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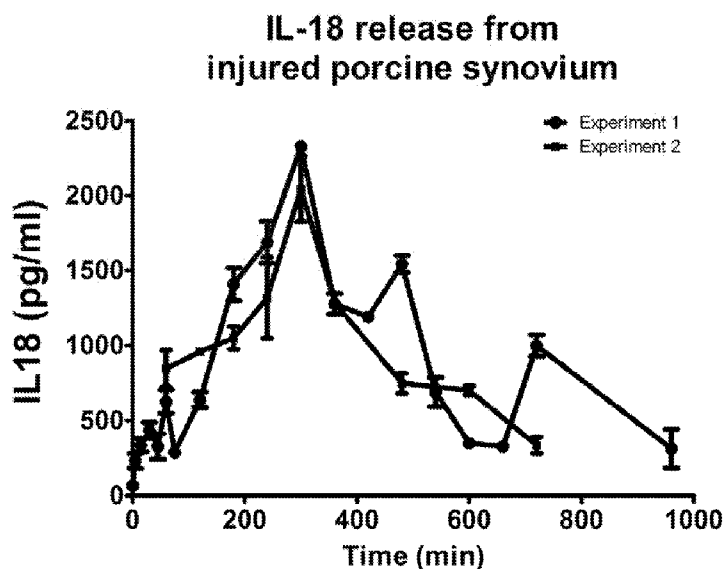
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Figure 4



(57) Abstract: There is provided an interleukin-18 (IL-18) inhibitor for use in the prevention or treatment of injury-induced osteoarthritis in a joint of a subject. Also provided is a method for treating or preventing injury-induced osteoarthritis in a joint of a subject, comprising administering to the subject an effective amount of an interleukin-18 (IL-18) inhibitor. Also provided is an in vitro method for diagnosing or predicting the risk of acute injury osteoarthritis in a joint of a subject, said method comprising (i) determining the amount of IL-18 in a sample from said subject; (ii) comparing the amount of IL-18 in the sample with a reference standard; and (iii) identifying a difference in the amount of IL-18 biomarker in the sample relative to the reference standard; wherein an increase in the amount of IL-18 in the sample compared to the reference standard correlates with the presence of, or an increased risk of, injury-induced osteoarthritis; and a decrease, or no change, in the amount of IL-18 in the sample compared to the reference standard correlates with the absence of, or a lack of increased risk of, injury-induced osteoarthritis.

PREVENTION AND TREATMENT OF OSTEOARTHRITIS

This patent application claims priority to GB 1213968.9 filed on 6 August 2012, which is hereby incorporated by reference in its entirety.

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The present invention relates to therapeutics and corresponding therapies for the treatment of osteoarthritis, in particular injury-induced osteoarthritis. The present invention also relates to *in vitro* and *ex vivo* methods for diagnosing and predicting injury-induced osteoarthritis.

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Osteoarthritis (OA) is a highly prevalent joint disorder for which no current preventative or disease-modifying treatment exists. The development of OA leads to pain and dysfunction in the affected joint, with an associated reduction in joint mobility and quality of life. Consequently, OA is a leading cause of pain and disability throughout the world.

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OA can affect any synovial joint (a joint having a cavity), such as those of the knees, hips or hands. Central to disease progression is the breakdown of the articular cartilage that protects the joint and allows smooth articulation. However, the development of OA is not simply a purely mechanical process but rather a metabolically active one that can involve changes to all of the tissues of an affected joint (such as cartilage, synovium, synovial fluid, bone, muscle and ligaments).

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Synovial joints are highly complex structures with multiple components, each having different functions. An example of a synovial joint which may commonly be affected by OA is the human knee joint, which joins the femur in the thigh to the tibia in the lower leg. Within the knee joint, the ends of the femur and tibia are coated with articular cartilage, which provides protection and allows smooth movement of the joint. The joint is surrounded by an envelope known as the joint capsule (or articular capsule), which is covered by a thin layer of synovial membrane and contains synovial fluid that lubricates and cushions the joint. The knee joint is stabilised by a number of ligaments and the menisci. Ligaments located within the knee joint capsule include the anterior and posterior cruciate ligaments, which prevent excessive forward

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and backward movement of the femur relative to the tibia. Ligaments external to the joint capsule include the lateral and medial collateral ligaments.

OA is often regarded as a progressive disease of ageing, and occurs much more frequently in individuals over the age of 50 than in younger subjects. OA is a separate condition from the inflammatory disease rheumatoid arthritis (RA), and thus the efficacy of a treatment for RA is not in any way predictive of its efficacy for treatment of OA. Osteoarthritis (OA) and Rheumatoid arthritis (RA) are readily distinguishable through a range of clinical, laboratory and radiographic features. Typically patients with RA present with an acute (rapid onset) symmetrical joint disease with evidence of synovial swelling and inflammation. They have evidence of raised inflammatory blood indices and serological markers are positive such as rheumatoid factor and cyclic citrullinated peptide antibodies. X-ray features include bone erosion and peri-articular osteoporosis. Patients with OA typically have asymmetrical joint disease of insidious onset. Pain and stiffness are often present but active synovitis is unusual and when present is less marked than in RA. There is rarely evidence of a systemic inflammatory response. X-ray changes are pathognomonic and include subchondral bone sclerosis, cyst formation, osteophyte formation and bone expansion. Patients with 'burnt out' RA (usually after several decades of disease) may develop secondary OA in the damaged joint.

Despite the prevalence of OA in elderly subjects, the disease can also occur in a joint of a young or middle-aged individual as a consequence of an injury to that joint (such as a sports injury). By way of example, a common injury incurred by individuals participating in sporting activity is damage to or rupture of the anterior cruciate ligament (ACL). Such an injury may occur when the knee receives a high impact or is forced to undergo a sudden, sharp movement. Symptoms may include pain and swelling. It is likely that a combination of the injury and the loss of the joint-stabilising function of the ACL sets in train the processes that lead to loss of cartilage and the development of injury-induced osteoarthritis.

Individuals who have suffered a joint injury have an increased risk of later developing injury-induced osteoarthritis in the injured joint. An individual who has suffered an acute destabilising knee injury has a 50% risk (approximately) of developing injury-

induced osteoarthritis in that knee within 5-10 years of the injury, as compared to the risk in an uninjured individual. This occurs irrespective of the age of the patient although the risk also increases with age.

- 5 Current OA therapeutics and related therapies are focused on the management of symptoms in OA where the disease is already established. Examples include the use of painkillers such as paracetamol, non-steroidal anti-inflammatories (NSAIDs) such as aspirin and ibuprofen, and local injections of corticosteroids.
- 10 However, while these treatments can lead to a reduction in symptoms such as pain and reduced mobility, they are not very effective, and do not prevent the underlying cartilage degradation and disease progression either with age or following acute joint injury.
- 15 There is therefore a need for new therapeutics and associated therapies and methods that can be used to both treat injury-induced osteoarthritis and to prevent or suppress the development of injury-induced osteoarthritis in an at-risk joint. In addition, there is also a related need for new methods of identifying patients at risk of developing injury-induced osteoarthritis in a joint, such that suitable treatment or preventative
- 20 therapies may be initiated.

The present invention solves one or more of the above problems by providing new therapeutics for use in preventing or treating injury-induced osteoarthritis in a subject (such as a human subject), together with corresponding methods for preventing or

25 treating injury-induced osteoarthritis. The present invention also provides *in vitro* or *ex vivo* methods of diagnosing or predicting the risk of injury-induced osteoarthritis.

In one aspect, the invention provides an interleukin-18 (IL-18) inhibitor for use in the prevention or treatment of injury-induced osteoarthritis in a joint of a subject.

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In a related aspect, the invention provides a method of preventing or treating injury-induced osteoarthritis in a joint of a subject comprising administering to the subject an effective amount of an interleukin-18 (IL-18) inhibitor. As used herein, an “effective

amount” is a dosage or amount that is sufficient to achieve the desired biological outcome of the prevention or treatment of acute injury osteoarthritis.

The present inventors have found that inhibition of IL-18 can prevent or treat injury-induced osteoarthritis. Advantageously, inhibition of IL-18 can prevent the breakdown of articular cartilage that underlies OA development and progression. Thus, inhibition of IL-18 can prevent or treat injury-induced osteoarthritis in a joint of a subject who has suffered an injury to that joint.

Without wishing to be bound by any particular theory, the inventors believe that joint damage following injury triggers the release of IL-18 in the joint, which subsequently activates multiple processes that lead to the development of injury-induced osteoarthritis. The inventors have found that levels of IL-18 in the synovial fluid of a joint increase significantly following a joint injury, and genes known to drive OA are regulated in an IL18-dependent manner following surgical destabilisation of the knee joint. Thus, articular cartilage breakdown in the joint subsequent to injury (which would lead to OA) can be suppressed or prevented by inhibition of IL-18, for example by neutralisation of IL-18 or by blocking of IL-18-mediated actions.

Thus, administration of an IL-18 inhibitor to a subject can be used to treat established injury-induced osteoarthritis in a joint, or to prevent injury-induced osteoarthritis from developing. In the present context, administration means that the inhibitor is applied to the subject such that it reaches the joint.

IL-18 is a protein and a member of the cytokine group (intercellular signalling molecules with immunomodulatory roles). IL-18 is a member of the interleukin-1 (IL-1) family of cytokines and is known for its pro-inflammatory actions. Amongst other effects, IL-18 induces inflammatory mediators (such as TNF-alpha), enhances the cytotoxic activities of NK cells and T cells, and augments the differentiation and activation of T-helper-1 cells.

IL-18 as encoded by human cDNA is 193 amino acids in length. IL-18 is produced as a biologically-inactive 24 kDa precursor protein, which is then activated by intracellular enzymic cleavage prior to secretion. Examples of enzymes which are

able to activate IL-18 and stimulate its secretion include caspase-1 (also known as ICE), Fas, and FasL. Activation and secretion of IL-18 can be stimulated by *inter alia* LPS (lipopolysaccharide) acting on TLRs (Toll-like Receptors). A number of different cell types are able to secrete IL-18, including macrophages, keratinocytes, osteoblasts and chondrocytes.

IL-18 exerts its effects by signalling through the transmembrane IL-18 receptor, which comprises alpha and beta subunits. Binding of IL-18 to its receptor may be inhibited *in vivo* by the endogenous IL-18 binding protein.

Signalling through the IL-18 receptor following IL-18 binding may include the following events: binding of the adaptor molecule MyD88 to the intracellular portion of the receptor; recruitment to MyD88 of the kinases IRAK1 and IRAK4, leading to IRAK1 phosphorylation by IRAK4; and translocation of IRAK1 to the cytosol, leading to eventual activation of IL-18-dependent gene expression via pathways including the NF-kappaB and MAPK pathways.

The inventors have found that IL-18-dependent genes upregulated in a joint following acute injury include those encoding the enzymes Adamts5, Adamts1 and Arginase-1 (Arg1). Adamts5 drives cartilage breakdown and the development of injury-induced osteoarthritis.

As described herein, an IL-18 inhibitor can be any chemical compound that reduces (i.e. inhibits) the biological activity of IL-18. The activity of IL-18 is dependent on the interactions of multiple molecules (including ligand, receptor, and signal transduction molecules). Thus, an IL-18 inhibitor can reduce the biological activity of IL-18 by acting directly on the IL-18 protein itself, or by acting on another molecule in the IL-18 signalling pathway. By way of example, an IL-18 inhibitor can reduce IL-18 activity by binding to IL-18 itself (i.e. to the IL-18 protein), by binding to the IL-18 receptor, or by binding to or otherwise interacting with a component of an upstream or downstream IL-18 signalling pathway.

In one embodiment, the IL-18 inhibitor is selected from an anti-IL-18 antibody, an antibody against an IL-18-receptor, an inhibitor of an IL-18 signalling pathway, an IL-18-receptor antagonist, an IL-18 binding protein, and a caspase-1 (ICE) inhibitor.

- 5 In one embodiment, the IL-18 inhibitor is an anti-IL-18 antibody. By way of example, such an antibody may be a monoclonal antibody or a polyclonal antibody.

The term antibody encompasses proteins that, *in vivo*, are produced by the body in response to the presence of an antigen and that bind to that antigen. The term antibody
10 also encompasses antibodies produced *in vitro*, and antigen-binding fragments and engineered variants of antibodies. Thus, the term antibody encompasses polyclonal antibodies, monoclonal antibodies (antibodies that are derived from a single clone and which are thus identical), and antigen-binding antibody fragments (e.g. F(ab')₂ and Fab fragments). Also encompassed are genetically engineered intact antibodies and
15 fragments, for example chimeric antibodies, humanised antibodies (such as humanised monoclonal antibodies), single-chain Fv fragments, single-chain antibodies, diabodies, minibodies, linear antibodies, and multivalent or multispecific hybrid antibodies. The term antibody may include any protein that comprises an antigen-binding site of an antibody and is capable of binding to its antigen. An
20 antigen-binding site of an antibody is the antibody portion that is required for binding to its antigen. Examples include Fv fragments, single-chain Fv fragments, Fab fragments, diabodies, and minibodies.

Thus, an anti-IL-18 antibody will bind to IL-18 (i.e. to the IL-18 protein).

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Methods for preparing and isolating antibodies, such as polyclonal antibodies and monoclonal antibodies, are well known in the art. By way of example, polyclonal antibodies may be obtained by the inoculation of any one of a variety of mammals such as mice, rats, rabbits, goats, and sheep with a suitable peptide/protein or
30 immunogenic fragment thereof, followed by subsequent harvesting of serum and antibody purification. Monoclonal antibodies may be obtained by fusing a specific antibody-producing B cell (such as isolated following immunisation of a mouse) with an immortal myeloma cell and culturing the resultant hybridoma, before standard

screening techniques are used to identify hybridomas producing antibodies with the desired properties.

By way of example, an anti-IL-18 antibody may be used to bind IL-18, thus reducing its ability to bind to and activate the IL-18 receptor (for example, by way of steric hindrance). In this way, IL-18-mediated actions in the joint are inhibited.

An anti-IL-18 antibody may bind to IL-18 such that the antibody-bound IL-18 cannot activate the IL-18 receptor at all (e.g. because the IL-18 can no longer bind to the IL-18 receptor). Thus, in one embodiment, the anti-IL-18 antibody neutralises IL-18 and is a neutralising antibody. Alternatively, an anti-IL-18 antibody may bind to IL-18 such that only partial activation of the IL-18 receptor by IL-18 is possible. Thus, in one embodiment, the anti-IL-18 antibody partially-neutralises IL-18 and is a partially-neutralising antibody.

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IL-18 may be inhibited by the use of an antibody directed against the IL-18 receptor. By way of example, such an antibody may be a monoclonal antibody or a polyclonal antibody. The antibody may be directed against an alpha subunit of the IL-18 receptor, or against a beta subunit of the IL-18 receptor.

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An antibody directed against the IL-18 receptor may bind to the receptor such that IL-18 is prevented from activating the receptor (for example, by preventing binding of IL-18 to the receptor); thus, the receptor may be fully inhibited by the antibody. An antibody directed against the IL-18 receptor may bind to the receptor such that IL-18 is prevented from fully activating the receptor (for example, by causing IL-18 to bind to the receptor with reduced affinity compared to in the absence of the antibody); thus, the receptor may be partially inhibited by the antibody.

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The actions of IL-18 are mediated via a number of signalling pathways, both upstream and downstream. Thus, an IL-18 inhibitor may target a component of an IL-18 signalling pathway. By way of example, an IL-18 inhibitor may reduce or block the activity of a downstream effector of IL-18 activity. Examples of such downstream effectors are Adamts5, Adamts1, and Arg1. Thus, in one embodiment, the IL-18 inhibitor is an inhibitor of Adamts5. In one embodiment, the IL-18 inhibitor is an

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inhibitor of Adamts1. In one embodiment, the IL-18 inhibitor is an inhibitor of Arg1. In one embodiment, the IL-18 inhibitor blocks the action of, or reduces the activity of, the adaptor protein MyD88. In one embodiment, the IL-18 inhibitor is a MyD88 inhibitor.

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An IL-18 inhibitor may be an IL-18-receptor antagonist. An IL-18-receptor antagonist may be a small molecule which binds to the IL-18 receptor such that binding of IL-18 is reduced or prevented. Thus, an IL-18 inhibitor may be a competitive inhibitor at the IL-18 receptor.

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An IL-18 inhibitor may be an IL-18 binding protein. An example of such a protein is the endogenous IL-18-binding protein (IL18BP), which binds to IL-18 and prevents it from binding to and activating the IL-18 receptor. A further example of an IL-18 binding protein is a soluble form of the IL-18 receptor. A soluble receptor is a receptor protein that is not bound to a cellular membrane, for example due to a lack of the requisite membrane insertion domain. A soluble form of the IL-18 receptor may be provided by using protein engineering techniques to modify the endogenous IL-18 receptor. Methods of preparing soluble forms of receptors are known in the art.

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20 An IL-18 inhibitor may be an inhibitor of caspase-1 (also known as interleukin-1-beta converting enzyme or ICE). Caspase-1 acts on the inactive precursor form of IL-18, converting it into the active IL-18 molecule. Thus, inhibition of caspase-1 prevents the production of (active) IL-18. An example of a caspase-1 inhibitor is Z-VAD-FMK (carbobenzoxy-valyl-alanyl-aspartyl-[O-methyl]-fluoromethylketone). In one embodiment, the IL-18 inhibitor is an anti-caspase-1 antibody.

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As described herein, injury-induced osteoarthritis is a specific type of osteoarthritis that develops as a result of a subject sustaining an injury to a joint (i.e. a joint injury). Thus, unlike age-related osteoarthritis which develops in elderly individuals (e.g. over 30 60 years of age) as a result of the ageing process and associated wear on joints, injury-induced osteoarthritis can develop in younger individuals who are not at risk of osteoarthritis associated with ageing. Thus, by way of example, injury-induced osteoarthritis can develop in individuals less than or equal to 50, 40, or 30 years of age.

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An injury may be defined as physical damage to the body. Thus, a joint injury represents an incidence of damage sustained by the joint. A joint injury may be the result of trauma, for example a sudden, significant physical injury such as from an accident. Thus, the joint injury may be a traumatic injury or trauma-related injury. A
5 traumatic injury may directly damage cartilage in a joint. Thus, in one embodiment, the injury is a trauma-related cartilage injury.

A joint injury may be the result of sporting activity, i.e. a sports injury.

10 Many joint injuries are acute joint injuries, i.e. an injury with a sudden onset, often as the result of a single event. Thus, in one embodiment, the injury is an acute injury. An acute injury may be the result of trauma (for example, as defined above) or of sporting activity. Thus, in one embodiment, the term acute injury comprises traumatic injury and sports injury. By way of example, a fall resulting in a sudden impact to the knee
15 can produce an acute injury to the knee joint. Acute injuries may be caused when a joint is forced to undergo a movement that is out of its normal range of motion, for example a forced twisting of a knee joint. Acute injuries can be a common result of sporting activity.

20 A joint injury (for example, an acute joint injury) may result in a joint effusion (an increase in the amount of intra-articular fluid). In addition, there may be evidence of structural joint damage, such as meniscal, ligamentous or other damage. Methods for assessment of an injury to a joint are known in the art, for example magnetic resonance imaging (MRI). In one embodiment, an acute joint injury is defined as a
25 single traumatic event resulting in a joint effusion with evidence of structural joint damage.

According to the invention, the IL-18 inhibitor is administered to the subject using any suitable method that enables the IL-18 inhibitor to reach the target joint.

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In one embodiment, the IL-18 inhibitor is administered to the subject orally. In one embodiment, the IL-18 inhibitor is administered to the subject parenterally. In one embodiment, the IL-18 inhibitor is administered to the subject intravenously.

In one embodiment, the IL-18 inhibitor is administered to the subject by local administration in the vicinity of the joint. By way of example, the IL-18 inhibitor may be administered by local injection into the vicinity of the joint. As used herein, the term injection comprises the use of any needle or cannula to deliver a substance or composition into the body of a subject.

In one embodiment, the IL-18 inhibitor is administered directly to the joint. The IL-18 inhibitor may be administered to the joint space or to any of the tissues that make up the joint. In one embodiment, the IL-18 inhibitor is administered to the synovial fluid of the joint.

In one embodiment, the IL-18 inhibitor is administered to the joint by local injection. Administration may be by intra-articular injection. Local injection may be into the joint space or into any of the tissues that make up the joint (for example, cartilage, synovium, synovial fluid, bone, muscle, or ligament). Methods for performing local injections into joints are known in the art and will be familiar to a skilled person.

Administration of the IL-18 inhibitor directly to the joint (for example, by local injection as described above) advantageously directs the IL-18 inhibitor to the immediate location where IL-18 levels are raised following an injury to the joint. In one embodiment, the IL-18 inhibitor is administered to the synovial fluid of the joint by local injection.

According to the present invention, injury-induced osteoarthritis may be prevented or treated in any synovial joint. By way of example, the joint may be a knee joint, an elbow joint, a hip joint, an ankle joint, a hand joint, a foot joint, or a neck joint.

In one embodiment, the joint is a knee joint. In one embodiment, the joint is a knee joint and the IL-18 inhibitor is an anti-IL-18 antibody. In one embodiment, the subject has sustained an acute knee injury and the IL-18 inhibitor is an anti-IL-18 antibody.

The IL-18 inhibitor may be administered prior to, or following, an injury to a joint.

In one embodiment, the treatment is a prophylactic treatment and suppresses or prevents the development of injury-induced osteoarthritis in the joint. Thus, the present invention may advantageously be used in cases where a subject is at an increased risk of developing injury-induced osteoarthritis in a joint, but where the disease process has yet to produce significant symptoms or cartilage damage. By way of example, the subject may have suffered an injury to a joint and thus be at increased risk of developing injury-induced osteoarthritis – an IL-18 inhibitor is then administered to the subject to prevent injury-induced osteoarthritis. The IL-18 inhibitor prevents the raised IL-18 levels subsequent to injury from effecting the processes that lead to cartilage degradation.

In one embodiment, the IL-18 inhibitor is administered following an injury to the joint. In one embodiment, the joint is a knee joint. In one embodiment, the injury is an acute injury.

In one embodiment, the IL-18 inhibitor reduces the symptoms of injury-induced osteoarthritis in the joint. By way of example, symptoms of injury-induced osteoarthritis may include pain, swelling and/or decreased mobility of the joint. Thus, in one embodiment, the IL-18 inhibitor reduces at least one injury-induced osteoarthritis symptom selected from pain, swelling and decreased joint mobility.

The amount of IL-18 inhibitor administered to a subject (i.e. dosage) may vary depending on the IL-18 inhibitor used. In one embodiment, a dosage may range from about 0.1 µg/kg to about 100 mg/kg, or from about 1 µg/kg to about 50 mg/kg, or from about 10 µg/kg to 5 mg/kg, of the subject's body weight.

The dosage of the IL-18 inhibitor may be determined by a medical professional, taking into account the severity of the joint injury.

The IL-18 inhibitor may be administered to the subject in a single delivery, such as a bolus delivery. Alternatively, the IL-18 inhibitor may be administered to the subject using a continuous delivery technique, such as a timed infusion. The IL-18 inhibitor may be administered using a repeated delivery regimen, for example on an hourly, daily or weekly basis.

IL-18 inhibitor dosages may be achieved by single or multiple administrations. By way of example, the IL-18 inhibitor may be administered to the subject in a regimen consisting of a single administration. Alternatively, the IL-18 inhibitor may be administered to the subject in a regimen comprising multiple administrations. For example, an administration regimen may comprise multiple administrations per day, or daily, weekly, bi-weekly, or monthly administrations. An example regimen comprises an initial administration followed by multiple, subsequent administrations at weekly or bi-weekly intervals. Another example regimen comprises an initial administration followed by multiple, subsequent administrations at monthly or bi-monthly intervals. Alternatively, administration of the IL-18 inhibitor can be guided by monitoring of the acute injury osteoarthritis status of the joint. Thus, an example regimen comprises an initial administration followed by multiple, subsequent administrations carried out on an irregular basis as determined by monitoring of IL-18 levels in the joint.

In one embodiment, wherein the IL-18 inhibitor is administered to the subject following an injury to a joint as described above, the IL-18 inhibitor is administered in a first administration step during a period of 0-24 hours following an injury to the joint (for example, 0.5, 1, 2, 3, 4, 5, 6, 12, 18, or 24 hours).

In one embodiment, wherein the IL-18 inhibitor is administered in a first administration step as described above, the IL-18 inhibitor is administered in at least one subsequent administration step during a time period of 0-28 days following the first administration step (for example, 1, 2, 3, 4, 5, 6, 7, 10, 14, 21, or 28 days).

In one embodiment, wherein the IL-18 inhibitor is administered to the subject following an injury to a joint as described above, the IL-18 inhibitor is administered in a first administration step during a time period of 0-28 days following an injury to the joint (for example, 1, 2, 3, 4, 5, 6, 7, 10, 14, 21, or 28 days).

In one embodiment, wherein the IL-18 inhibitor is administered in a first administration step as described above, the IL-18 inhibitor is administered in at least one subsequent administration step during a time period of 0-28 days following the first administration step (for example, 1, 2, 3, 4, 5, 6, 7, 10, 14, 21, or 28 days).

In one embodiment, wherein the IL-18 inhibitor is administered in a first administration step as described above, the IL-18 inhibitor is administered in at least one subsequent administration step during a time period of 4-52 weeks following the first administration step (for example, 4, 5, 6, 8, 10, 12, 26, or 52 weeks).

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In one embodiment, wherein the IL-18 inhibitor is administered following an injury to a joint, the joint is a knee joint. In one embodiment, the injury to the knee joint is selected from an anterior cruciate ligament injury, a posterior cruciate ligament injury, a meniscus injury, a lateral collateral ligament injury, and a medial collateral ligament injury.

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In one embodiment, the injury is a sports injury. In one embodiment, the injury is a sports injury to the knee (for example, a knee injury as described above).

15 In one embodiment, the prevention or treatment of injury-induced osteoarthritis further comprises one or more additional steps as described below. These additional steps may be taken prior to, concurrently with, or subsequent to, administration of the IL-18 inhibitor to the subject. Additional steps include immobilisation of the joint following an injury (e.g. by splinting); administration of at least one of an analgesic (e.g. paracetamol), an anti-inflammatory (e.g. aspirin or ibuprofen), and a corticosteroid; and surgical treatment of the injury (for example, surgical treatment of a ruptured tendon).

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In one embodiment, the subject is a human and the subject is less than or equal to 40 years of age, preferably less than or equal to 30 years of age, preferably less than or equal to 25 years of age. The subject may be male or female. By way of example, the present invention may advantageously be employed wherein the subject takes part in sporting activities. The subject may be an amateur sports person or a professional sports person. Individuals participating in sporting activities at a high level are often young, for example less than or equal to 40 years of age, less than or equal to 30 years of age, or less than or equal to 25 years of age. Such individuals are at a higher risk of sustaining an injury to a joint than sedentary individuals, and thus at a higher risk of developing injury-induced osteoarthritis.

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Whilst the present invention is particular suitable for application to human subjects, in certain embodiments the present invention may be applied to non-human mammal subjects. For example, the present invention may be used to prevent or treat injury-induced osteoarthritis in a domesticated animal such as a cat, a dog, or a horse. For example, horses may incur an injury to a joint when taking part in equestrian events; this may subsequently lead to injury-induced osteoarthritis in the injured joint. A horse may have significant monetary value and thus the prevention or treatment of injury-induced arthritis in joint of a horse may be economically advantageous. Thus, in one embodiment the subject is a horse.

For administration to a subject, the IL-18 inhibitor may be formulated as a pharmaceutical composition comprising an IL-18 inhibitor (as active ingredient). A pharmaceutical composition comprising an IL-18 inhibitor can be formulated according to known methods for preparing pharmaceutical compositions, such as by combining an IL-18 inhibitor with a pharmaceutically-acceptable carrier. Non-limiting examples of pharmaceutically acceptable carriers include water, saline, and phosphate-buffered saline.

The pharmaceutical composition in addition to a pharmaceutically acceptable carrier can further be combined with one or more of a salt, excipient, diluent, albumin, immunoregulatory agent and/or antimicrobial compound. Pharmaceutically acceptable salts include acid addition salts formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or with organic acids such as acetic, oxalic, tartaric, maleic, and the like. Salts formed with the free carboxyl groups may also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol, or the like and combinations thereof.

In addition, if desired, the pharmaceutical compositions may contain minor amounts of auxiliary substances such as wetting or emulsifying agents, and/or pH buffering agents. Examples of buffering agents include, but are not limited to, sodium succinate (pH 6.5), and phosphate buffered saline (PBS; pH 6.5 and 7.5).

Thus, in one aspect, the invention provides a pharmaceutical composition, comprising an IL-18 inhibitor for use as described above and a pharmaceutically acceptable carrier. The pharmaceutical composition may contain 5% to 95% of IL-18 inhibitor, such as at least 10% or 25% of IL-18 inhibitor, or at least 40% of IL-18 inhibitor, or at least 50, 55, 60, 70 or 75% IL-18 inhibitor.

In one aspect, the invention provides an *in vitro* or *ex vivo* method for diagnosing or predicting the risk of injury-induced osteoarthritis in a joint of a subject, said method comprising:

- (i) determining the amount of IL-18 in a sample from said subject;
- (ii) comparing the amount of IL-18 in the sample with a reference standard; and
- (iii) identifying a difference in the amount of IL-18 in the sample relative to the reference standard;

wherein an increase in the amount of IL-18 in the sample compared to the reference standard correlates with the presence of, or an increased risk of, injury-induced osteoarthritis; and

wherein a decrease, or no difference, in the amount of IL-18 in the sample compared to the reference standard correlates with the absence of, or a lack of increased risk of, injury-induced osteoarthritis.

Advantageously, the *in vitro* or *ex vivo* method of the invention enables the identification of subjects having or at risk of injury-induced osteoarthritis, enabling the commencement of appropriate treatment or prophylaxis. By way of example, a subject identified by the *in vitro* or *ex vivo* method of the invention as having or being at risk of injury-induced osteoarthritis may be administered an IL-18 inhibitor as described above.

In one embodiment, the joint of the subject has sustained an injury. In one embodiment, the injury is a sports injury. In one embodiment, the injury is a traumatic injury. In one embodiment, the injury is an acute injury.

The sample may be a sample from the subject of any suitable tissue. The sample may be a blood sample, a plasma sample, a serum sample, a urine sample, or a synovial fluid sample. In one embodiment, the sample is from the joint of said subject. In one

embodiment, wherein the sample is from the joint of said subject, the sample is a synovial fluid sample.

5 The amount of IL-18 in the sample may be determined by any suitable method known in the art. In the present context, the amount of IL-18 refers to the level or quantity of IL-18, for example as measured in units mass protein per units volume sample.

10 The reference standard acts as a control and enables the comparison of the amount of IL-18 in the sample from the subject (which is thus the test sample, from the test subject) with the amount of IL-18 in a reference sample.

15 In one embodiment, a reference standard comprises (or consists of) a sample from a joint of a reference subject or subjects, wherein the reference subject is a subject other than the test subject, and wherein the reference subject has not incurred an injury to the joint and does not have injury-induced osteoarthritis.

20 In one embodiment, a reference standard comprises (or consists of) a set of data relating to the amount of IL-18 in a reference sample or samples derived from a reference subject or subjects, wherein the reference subject is a subject other than the test subject, and wherein the reference subject has not incurred an injury to the joint and does not have injury-induced osteoarthritis. The set of data is derived by measuring the amount of IL-18 in the reference sample or samples. Said measuring may be carried out using any suitable technique known in the art.

25 The reference standard may be matched to the test sample. Thus, in one embodiment, when the sample is a synovial fluid sample, the reference standard relates to the amount of IL-18 in synovial fluid.

30 In one embodiment, the sample is from the joint of the subject and the reference sample is from a matched joint that has not incurred an injury and which does not have injury-induced osteoarthritis.

The method of the invention may be used to compare the levels of IL-18 in a joint that has suffered a joint injury with the levels of IL-18 in a joint that has not suffered a joint injury, in the same subject. In one embodiment, a reference standard comprises

(or consists of) a reference sample from a joint of the test subject other than the test joint, wherein said joint other than the test joint has not incurred an injury and does not have injury-induced osteoarthritis. Thus, by way of example, a comparison may be made between the amount of IL-18 in the test joint (a joint having incurred an injury) and the amount of IL-18 in a reference joint (a joint that has not incurred an injury). By way of further example, a (human) test subject may incur an injury to one of his/her knees; it may then be desired to compare the amount of IL-18 in the injured knee with the amount of IL-18 in the uninjured knee.

- 10 In one embodiment, the amount of IL-18 is determined by measuring the concentration of IL-18 protein in the sample. Said measuring may be carried out using any suitable technique known in the art. By way of example, suitable techniques include enzyme linked immunosorbant assay (ELISA), and multi-array technology combined with electrochemiluminescence (for example, as provided by Meso Scale
15 Discovery platforms).

- In one embodiment, the amount of IL-18 is determined by measuring the concentration of IL-18 mRNA in the sample. The concentration of IL-18 mRNA correlates with IL-18 expression levels and can be used to indirectly determine the
20 amount of IL-18 in a sample. Techniques for measuring mRNA concentration are well known in the art, and include reverse transcriptase polymerase chain reaction (RTPCR) and quantitative RTPCR.

- In one embodiment, the amount of IL-18 is determined by measuring the
25 concentration of a protein or an mRNA associated with an IL-18-dependent gene. In one embodiment, the IL-18-dependent gene is selected from Adamts1, Adamts5, and Arg1. Thus, in one embodiment, the amount of IL-18 is determined indirectly by measuring the expression levels of an IL-18-dependent gene.

- 30 In one embodiment, the amount of IL-18 protein in the sample is equal to or greater than 50 pg/ml. In one embodiment, an IL-18 protein amount of equal to or greater than 50 pg/ml in the (test) sample correlates with an increased risk of injury-induced osteoarthritis in the (test) joint. In one embodiment, an IL-18 protein amount of equal

to or greater than 50 pg/ml in the (test) sample correlates with the presence of injury-induced osteoarthritis in the (test) joint.

5 The method of the invention may be used to monitor IL-18 levels in a subject over a period of time, for example following a joint injury. Thus, in one embodiment, wherein the subject has sustained a joint injury, the method further comprises one or more repetitions (e.g. 1, 2, 3, 4 or 5) of steps (i) to (iii) using at least one (e.g. 1, 2, 3, 4 or 5) further sample (or samples) that has (or have) been taken from the subject in a serial fashion over a period of time following the joint injury. Thus, the level of IL-18
10 in each sample may be determined to provide data on IL-18 levels over a period of time. In one embodiment, steps (i) to (iii) are repeated using samples that have been taken from a subject at intervals of 1, 2, 6, 12 or 24 hours; or 1, 2, 7, 14 or 28 days; or 1, 2, 3, 6 or 12 months. In one embodiment, the method of the invention is repeated using samples that have been taken from a subject at intervals of 1, 2, 6, 12 or 24
15 hours; or 1, 2, 7, 14 or 28 days; or 1, 2, 3, 6 or 12 months; following the joint injury.

The amount of IL-18 determined to be in a first sample from the subject may subsequently form the basis of a reference standard, against which the amount of IL-18 in subsequent samples that have been taken from the same subject may be
20 compared. Thus, in one embodiment, the reference standard is derived from a first sample that has been taken from the subject at a first time point; and step (i) is carried out on a second sample that has been taken from the subject subsequent to the first time point. Said embodiment may further comprise the steps of determining the amount of IL-18 in further samples (e.g. 1, 2, 3, 4, 5, 6 or 10 further samples) that
25 have been taken from the subject in a serial fashion over a period of time, and comparing the amount of IL-18 in each further sample with the amount of IL-18 in the reference sample. By way of example, the second and further samples may be samples that have been taken from the subject at intervals of 1, 2, 6, 12 or 24 hours; or 1, 2, 7, 14 or 28 days; or 1, 2, 3, 6 or 12 months; following the first time point.

30

In one aspect, the invention provides a data storage medium comprising data obtained by an *in vitro* or *ex vivo* method for diagnosing or predicting the risk of injury-induced osteoarthritis in a joint of a subject as described above.

In one embodiment, said device is capable of performing the step of identifying a difference in the amount of IL-18 biomarker in the sample relative to the reference standard.

List of figures**Figure 1**

Graph showing OA scores in mice at 4, 8 and 12 weeks post surgery using a surgical model of joint destabilisation (DMM). Each set of 4 bars shows (left to right): MyD88
 5 -/- sham; C57B/6 sham; MyD88 -/- DMM; C57B/6 DMM. MyD88 -/- indicates mice deficient in the MyD88 gene (i.e. knockouts); C57B/6 indicates control mice (which is the background strain for MyD88-/- mice). OA scores are indicative of the severity and extent of cartilage degradation within the knee joint. Scores range from 0 (no damage) to a maximum possible score of 72 (full thickness cartilage loss in each
 10 compartment of the joint in three separate joint sections taken at least 80 microns apart).

Figure 2

Upper graph: graph showing OA scores in mice with the following gene knockouts
 15 (left to right) – Wildtype, MyD88, IL1R, IL33R, TLR2, TLR4, IL-18, TLR9. OA scores are significantly decreased versus wildtype in MyD88 and IL-18 knockouts (statistical significance indicated with $p < 0.01^{**}$).

Lower graph: graph showing cartilage degradation in IL-18 knockout (IL-18 -/-) mice versus controls (IL-18 positive) at 8 weeks and 12 weeks post surgery using the DMM
 20 model. Statistical significance indicated with ** ($p < 0.01$) and *** ($p < 0.001$).

Figure 3

Graphs showing Adamts5 (left hand graph) and Arg1 (right hand graph) expression in wildtype and MyD88-knockout mice at 0 hours and 4 hours following *in vitro*
 25 cartilage injury. Statistical significance indicated with * ($p < 0.05$) and ** ($p < 0.01$).

Figure 4

Graph showing IL-18 protein levels in porcine synovium over a 1000-minute time course following synovium injury.

30

Figure 5

Graph showing IL-18 levels in sera and knee synovial fluid in human individuals (control, having rheumatoid arthritis (RA), and within 2 weeks of an acute knee injury (KICK)).

Examples

Example 1

5 Mice deficient in MyD88, an adaptor protein essential for signalling through the IL-18 receptor, are strongly protected from acute injury osteoarthritis.

Surgical destabilisation of the medial meniscus where the joint is opened and the menisco-tibial ligament is cut (DMM model) was carried out in mice. This procedure represents a model of an injury to a joint. Osteoarthritis in the joint was measured in
10 the mice at 4, 8 and 12 weeks post surgery by histological assessment of cartilage degradation according to a validated scoring system. It was shown that mice deficient in MyD88 were strongly protected from developing injury-induced osteoarthritis (Figure 1).

15 **Example 2**

The protection against injury-induced osteoarthritis seen in MyD88-deficient mice is also shown in IL-18-deficient mice.

Subsequent screening of several up-stream activators was performed in order to
20 establish which receptor/ligand was driving the mouse osteoarthritis following surgical destabilisation in a MyD88-dependent manner. The DMM model was used to test mice having one of the following genes knocked out: IL1R, IL33R, TLR2, TLR4, TLR9, and IL-18. Only those mice lacking the IL-18 gene were protected against DMM-induced osteoarthritis. IL-18 knockout mice showed significantly less cartilage
25 degradation than control mice. Together these experiments showed that IL-18 was responsible for the development of the injury-induced osteoarthritis shown in the mouse DMM model (Figure 2).

Example 3

30 Gene expression in the articular cartilage *in vitro* after injury leads to the up-regulation of IL-18-dependent genes

Hip cartilage injury experiments were performed using a method described by the inventors involving avulsion of the cartilaginous cap of the head of the femur in 5

week old mice. Testing showed that several genes were regulated upon injury including the disease relevant enzyme Adamts5, and Arg1 (arginase-1). However, this regulation did not occur when the tests were performed in tissue taken from MyD88-deficient (Figure 3) or IL-18-deficient mice (Table 1). Table 1 shows the difference in the levels of Adamts5 and Arg1 expression between 0 hours and 4 hours post injury, as measured in wildtype and IL-18 knockout mice. Adamts5 and Arg1 induction following cartilage injury *in vitro* is significantly lower (0.66- and 0.45-fold) in IL-18^{-/-} compared to the wildtype. Thus, it is clear that IL-18 is required for induction of both Adamts5 and Arg1 following cartilage injury.

Genes	WT		IL-18 ^{-/-}		Fold difference IL-18 ^{-/-} / WT	
	4h / 0h	p value	4h / 0h	p value	Fold difference	p value
Adamts5	2.008 ± 0.419	p≤0.001	1.33 ± 0.143	ns	0.66	p≤0.05
Arg1	10.005 ± 2.33	p≤0.01	4.536 ± 1.047	p≤0.001	0.45	p≤0.05

Table 1. Adamts5 and Arg 1 induction is IL18-dependent in injured cartilage.

Example 4

IL-18 is released from synovium following mechanical injury

Synovial membrane was dissected (mechanical injury) from the joint into serum-free medium and cultured for varying periods up to 1000 minutes. Medium was collected and analysed by ELISA for levels of released IL18 protein. A peak of IL18 protein was evident at 4h post dissection in two separate experiments (Figure 4).

Example 5

Levels of IL-18 are raised in the knee synovial fluid of human individuals who have recently sustained an acute injury to the knee.

Levels of IL-18 in the serum and knee synovial fluid were measured in human individuals falling into one of the following categories: control (no injury or arthritis condition); having established age-related osteoarthritis (OA); having rheumatoid arthritis (RA); having recently sustained an acute (within 2 weeks) destabilising injury to the knee (KICK). Samples were measured using the Meso Scale Delivery platform. IL-18 levels were significantly elevated in the synovial fluid of individuals who had recently suffered an acute knee injury compared to IL-18 levels in the synovial fluid of control individuals.

10 **Example 6**

A 25 year old male presents with swelling and pain in the knee, following a fall sustained while skiing. MRI scanning shows an effusion and a tear to the anterior cruciate ligament. Within 36 hours of injury, the joint is splinted and the patient is administered 1 mg/kg of anti-IL-18 antibody by intravenous injection. Administration is repeated at twice weekly intervals for the first 4 weeks after injury. MRI scanning of the joint at 1 and 5 years post injury indicates no loss of cartilage.

Claims

1. An interleukin-18 (IL-18) inhibitor for use in the prevention or treatment of injury-induced osteoarthritis in a joint of a subject.

5

2. The IL-18 inhibitor for use according to claim 1, wherein the IL-18 inhibitor is selected from an anti-IL-18 antibody, an antibody against an IL-18-receptor, an inhibitor of an IL-18 signalling pathway, an IL-18-receptor antagonist, an IL-18 binding protein, and a caspase-1 (ICE) inhibitor.

10

3. The IL-18 inhibitor for use according to any preceding claim, wherein the IL-18 inhibitor is an anti-IL-18 antibody.

4. The IL-18 inhibitor for use according to any preceding claim, wherein the IL-18 inhibitor is administered directly to the joint.

15

5. The IL-18 inhibitor for use according to any preceding claim, wherein the IL-18 inhibitor is administered to the synovial fluid of the joint.

6. The IL-18 inhibitor for use according to claim 4 or claim 5, wherein the IL-18 inhibitor is administered by local injection.

20

7. The IL-18 inhibitor for use according to any preceding claim, wherein the joint is selected from a knee joint, an elbow joint, a hip joint, an ankle joint, a hand joint, a foot joint, and a neck joint.

25

8. The IL-18 inhibitor for use according to any preceding claim, wherein the treatment is a prophylactic treatment and wherein said treatment suppresses or prevents the development of injury-induced osteoarthritis in the joint.

30

9. The IL-18 inhibitor for use according to any preceding claim, wherein the IL-18 inhibitor reduces the symptoms of injury-induced osteoarthritis in the joint.

10. The IL-18 inhibitor for use according to any preceding claim, wherein the IL-18 inhibitor is administered to the subject following an injury to the joint.

11. The IL-18 inhibitor for use according to claim 10, wherein the IL-18 inhibitor
5 is administered in a first administration step during a time period of 0-28 days following an injury to the joint.

12. The IL-18 inhibitor for use according to claim 11, wherein the IL-18 inhibitor
10 is administered in at least one subsequent administration step during a time period of 0-28 days following the first administration step.

13. The IL-18 inhibitor for use according to claim 11, wherein the IL-18 inhibitor
is administered in at least one subsequent administration step during a time period of
4-52 weeks following the first administration step.

15

14. The IL-18 inhibitor for use according to any one of claims 10-13, wherein the
joint is a knee joint.

15. The IL-18 inhibitor for use according to claim 14, wherein the injury to the
20 knee is selected from an anterior cruciate ligament injury, a posterior cruciate
ligament injury, a meniscus injury, a lateral collateral ligament injury, and a medial
collateral ligament injury.

16. The IL-18 inhibitor for use according to any preceding claim, wherein the
25 injury is a sports injury.

17. The IL-18 inhibitor for use according to any previous claim, wherein the
subject is a human and wherein the subject is less than or equal to 40 years of age,
preferably wherein the subject is less than or equal to 30 years of age.

30

18. An *in vitro* or *ex vivo* method for diagnosing or predicting the risk of injury-
induced osteoarthritis in a joint of a subject, said method comprising:

- (i) determining the amount of IL-18 in a sample from said subject;
- (ii) comparing the amount of IL-18 in the sample with a reference standard; and

(iii) identifying a difference in the amount of IL-18 in the sample relative to the reference standard;

wherein an increase in the amount of IL-18 in the sample compared to the reference standard correlates with the presence of, or an increased risk of, injury-

5 induced osteoarthritis; and

wherein a decrease, or no difference, in the amount of IL-18 in the sample compared to the reference standard correlates with the absence of, or a lack of increased risk of, injury-induced osteoarthritis.

10 19. The method according to claim 18, wherein the joint is selected from a knee joint, an elbow joint, a hip joint, an ankle joint, a hand joint, a foot joint, and a neck joint.

15 20. The method according to any one of claims 18-19, wherein the sample is selected from a blood sample, a plasma sample, a serum sample, a urine sample, or a synovial fluid sample.

21. The method according to any one of claims 18-20, wherein the injury is a sports injury.

20

22. The method according to any one of claims 18-21, wherein the amount of IL-18 is determined by measuring the concentration of IL-18 protein in the sample.

25 23. The method according to any one of claims 18-21, wherein the amount of IL-18 is determined by measuring the concentration of IL-18 mRNA in the sample.

24. The method according to any one of claims 18-21, wherein the amount of IL-18 is determined by measuring the concentration of a protein or an mRNA associated with an IL-18-dependent gene selected from Adamts1, Adamts5 and Arginase 1.

30

25. The method according to claim 22, wherein an amount of IL-18 protein in the sample of equal to or greater than 50 pg/ml correlates with the presence of, or an increased risk of, injury-induced osteoarthritis.

26. The method according to any one of claims 18-25, wherein the subject has sustained a joint injury, and wherein the method further comprises one or more repetitions of steps (i) to (iii) using a further sample (or samples) that has (or have) been taken from the subject in a serial fashion over a period of time following the joint injury.

27. The method according to any one of claims 18-26, wherein the reference standard is derived from a first sample that has been taken from the subject at a first time point; and step (i) is carried out on a second sample that has been taken from the subject subsequent to the first time point.

28. A data storage medium comprising data obtained by the method of any one of claims 18-27.

29. A device for use in the method of any one of claims 18-27, wherein said device is capable of performing the step of identifying a difference in the amount of IL-18 biomarker in the sample relative to the reference standard.

30. A pharmaceutical composition, comprising an IL-18 inhibitor for use according to any one of claims 1-17 and a pharmaceutically acceptable carrier.

31. A method for treating or preventing injury-induced osteoarthritis in a joint of a subject, comprising administering to the subject an effective amount of an interleukin-18 (IL-18) inhibitor.

32. The method according to claim 31, wherein the IL-18 inhibitor is selected from an anti-IL-18 antibody, an antibody against an IL-18-receptor, an inhibitor of an IL-18 signalling pathway, an IL-18-receptor antagonist, an IL-18 binding protein, and a caspase-1 (ICE) inhibitor.

33. The method according to claim 31 or claim 32, wherein the IL-18 inhibitor is an anti-IL-18 antibody.

34. The method according to any one of claims 31-33 wherein the IL-18 inhibitor is administered directly to the joint.

35. The method according to any one of claims 31-34, wherein the IL-18 inhibitor
5 is administered to the synovial fluid of the joint.

36. The method according to claim 34 or claim 35, wherein the IL-18 inhibitor is administered by local injection.

10 37. The method according to any one of claims 31-36, wherein the joint is selected from a knee joint, an elbow joint, a hip joint, an ankle joint, a hand joint, a foot joint, and a neck joint.

38. The method according to any one of claims 31-37, wherein the treatment is a
15 prophylactic treatment and wherein said treatment suppresses or prevents the development of injury-induced osteoarthritis in the joint.

39. The method according to any one of claims 31-38, wherein the IL-18 inhibitor reduces the symptoms of injury-induced osteoarthritis in the joint.

20 40. The method according to any one of claims 31-38, wherein the IL-18 inhibitor is administered to the subject following an injury to the joint.

41. The method according to claim 40, wherein the IL-18 inhibitor is administered
25 in a first administration step during a time period of 0-28 days following an injury to the joint.

42. The method according to claim 41, wherein the IL-18 inhibitor is administered in at least one subsequent administration step during a time period of 0-28 days
30 following the first administration step.

43. The method according to claim 41, wherein the IL-18 inhibitor is administered in at least one subsequent administration step during a time period of 4-52 weeks following the first administration step.

44. The method according to any one of claims 40-43, wherein the joint is a knee joint.
- 5 45. The method according to claim 44, wherein the injury to the knee is selected from an anterior cruciate ligament injury, a posterior cruciate ligament injury, a meniscus injury, a lateral collateral ligament injury, and a medial collateral ligament injury.
- 10 46. The method according to any one of claims 31-45, wherein the injury is a sports injury.
47. The method according to any one of claims 31-46, wherein the subject is a human and wherein the subject is less than or equal to 40 years of age, preferably
- 15 wherein the subject is less than or equal to 30 years of age.

Figure 1

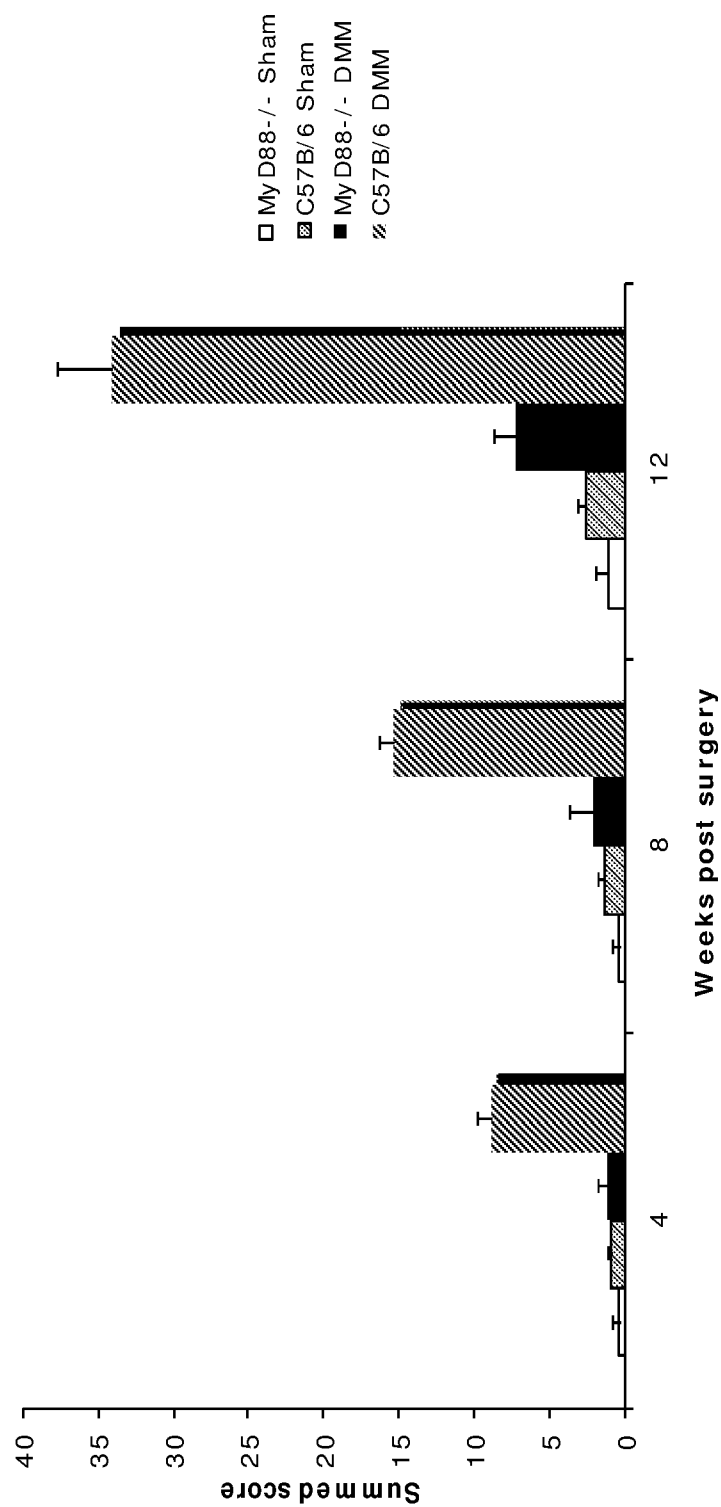


Figure 2

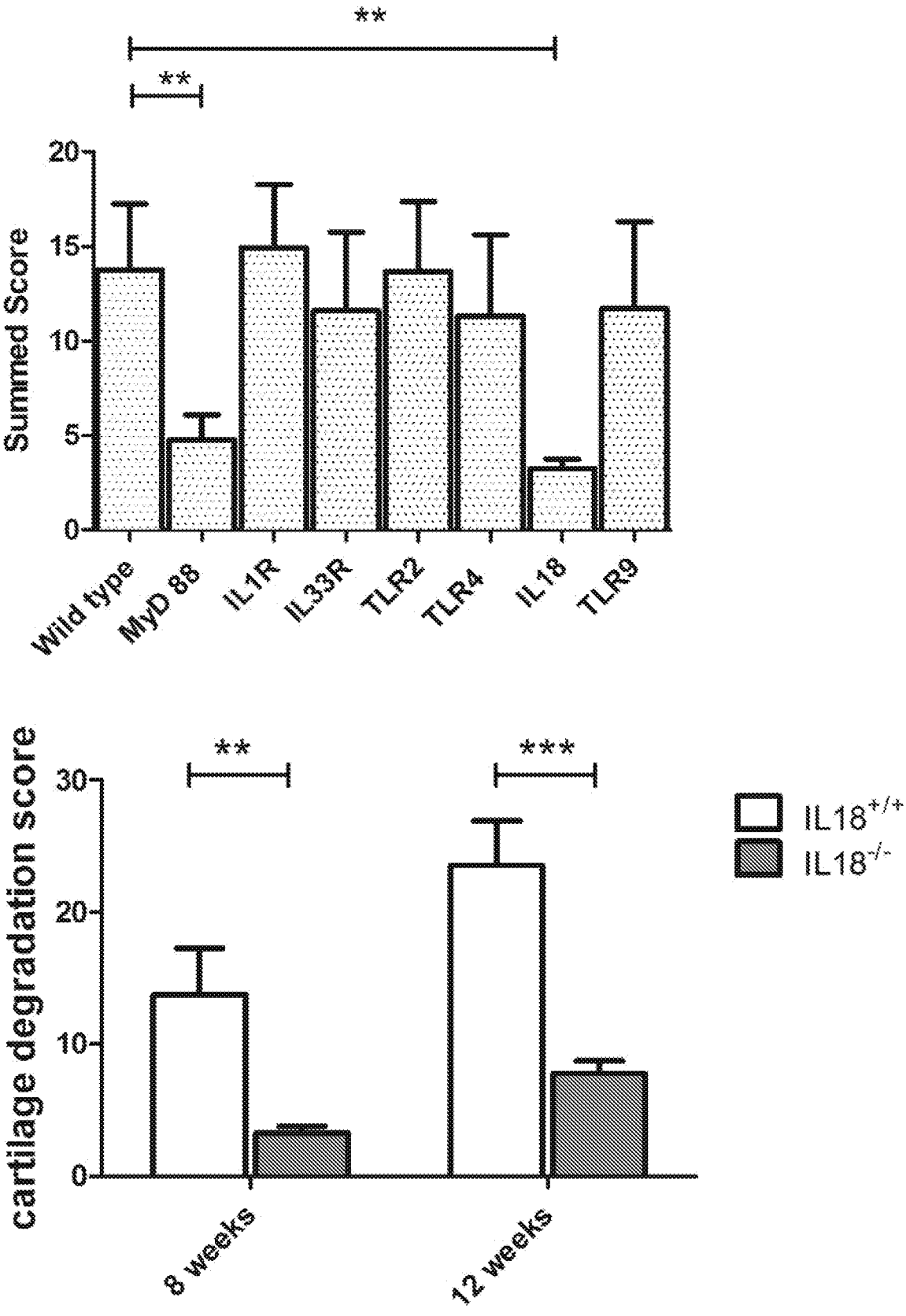


Figure 3

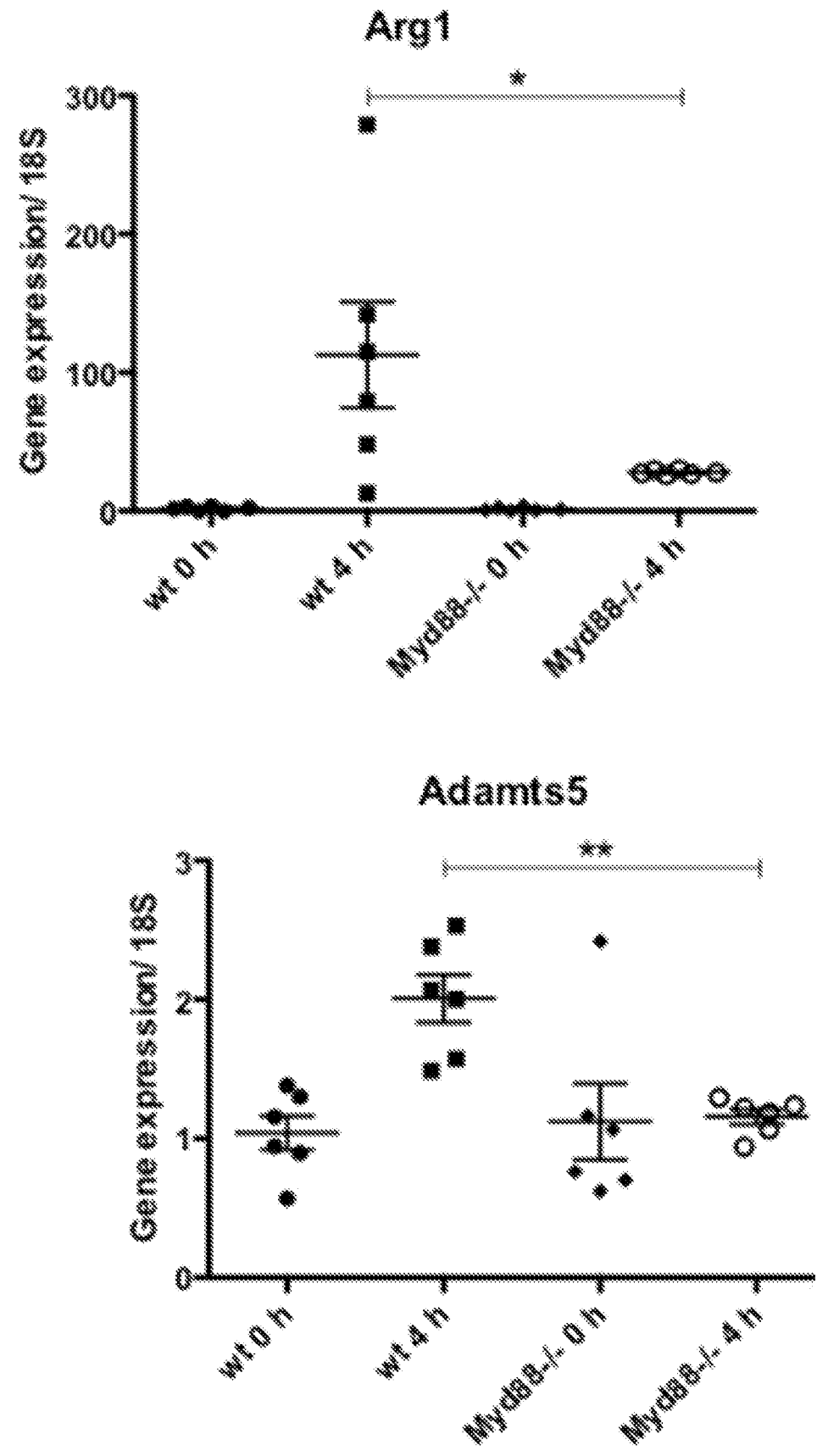


Figure 4

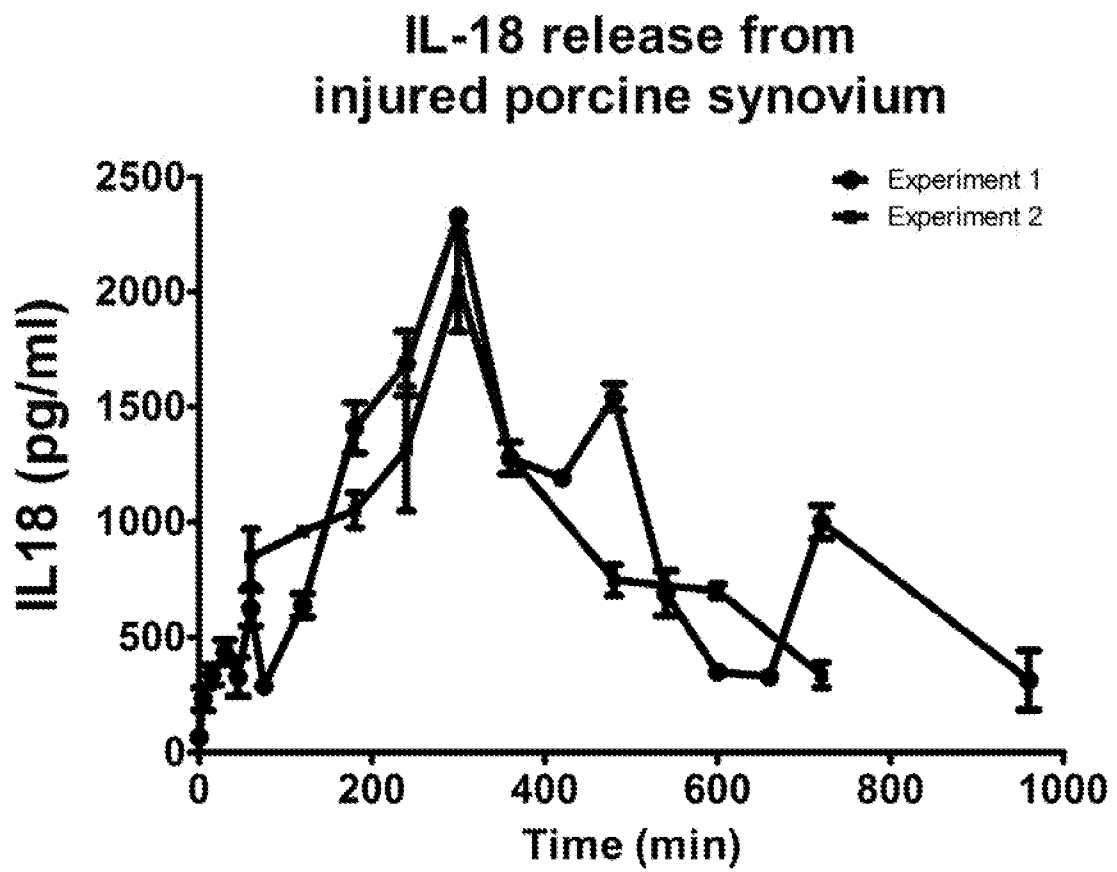


Figure 5

