment with the pan retinoid receptor ligand 9-cis-RA causes elevations in plasma cholesterol and triglyceride levels that are associated with significant decreases in high-density lipoproteins. These findings suggest that changes in triglyceride metabolism and less favorable alterations in cholesterol metabolism are mediated by the RARs. Since hyperlipidemia and hypothyroidism are anticipated adverse events, they can be managed proactively with proper planning, oral medications, and careful patient monitoring. Bexarotene should be used with caution in patients predisposed to pancreatitis and liver dysfunction. Baseline fasting triglyceride and cholesterol levels should be optimized before starting bexarotene therapy. Atorvastatin or fenofibrate are the most extensively used antilipid agents; gemfibrozil is not recommended because of its interaction with bexarotene [76]. Lipid levels and liver function should be monitored regularly.

Chapter 7 : Targeting Angiogenesis for Treatment of Human Cancer

Tanomastat (BAY), prinomastat (AG), rebimastat (BMS), and CGSA (MMI) are included in this generation. Tanomastat (BAY) is structurally distinct from other MMPIs and is a butanoic acid analog.

Hence targeting the angiogenesis, inhibits the growth of blood vessels around it and responsible for death of the tumour due to starvation and accumulation of toxic waste. The therapy, thus, indirectly cytotoxic to the tumour cells by targeting newly developing blood vessels. In this review, we summarised the various antiangiogenic agents with their clinical uses and current status. In blood capillaries from existing small blood vessels. Hence, it was hypothesised that angiogenesis is a factor enabling malignant tumour Effects of growth factors: As shown in fig. When they encounter In order to get oxygen and nutrients, tumour endothelial cells, they bind with specific receptors cells secrete growth factors. This binding causes the receptor endothelial cells of the parent blood vessels to release proteases. This enzyme responsible for digestion of basement membrane present on the same cells and allows movement of these endothelial cells from their original place and allows the cells to migrate in the direction of secretion of growth factor to form a sprout. This group of Bevacizumab Inhibition Avastin Approved by US FDA enzymes is responsible for the degradation of the of VEGF for the treatment of basement membrane present on the endothelial cells metastatic colorectal cancer in combination of blood vessel and making them to migrate towards with 5 Fluorouracil[8] and the stimulus[3]. Antiangiogenic agents induce their effect by Panitumumab Inhibition Vectibix Approved by US FDA for the inhibiting the enzymes responsible for proliferation, of EGFR treatment of EGFR positive refractory metastatic or sequestering the growth factor or inhibiting the colorectal cancer[11,12] receptor responsible for binding with growth factors. These agents are specific for carcinoma[29] particular protein, e. Inhibitors of MMPIs are categorised as peptidomimetic inhibitors, Matrix metalloproteinases inhibitors: Compounds of peptidomimetic inhibitors first They play an important role in normal turnover generation MMPIs class are hydroxamic acid and remodelling of extracellular matrix. It has been derivatives designed to mimic the structure of reported that, MMPs are over expressed in a variety collagen at the site where the MMPs are thought to of malignant tumour types and this is associated bind for the cleavage. Compounds like marimastat and with tumour growth and metastasis potential. Inhibition First generation MMPIs are nonselective and also of MMPs prevents metastasis and progression of exhibits poor oral bioavailability due to peptide nature. These agents are There are many CMT from has been suspended [16]. Table 2 describes of tumour growth and angiogenesis in xenograft the details of the MMPIs inhibitors. In vitro, BMS exhibits Small molecule tyrosine kinase inhibitors: Depending upon the type of enzyme targeted by the agents they are divided into following Modified tetracycline derivatives not only inhibit the categories: Peptidomimetic matrix metalloproteinases inhibitors. Nonpeptidomimetic matrix metalloproteinases inhibitors. Thus, by varying the substitution molecule 4-anilinoquinazoline. Structure-activity on suitable position, most active molecule was relationship SAR studies proved that quinazoline reported as 1- 4-chlorophenyl 4-pyridylmethyl moiety is absolutely essential for activity. Sixth phthalazine and known as PTK [34]. Second, seventh and eighth position 6 like SU was one of the initial, and probably must remain unsubstituted. The anilinic nitrogen the most extensively studied kinase insert domain must be secondary for optimal activity. Anilinic NH is renal carcinoma and required for good inhibitory activity. Endothelial growth factor receptor tyrosine kinase inhibitors. Vascular endothelial growth factor receptor tyrosine kinase inhibitors. Multiple tyrosine kinase inhibitors. The antiangiogenic agents have advantages for human endothelial cells [38]. However, they have also suffered from few disadvantages which includes the Angiogenesis is an important and necessary inhibition of the initial phase of tumour growth, phenomenon in tissue growth or in wound healing. Rather than designing the selective driven angiogenesis for the purpose of its survival inhibitors of RTK, multiple TKIs can be better and growth. This tumour-driven angiogenesis is candidate for antiangiogenic drug discovery. As stimulated by the abnormal activation of RTK by the possibility of developing resistance due to interaction of growth factors

with the tyrosine selective inhibitors will be less and if developed kinase receptor. Inhibitors of angiogenesis thus, help antiangiogenic effect will be due to the inhibition of in blocking progression, growth and development other RTKs as well. Matrix metalloproteinases and their inhibition in periodontal treatment. Curr Opin Periodontol ;3: Tetracyclines inhibit tissue collagenase activity. What is the evidence that tumours are angiogenesis mechanism in the treatment of periodontal disease. J Natl Cancer Inst ; Regulators and clinical Proc Am Soc Clin Oncol 5. Angiogenesis as a therapeutic target. The tetracycline analogs antibody cancer therapeutics. Nat Rev Drug Discov ;6: Bevacizumab plus irinotecan, fluorouracil, and Pharmacol ; Marimastat in recurrent colorectal cancer: Bevacizumab, a humanized antiangiogenic Exploratory evaluation of biological activity by measurement of monoclonal antibody for the treatment of colorectal cancer. Br J Cancer ; Clin Cancer Res ; FDA prostate cancer patients with bone metastases. Clin Cancer Res drug approval summary: Invest New Drugs ; Current developments and future perspectives. Eur J Biochem ; Results of single and repeat dose studies of the drug approval summary: Oncologist oral matrix metalloproteinase inhibitor marimastat in healthy male ; Br J Clin Pharmacol ; Broad antitumour and antiangiogenic activities of AG, a potent and selective MMP inhibitor undergoing advanced New anilinophthalazines as potent and orally well absorbed inhibitors oncology clinical trials. Ann N Y Acad Sci ; Marked antiangiogenic and antitumour efficacy of Efficacy and toxicity of the angiogenesis inhibitor SU as a Single agent and combination chemotherapy studies. Clin Cancer Res single agent in patients with advanced renal cell carcinoma, melanoma, ;5: Clin Cancer Res ;9: Sunitinib in patients with metastatic renal cell carcinoma. Mol Cancer Ther ;5: Adv Dent Res ; AMG , an oral, multikinase inhibitor that selectively targets Sorafenib for the treatment of unresectable kit receptors, potently inhibits angiogenesis and induces regression in hepatocellular carcinoma. Accepted 30 December Sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumours and Received 17 March advanced renal cell carcinoma. Indian J Pharm Sci ;75 1:

DOWNLOAD PDF X.33. SELECTIVE MMP INHIBITORS BMS 275291, BAY12-9566, MARIMASTAT, PRINOMASTAT.

Chapter 8 : OMICS International eBooks | OMICS International Publishing

Marimastat belongs to a second generation of MMP inhibitors. In contrast to batimastat, marimastat is orally available. Both of these agents are currently in Phase I/II trials in US, Europe and.

This inhibitor is yet to be found. The reasons for this failure include shortcom- ings in the chemistry of these compounds including broad MMP sub-type selectivity, metabolic lability, and toxicity as well as the emerging, and arguably extraordinary, complex- ity of MMP cell and cancer biology. Together these suggest that the successful anticancer inhibitor must possess MMP selectivity against the MMP subtype whose involvement is critical, yet highly temporally with respect to metastatic pro- gression and mechanistically with respect to matrix degra- dation regulated. This review summarizes the progression of chemical structure and mechanistic thinking toward these objectives, with emphasis on the disappointment, the perse- verance, and the resilient optimism that such an inhibitor is there to be discovered. Introduction The challenge of bringing a matrix metalloproteinase in- hibitor to the point of clinical value was exquisitely summa- rized by Breuer et al. While recent chemistry efforts have sustained measurable progress toward the former objective, progress toward the understanding of the latter has served primarily to reveal that the processes determining MMP enzymatic activity are characterized by incredible complexity and interdependency. Nonetheless, these same complexities have affirmed the role of the MMP enzymes as contributors to the pathophysiology of a host of diseases, and have justified the perseverance of the medicinal chemist with respect to MMP inhibitor design. MMP inhibitor design over the past decade is not simply that of evolutionary structural progression toward sub-type selective inhibitors, but arguably as well revolutionary im- provements in the design of structures that target the zinc catalytic center of these enzymes. The focus of this review is the recent structural progression of MMP inhibitor de- sign, as evidenced by the inhibitors themselves. A critical measure of the importance of this area is the review litera- ture. Within the past year every area of MMP research has been critically evaluated by review, including MMP inhibi- tion in cancer chemotherapy [1, 3â€”8] and advances in in- hibitor design [9â€”18]. This review is organized by chemical structure. We use the customary division between hydroxam- ate peptidomimetic and non-hydroxamate peptidomimetic and non-peptidomimetic based MMP inhibitors, with an emphasis on the trends as demonstrated by the inhibitor structure in recent medicinal chemistry design. It will be evident that not only is there significant progress toward the transition from broadly inhibitory hydroxamate to subtype- selective hydroxamate and non-hydroxamate inhibitor de- sign, but that this transition is occurring with an optimism Springer Cancer Metastasis Rev While the primary focus is anti- cancer MMP inhibitors, the substantial promise that MMP inhibitors offer in other disease states [19â€”28] will be noted in connection with the subtype focus of new MMP inhibitors. The sub-type selective inhibitor designed today with for ex- ample an osteoarthritis therapeutic endpoint, may prove its value in cancer tomorrow. The inhibitors presented in this review are identified in boldface by either their compound code where the code is the primary identifier in the litera- ture or by their 9-digit Chemical Abstracts Registry number where the compound is exploratory, and the code numbers are either unavailable or not yet assigned. Our use of the CAS Registry Number to identify compounds is due to the uniqueness of this number to compound structure, and to en- able facile literature searching of the compound beyond the timeframe of this review. The structure schemes also sum- marize the MMP sub-type selectivity of the new inhibitors, insofar as the literature data allow. No inference as to the selectivity of an inhibitor should be made where these data are absent. Pioneering hydroxamate structures Notwithstanding the perspicacity, effort, and expense of their creation, the many early hydroxamate-based MMP inhibitor structures Fig. This class of structuresâ€”whose structural interrelationship as collagen-based peptidomimetic MMP inhibitors is evident by inspectionâ€”displays excellent anticancer activity in tumor cell and animal models. The clinical performances of these compounds, while not those of failure, are frequently de- scribed and correctly so as disappointing. The first of these relate to the compounds themselves. All of the structures are based on a hydroxamate

zinc-binding group, subsequently determined to be metabolically labile. As a class, these are broad-spectrum inhibitors of many MMP sub-types the profile provided for Ilomastat in Fig. Only upon clinical patient exposure did it become evident that these compounds as a class induced dose-limiting muscular and skeletal pain in a substantial number of patients. With the unraveling of the complexity of MMP physiologyâ€"Fingleton [8] enumerates metastasis, tumor growth, angiogenesis, apoptosis, and im- mune modulation as the five fundamental processes thus far identifiedâ€"the realization has grown that optimal clinical performance of an MMP must structurally and temporally coincide with intervention at the critical MMP enzymatic event in the particular cancer. The accomplishment of this goal requires a far better grasp of what constitutes appro- priate clinical biomarkers and diagnostics [29â€"35] than was appreciated during the early years of MMP inhibitor creation. Compelling evidence exists that MMP inhibitors may most favorably act earlier, rather than later, in the cancer metastatic process [8, 13]. Last, there is increased appreciation that the Fig. The situation with the earlier generation MMP inhibitors is well exemplified by the recent clinical reports for Marimastat an inhibitor of MMPs-1, -2, -3, -7, -9, and While MST was also an issue in a Phase I com- bination with carboplatin and paclitaxel therapy against advanced non-small cell lung cancer, partial response were seen in 12 of 21 patients and disease stabilization occurred in another 5 patients [40]. In exploratory anti-angiogenesis combination therapy with low molecular mass heparin and captopril in advanced cancer, Marimastat again 10 mg bid, oral was well tolerated and the chemotherapy resulted in partial response 1 of 10 patients or disease stabilization 3 patients [41]. The sense from these and earlier and concurrent clinical studies, as fully summarized by Mannello et al. Notwithstanding the reality that this refrain has been heard innumerable times in cancer chemotherapeutic design, the belief in this hope sus- tains a vibrant effort toward these objectives. Design objectives of new MMP inhibitors The chemical objectives that coincide with this hope comprise several structural classes. New generation pep- tidomimetic hydroxamate structures are still being disclosed. However, three new trends in compound design are seen. The first is the use of non-hydroxamate inhibitors [1]. The hydroxamate is regarded as extremely effective, but un- less the structure is highly optimized, the hydroxamate is prone to metabolic transformation, and moreover may non-productively chelate the metals of other metalloproteins. Alternative, newer generation inhibitors that use different zinc-binding groups within both peptidomimetic and non- peptidomimetic motifs , or are based on new design prin- ciples exemplified by the tetracycline and bisphosphonate derivatives, and the endogenous MMP inhibitors , represent an expanding portion of the MMP inhibitor literature. The second trend is the design of sub-type selective MMP inhibitors in order to achieve improved anticancer therapy, or to specifically address the MMP subtype involved in other MMP-dependent pathophysiology such as MMP in os- teoarthritis. An additional objective, also explicit in sub-type selective inhibitor design, is the elimination of the MTS tox- icity that presents in the clinical evaluation of many MMP inhibitors typically after several weeks of administration at the higher dose levels. The origin of the MTS toxicity is not known. An early hypothesis was a direct relation- ship to non-specific sub-type inhibition, especially inhibi- tion of MMP-1 human fibroblast collagenase, responsible for normal turnover of the extracellular matrix in connec- tive tissue. The difficulty in removing from the in- hibitor structure the basis for this toxicity is exemplified by Solimastat, a broad-spectrum MMP and TACE inhibitor. Pre-clinical study implied that Solimastat had diminished toxicity compared to the structurally-related inhibitor Mari- mastat. Nonetheless, clinical evaluation of Solimastat was terminated prematurely due to the appearance of MTS toxi- city [47]. The third trend is the use of MMP structure as a basis for in- hibitor design [15]. While verification that selective MMP in- hibition will coincide with efficacy and minimal toxicity will remain firmly an experimental determination, the creation of selective inhibitors with the properties that will enable the experiment is already occurring. Indeed, no new MMP in- hibitor is now prepared without the guidance of structure- based design. At this time the number and breadth of MMP structure determined by both X-ray and NMR, and includ- ing both pro-enzyme [48] and numerous inhibitor complexes [10, 14, 15] is substantial. These structures have been used for pharmacophore mapping for QSAR analysis [12, 49], for pharmacophore mapping for virtual

screening [50], for MMP NMR-validation of pharmacophore hypotheses [51, 52], and for the computational determination of the points of binding pocket similarity and difference [53â€”57]. These latter analyses by Balaz et al. Not surprisingly, MMP domain involvement in endogenous substrate recognition and prote- olysis is considerably more complex see Xu et al. The following sections give a synopsis of the new MMP in- hibitor structures. The particular structural features of these inhibitors coincide with particular hypotheses as to MMP selectivity, many of which have yet to receive full experi- mental evaluation. Nonetheless, there exists for all of these inhibitors the decisive opinion that the concurrent refinement of hypothesis, structure, and pharmacological attribute is pro- viding fresh opportunity for MMP intervention in cancer and other diseases. This molecule features oral availability, water solubility, and low molecular mass in a broad-spectrum inhibitor. While the salient features of this molecule have precedent in the structures of Fig. These include examining the struc- ture from left to right a substituted aryl and an acyl hydro- gen bond acceptor here, a sulfonamide that is separated by two atoms from the hydroxamate zinc-binding group. There is also an amino acid sidechain-type substitutent on the carbon alpha to the hydroxamate, and a second sidechain substitution on the sulfonamide nitrogen later shown as un- necessary. The limitations of this prototype metabolic la- bility, clinical appearance of MST [62] are addressed to some degree in the remaining structures of Figs. Cipemastat, which also has this succinate motif, was devel- oped as an MMP-1, -3 and -9 collagenase inhibitor for the treatment of rheumatoid and osteo arthritis. Despite animal efficacy, its clinical trial was terminated prematurely [63]. While it has shown anticancer activity in numerous animal models of human cancer in- cluding implanted lung cancer, melanoma, squamous carci- noma, colon and cervical [64, 65], there are no data as to its clinical performance. This feature, which appeared virtually simultaneously in all of the concurrent MMP SAR efforts, is immediately recog- nizable in the remaining structures of Fig. In MMI two phenyl rings are connected by a tetrazole ring; in ABT- and PD, the two phenyl rings are directly con- nected; and in Prinomastat, an oxygen atom connects the two phenyl rings. PD has efficacy in hypertensive heart failure see [66, 67] and references cited therein. A key structural change contributing to the optimized selec- tivity was the replacement the biphenyl of ABT with a diphenylether as is also present in Prinomastat [68]. Both ABT and ABT have significant anticancer activity in animal models, but are easily human metabolized and in the case of ABT, to an amine metabolite that caused phospholipidosis [69]. Prinomastat showed excellent pre- clinical animal anticancer efficacy, including synergy with paclitaxel and carboplatin, and provided evidence that in- creased MMP-9 gelatinase specificity correlated with MMP inhibitor efficacy [71]. It also has been used to indicate that the relationship between MMP inhibition and metastasis is complex, wherein Prinomastat inhibition of MT1-MMP pro- teolysis of vitronectin promoted metastasis [72] see also [73]. More recently Prinomastat was efficacious in a type I diabetes animal model [74] and was successful as an adjuvant in a model of photodynamic therapy [75]. A Phase I study [76] describes moderate but reversible arthralgia, myalgia, and MST at high doses, beginning 2 months after therapy initiation. Prinomastat in Phase III evaluation evaluated in a gemcitabine and cisplatin drug regimen against non-small cell lung cancer was ineffective [77]. A recurring limitation to these hydroxamates, and Prino- mastat in particular, is drug metabolism including loss of the hydroxamate zinc-binding group by its reduction to the amide, its hydrolysis to the carboxylate, and its conjuga- tion as a glucuronide. The foci of the ensuing generation of hydroxamate structures were suppression of metabolism, minimization of MMP-1 inhibitory activity, and control Springer Cancer Metastasis Rev Testament to the confluence of the chemical strategies toward this objective is provided by the astonishing similarityâ€”with nuanced yet significant differencesâ€”among the four structures of Fig. The first compound of this set, RS, entered into clinical evaluation as an MMP collagenase specific inhibitor for the treatment of osteoarthritis the outcome of this evaluation is not yet disclosed. Its annulated tetrahydropyran, located alpha to the hydroxamate, introduces a steric block that suppresses metabolism while acheiving the desired MMP selectivity. On the basis of a short-term rat fibro- plasias model as a surrogate indicator of clinical MST [79], and a cognate bicyclo tetrahydropyran were ad- vanced to clinical evaluation for osteoarthritis. It has excellent oral efficacy in an animal model of os- teoarthritis equal to or superior to RS

[80, 81]. SC was orally active as an anti-angiogenic mouse bFGF-stimulated corneal neovascularization and as an anticancer synergistic with paclitaxel in a mouse MX-1 carcinoma implant [82]. The pharmacological direction of these MMP inhibitors is evident from the supporting biology that is given. While the structures of Fig. This choice is a consequence of the uneven anticancer clinical performance of the preceding generation of structures, and an increasing focus on diseases that are believed to coincide with excessive activity of a single MMP subtype such as MMP in arthritis. Many of the newer hydroxamate and carboxylate MMP inhibitors confirm this trend. Given the structures of Fig. That both enantiomers bind more tightly than the racemate is, however, a conundrum that Sani et al. Each of the remaining structures presents a new structural advance in MMP inhibitor design, albeit at the cost of increased struc- tural and stereochemical complexity. FR is a broad spectrum MMP inhibitor with efficacy in a collagen-induced arthritis animal model [85]. As noted previously, its abil- ity to also inhibit MMP-1 would previously have been re- garded as a clinical liability. The data of Reiter et al. These models include inhibition of cancer [86â€”90], arthritis [91], restenosis [92], periodontal [93], hypercholesterolemia [94], and inflammatory cytokine colitis [95] activities. Clearly, while building upon the substantial medicinal chemistry knowledge that has accrued for MMP design as is also evident in the synthesis of anthrax lethal factor inhibitors [â€”] , the therapeutic objectives for these inhibitors is not cancer. The carboxylate MMP inhibitors of Fig. This compound has a thiol zinc-binding group, is orally avail- able, and has broad spectrum MMP inhibitor IC50 values:

Chapter 9 : Emerging Role of Rexinoids in Non-Small Cell Lung Cancer: Focus on Bexarotene

Marimastat is a synthetic MMPI with a low molecular weight and an orally bioavailable MMPI that was first used for clinical trials and can inhibit the activity of MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, and MMP