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THERAPEUTIC TARGETS FOR GOUT

L.A. Sorbera, S. Sharanya, C. Dulsat and E. Rosa

Thomson Reuters, Barcelona, Spain

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SUMMARY

Gout is a metabolic disorder caused by hyperuricemia and consequent deposition of uric acid crystals in the joints of the lower extremities. The result is swelling, inflammation and severe pain. The main goals of gout treatment are to manage the intense pain accompanying acute attacks and to arrest disease progression. Acute attacks are usually treated with nonsteroidal anti-inflammatory drugs (NSAIDs) or oral glucocorticoids. Treatment is also aimed at controlling uric acid levels and preventing the formation of new tophi. Several therapeutic strategies are available to patients suffering from gout and they include uricosuric agents, xanthine oxidase inhibitors, recombinant uricase preparations and anti-inflammatory agents. Researchers continue to search for more effective treatment strategies for gout with investigations concentrating on identifying novel targets for therapeutic intervention. This article presents those drug targets that are currently under active investigation for the treatment of gout.

INTRODUCTION

Gout is a metabolic disorder and a chronic type of inflammatory arthritis. It is caused by hyperuricemia that leads to the deposition of uric acid crystals and consequent swelling, inflammation and intense pain in the joints of the lower extremities and the kidneys. Gout is generally characterized by intermittent bouts of acute pain and, if untreated, may progress to chronic gouty arthritis. The National Institutes of Health (NIH) estimates that gout affects approximately 2.1 million people in the U.S. Worldwide it affects between 1-2% of adults in developed countries, with rates gradually increasing in other recently affected countries; increases tend to be in parallel to the growing prevalence of important risk factors such as obesity and metabolic syndrome. More men between the ages of 40 and 50 years are afflicted with gout as compared to women. However, the incidence in women tends to increase after menopause (1-3).

Correspondence: L.A. Sorbera, Thomson Reuters, Provença 388, 08025 Barcelona, Spain. E-mail: lisa.sorbera@thomsonreuters.com.

Uric acid is formed during the breakdown of purines that can be endogenous (e.g., generated during cell turnover) or from certain foods (e.g., meat, some plants). Unfortunately, humans lack the enzyme urate oxidase (uricase) that is present in most animals and is responsible for catalyzing the transformation of uric acid to allantoin. Gout occurs when, as a consequence of hyperuricemia, monosodium urate crystals deposit in the joints, kidneys and soft tissues, with trauma and/or irritation, local temperature and prior joint disorder all influencing further disease development. These urate crystals can stimulate the synthesis and release of cellular and humoral inflammatory mediators that potentiate and sustain intense inflammatory episodes (1-4).

Gout progresses in four stages. The first stage is asymptomatic hyperuricemia. Acute gout or acute gouty arthritis is the second stage that can occur with chronic hyperuricemia, although only a minority of patients with hyperuricemia actually progress to gout. Chronic hyperuricemia leads to the deposition of proinflammatory uric acid crystals in the joint space, causing extreme pain and intense articular and periarticular inflammatory responses. These attacks or flares usually develop at night, and if untreated, will resolve within 3-14 days; flares can recur, linger for a longer duration and progressively involve more joints. Stage three is known as interval or intercritical gout and is the period between acute attacks when there are no symptoms. Stage four, or chronic tophaceous gout (or advanced gout), is the most serious stage of the disease. It can take up to 10 years to develop and usually occurs due to lack of treatment. At this stage, solid deposits called tophi form in the joints, cartilage and bones and both the affected joints and kidneys may be permanently damaged (1, 3, 4).

Gout is one of the most manageable of the systemic rheumatic diseases and the main goal of gout treatment is to control the severe pain of acute attacks and to arrest disease progression. Acute attacks of gout are usually treated with nonsteroidal anti-inflammatory drugs (NSAIDs), or oral glucocorticoids as a second-line option to relieve pain and treat inflammation. Treatment is also aimed at dissolving monosodium urate crystals in the joints, simultaneously preventing the formation of new tophi and kidney stones, which to date is the only therapeutic approach to potentially modify the course of disease. Hyperuricemia is defined as blood uric acid levels above 6.8 mg/dL (≥ 360 μmol/L). Treatment with uricosuric agents such as probenecid or allopurinol is indicated to reduce these levels to a target of < 6 mg/dL, thereby preventing signs and symptoms of the disease. Recombinant uricase preparations are also under active development for the treatment of gout. However, immunogenicity

and safety continue to be sources of concern regarding these agents (1, 3, 5, 6).

The search for effective treatment strategies for gout continues, with research focusing on the identification of novel targets for drug development. Targets that are currently under active investigation are discussed below (see Fig. 1). Table I provides a selection of products under active development for each target and Table II includes selected patents.

TARGETS

Cyclooxygenase

Cyclooxygenase (COX; EC 1.14.99.1), also known as prostaglandin endoperoxide synthase, is an enzyme that catalyzes the two steps in prostaglandin (PG) synthesis, forming PG_2 and PGH_2 from arachidonic acid. The two major forms of the enzyme are COX-1 and COX-2. COX-3, a distinct COX-1 variant, and two smaller COX-1-derived proteins (partial COX-1 or PCOX-1 proteins) have also been cloned; COX-3 appears to be predominantly expressed in the cerebral cortex and heart and is selectively inhibited by NSAIDs, suggesting involvement of this isoform in pain and fever. COX-1 is constitutive and present in the endothelium, stomach and kidney. It is involved in the maintenance of platelet and kidney functions and considered a housekeeper enzyme, maintaining homeostasis. COX-2 is not present at baseline but is inducible during inflammation by cytokines and endotoxins. It has been shown to play a role in the propagation of inflammatory cascades, leading to disorders such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gout and gouty arthritis, among others. In gout, COX (COX-2 in particular) is involved in the acute granulocytic inflammation and inhibition of the COX subtypes may be effective in preventing the development and progression of these conditions, as well as for relieving associated pain and inflammation (7-10).

IL-1 receptor

The IL-1 receptor (IL-1R) is the cytokine receptor that binds members of the IL-1 superfamily IL-1α, IL-1β and the IL-1 receptor antagonist (IL-1RA). There are two identified subtypes, type I (CD121a) and type II

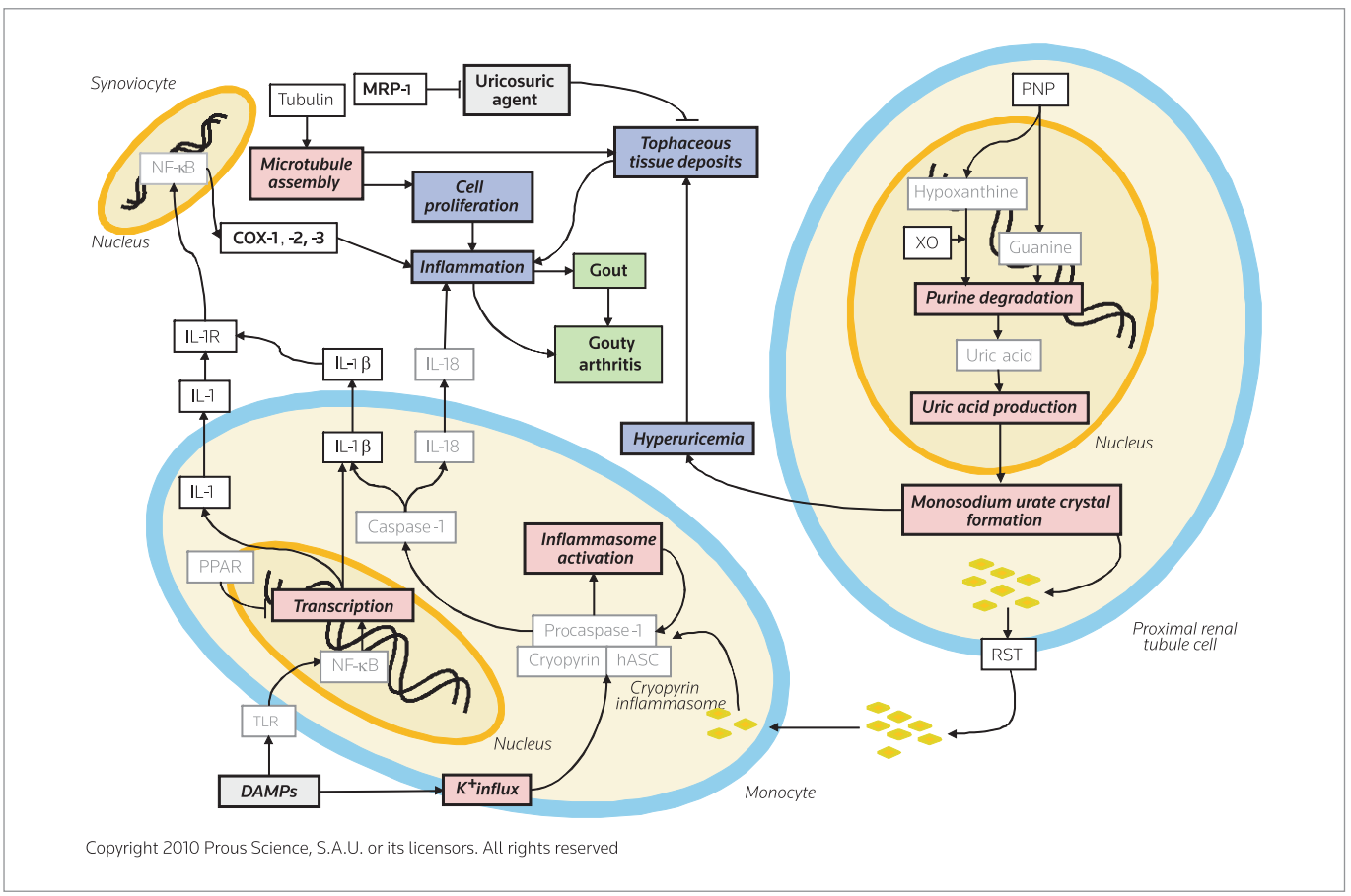

Figure 1. Gout targetscape. A diagram showing an overall cellular and molecular landscape or comprehensive network of connections among the current therapeutic targets for the treatment of gout and their biological actions. Gray or lighter symbols are targets that are not validated (i.e., targets not associated with a product that is currently under active development for gout). Abbreviations: hASC, apoptosis-associated speck-like protein containing a CARD; COX, cyclooxygenase; DAMPs, endogenous damage-associated molecular patterns; IL-1, interleukin-1; IL-1R, interleukin-1 receptor; MRP-1, multidrug resistance-associated protein 1; NF-κB: nuclear factor NF-κB; PNP, purine nucleoside phosphorylase; PPAR, peroxisome proliferator-activated receptor; RST, urate anion exchanger 1 (renal-specific transporter); TLR, Toll-like receptor; XO, xanthine oxidase.

Table I. *A selection of products under active development for each target (from Thomson Reuters Integrity℠).*

Target	Product	Source	Phase
Caspase-3	Celecoxib	Pfizer	III
COX-1	Diclofenac sodium	Novartis	L-1975
COX-2	Diclofenac sodium Celecoxib	Novartis Pfizer	L-1975 III
COX-3	Diclofenac sodium	Novartis	L-1975
IL-1	Rilonacept	Regeneron	III
IL-1β	Canakinumab XOMA-052	Novartis Xoma	III Preclinical
IL-1 receptor	Rilonacept APG-101.10	Regeneron Allostera	III Preclinical
MRP-1	Probenecid	Merck & Co.	L-1951
Purine nucleoside phosphorylase	DADMe-Immucillin-H	BioCryst	II
Tubulin	Colchicine	Mutual Pharmaceutical	L-2009
Urate anion exchanger 1	RDEA-594 RDEA-684	Ardea Biosciencees Ardea Biosciencees	II Preclinical
Xanthine oxidase	Febuxostat FYX-051	Teijin Pharma Fuji Yakuhin	Pre-reg II

(CD121b), that are involved in many cytokine-induced immune and inflammatory responses. Antagonism of these receptor subtypes may be effective in the treatment of inflammatory diseases such as gout and gouty arthritis (11-14).

Interleukin-1

Interleukin-1 (IL-1) is a soluble protein cytokine (17 kDa, 269 amino acids) that is a member of the IL-1 superfamily which includes IL-1α, IL-1β and the IL-1RA. IL-1α and IL-1β are proinflammatory cytokines that are involved in inflammatory and immune responses, while IL-1RA competes for receptor binding with these two isotypes, thus blocking inflammatory and/or immune activation. Both isotypes are secreted by monocytes, macrophages and/or accessory cells early during the immune response and they activate T and B cells, stimulate T-cell proliferation and enhance T- and B-cell responses to antigens. Overproduction of IL-1 has been implicated in several diseases, including gout and gouty arthritis. and inhibitors of this cytokine (particularly IL-1β) may be an effective treatment option for these disorders (11-14).

Multidrug resistance-associated protein 1

Multidrug resistance-associated protein 1 (MRP-1) is a member of the ATP-binding cassette subfamily C (CFTR/MRP). It is an integral membrane protein and is expressed in the blood, reproductive and respiratory organ systems of the body, where it transports organic anions and drugs from the cytoplasm and mediates ATP-dependent transport of glutathione and glutathione conjugates, leukotriene C_4 (LTC_4), estradiol-17β-*O*-glucuronide, methotrexate, antiviral drugs and other xenobiotics. It also confers resistance to anticancer drugs. The ATP-binding cassette (ABC) transporters are involved in a variety of physiological processes, such as lipid metabolism, ion homeostasis and immune functions, and they may be overexpressed in inflamed synovial tissue. Inhibition of MRP-1 may be effective in the treatment of various inflammatory conditions, including gout and gouty arthritis (15-17).

Purine nucleoside phosphorylase

Purine nucleoside phosphorylase (PNP; EC 2.4.2.1) is an enzyme involved in the purine salvage pathway, where it catalyzes the reaction between a purine nucleoside and orthophosphate to form a free purine plus ribose-5-phosphate. Thus, PNP metabolizes adenosine to adenine, inosine to hypoxanthine and guanosine to guanine; in the preceding step of the pathway, adenosine deaminase (ADA) metabolizes adenosine to inosine. Defects in the gene (*PNP*) encoding this enzyme account for ADA and PNP deficiency; both of these autosomal recessive disorders can lead to severe combined immunodeficiency (SCID). The enzyme deficiencies in these disorders cause accumulation of toxic metabolites, particularly in lymphocytes. In ADA and PNP deficiencies, accumulated toxic metabolites block T-cell development; B-cell and natural killer (NK) cell development are also blocked in the latter disorder. Moreover, deficiencies in PNP result in the degradation of hypoxanthine and guanine to uric acid, and the decrease in inositol monophosphate and guanosyl monophosphate leads to an increase in the conversion of 5-phosphoribosyl-1-pyrophosphate to 5-phosphoribosylamine. This further exacerbates uric acid overproduction and can result in hyperuricemia. PNP inhibitors may therefore be effective in blocking hyperuricemia which can lead to gout (18-20).

Table II. *Selected patents for targets being validated for gout (from Thomson Reuters Integrity℠).*

Target	Patent	Source	Phase
COX-1	WO 2005077896	Laboratorios del Dr. Esteve	Biological testing
COX-2	WO 2003014091	GlaxoSmithKline	Biological testing
	WO 2003029212	F. Hoffmann-La Roche	Biological testing/Preclinical
	WO 2003037330	Pfizer	Biological testing
	WO 2003037335	Pfizer	Biological testing
	WO 2003037336	Pfizer	Biological testing
	WO 2003037351	Pfizer	Biological testing
	WO 2005016924	GlaxoSmithKline	Biological testing
	WO 2005077896	Laboratorios del Dr. Esteve	Biological testing
IL-1β	US 2006128766	Leo Pharma	Biological testing
	WO 2003018535	Leo Pharma	Biological testing
Tubulin	WO 2007125197	Ipsen Pharma	Biological testing/Preclinical
Urate anion exchanger 1	WO 2007086504	Japan Tobacco	Biological testing
	WO 2008062740	Japan Tobacco	Biological testing
	WO 2009134995	Wellstat Therapeutics	Biological testing
	WO 2009145456	C&C Research Laboratories	Biological testing
Xanthine oxidase	JP 2000038389	Yamasa Shoyu	Biological testing
	JP 2002105067	Teijin	Biological testing
	JP 2008088107	Fuji Yakuhin	Biological testing
	WO 2003042185	Nippon Chemiphar	Biological testing
	WO 2003064410	Fuji Yakuhin Kogyo	Biological testing/Phase II
	WO 2004009563	Inotek Pharmaceuticals	Biological testing
	WO 2005121153	Nippon Chemiphar	Biological testing
	WO 2006022374	Astellas Pharma	Biological testing
	WO 2006022375	Astellas Pharma	Biological testing
	WO 2006028342	Biosynergen.	Preclinical
	WO 2006083687	Cardiome Pharma	Biological testing
	WO 2007043400	Kissei Pharmaceutical	Biological testing
	WO 2007043401	Kissei Pharmaceutical	Biological testing
	WO 2007043457	Astellas Pharma	Biological testing
	WO 2007004688	Nippon Chemiphar	Biological testing
	WO 2008072658	Nippon Zoki Pharmaceutical	Biological testing
	WO 2008126770	Astellas Pharma	Biological testing
	WO 2008126898	Kissei Pharmaceutical	Biological testing
	WO 2008126899	Kissei Pharmaceutical	Biological testing
	WO 2008126901	Kissei Pharmaceutical	Biological testing

Tubulin

Tubulins are cytoplasmic proteins that are divided into three classes: α, β and γ. The α- and β-tubulins form heterodimers that polymerize into cylindrical microtubule fibers that are found in almost all eukaryotic cell types and are involved in mitosis and motility. β-Tubulin binds GTP and hydrolyzes GTP to GDP. This process of hydrolysis is associated with tubulin polymerization and microtubule formation. α-Tubulin also binds GTP but does not possess GTP/GDP hydrolysis activity. However, α-tubulin can be modified by addition of a *C*-terminal tyrosine residue that affects polymerization rates. Disruption of microtubule formation and consequent arrest of the mitotic process is currently a successful anticancer strategy. Moreover, patients with arthritis and gout exhibit elevated levels of proinflammatory proteins (e.g., protein S100-A8/A9) in the synovial fluid. Studies have shown that monosodium urate monohydrate crystals induce the release of these proinflammatory proteins from neutrophils via a tubulin-associated pathway. Inhibition of tubulin polymerization may therefore be effective in the treatment of gout and gouty arthritis (3, 13, 21, 22).

Urate anion exchanger 1

The urate anion exchanger 1 (also known as the organic anion transporter 4-like protein and renal-specific transporter [RST]) is an antiporter located on the apical plasma membrane of proximal tubular cells and is required for efficient renal urate reabsorption. It is an electroneutral transporter that exchanges urate for intracellular anions (e.g., chloride ions). Mutations in the gene encoding urate anion exchanger 1 (*SLC22A12)* are responsible for renal hypouricemia, which is characterized by low serum urate levels due to defects in renal urate reabsorption and high urinary urate excretion. Intense alcohol use, dietary ketosis and prolonged anaerobic muscular activity promote renal urate reabsorption. On the other hand, certain other polymorphisms in *SLC22A12* impair renal uric acid excre-

tion, resulting in hyperuricemia in patients with primary gout. Inhibition of urate anion exchanger 1 could be an effective therapeutic strategy for the treatment of gout (23-25).

Xanthine oxidase

Xanthine oxidase (XO; EC 1.17.3.2) is an iron-molybdenum flavoprotein (FAD) and a key enzyme in purine degradation. XO catalyzes the oxidation of xanthine to uric acid and contributes to the generation of reactive oxygen species (ROS). It is irreversibly produced by proteolysis of xanthine dehydrogenase (EC 1.17.1.4) or reversibly generated through the oxidation of sulfhydryl groups. XO is implicated in joint inflammation (via generation of ROS) and inhibitors of this enzyme may therefore be effective in the treatment of ankylosing spondylitis, rheumatoid arthritis and gout. Inhibitors may also be effective in blocking uric acid production and may therefore be beneficial in the treatment of gout (7, 16, 26).

DISCLOSURES

The authors state no conflicts of interest.

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