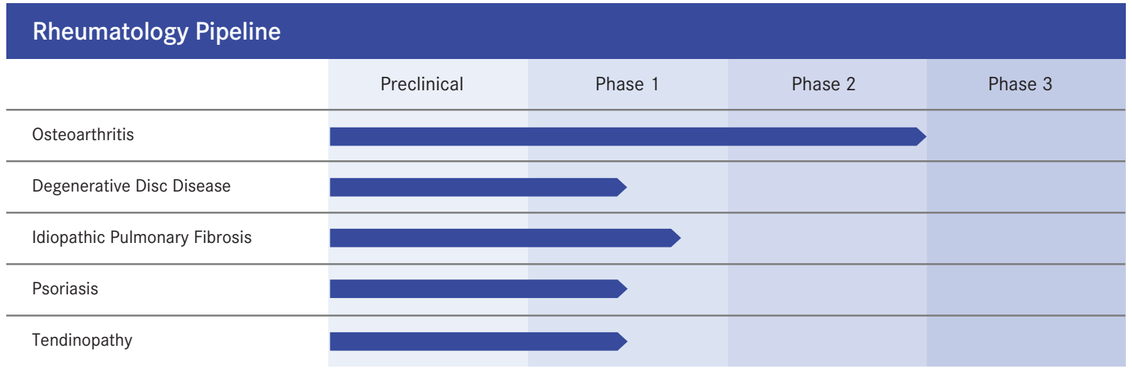
Rheumatology Pipeline



SAMUMED FACTS

- The company started operations in San Diego, CA, USA, in 2008 and has approximately 150 employees.
- The Wnt pathway is one of the primary signaling pathways regulating the renewal and differentiation of adult stem cells. The ability to modulate the Wnt pathway, and thereby potentially recover and restore the health of diseased tissues, presents an unprecedented opportunity in regenerative therapeutics.[1,2]
- Leveraging its core competence of modulating the Wnt pathway, in the span of four years, Samumed has taken seven different programs into clinical trials across a diverse set of disease areas: osteoarthritis, degenerative disc disease, idiopathic pulmonary fibrosis, psoriasis, tendinopathy, androgenetic alopecia, and oncology.
- Samumed continues to invest in preclinical research, expanding its technology platform while deepening its primary focus on the Wnt pathway and now has a broad pipeline of compounds in different stages of development.

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THE BURDEN OF OSTEOARTHRITIS (OA)

OA is the most common form of arthritis, affecting nearly 27 million Americans or 12% of the adult population of the United States.[1] This highly prevalent disease continues to increase in size and scope due to an aging population and rising rates of obesity.

- The risk of mobility disability (defined as needing help walking or climbing stairs) attributable to knee OA alone is greater than that attributable to any other medical condition in people aged 65 years and older.[2]
- OA is the leading indication for joint replacement surgery.[3]
- OA accounts for 6.3% of all years of life lost to disability in the US, ranking it third in the nation and making its disease burden larger than dementia and other degenerative and hereditary CNS disorders (5.0%), diabetes (3.3%), or HIV (1.7%).[4]

We at Samumed are dedicated to
finding innovative solutions for diseases like OA
through our understanding of Wnt pathway modulation.

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OSTEOARTHRITIS OF THE KNEE (OA)

Arthritis is the most common cause of disability among adults, and OA is the most common type of arthritis, accounting for much of this burden.[1] The global prevalence of symptomatic knee OA has been estimated to be 3.8% (4.8% for females and 2.8% for males).[2] According to a 2005 estimate, 9.3 million (4.9%) of US adults ages 26 and older had symptomatic knee OA.[1] The overall number of US adults affected by OA in any joint has increased during recent decades, from 21 million adults in 1995 to 27 million in 2005, primarily due to an aging population and an ever-increasing prevalence of obesity.[1] The combination of direct medical costs, pain and suffering, and loss of workplace productivity elevates OA to a major socioeconomic problem for health systems, the economy, and suffering patients.[3]

OA is characterized by the destruction of articular cartilage and structural changes in bone, which contribute to pain and loss of joint function.[4] The Wnt signaling pathway plays a central role in the processes that control whether resident stem cells in the joint become cartilage-forming cells (chondrocytes) or bone-forming cells (osteoblasts).[5,6] In OA joints, elevated Wnt activity has been shown to cause these stem cells to become osteoblasts instead of chondrocytes, and to cause the production of proteases that degrade cartilage.[7,8] Inhibition of Wnt signaling in OA joints may drive stem cells to become chondrocytes and block protease-mediated cartilage degradation, thus resulting in cartilage regeneration.[9] Therapies that target the Wnt pathway may therefore have potential in treating OA.

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DEGENERATIVE DISC DISEASE (DDD)

DDD is a condition characterized by age-related changes to the intervertebral discs, the gel-like cushions that separate vertebrae. Over time, these discs become less flexible and less able to cushion the spine. This can result in pain and stiffness in the neck and/or back, as well as pain that spreads to the back of the head, trunk, shoulders, arms, hands, legs, and feet.[1] DDD is a natural process of aging, and most people develop some degree of the condition over time. Pain and limited mobility associated with DDD is the most common physical impairment affecting otherwise healthy young and middle-aged adults.[2] It is estimated that as many as 80 percent of all adults experience back pain at some point during their lifetime, the chief cause of which is DDD.[2,3] Globally, back pain is the leading cause of disability with 651 million people affected worldwide.[4] The annual cost of back pain in the US is estimated to be as high as $500 billion.[5]

Recent studies have shown that the Wnt pathway may be involved in the disease processes of DDD. Elevated levels of β-catenin, a central component of the pathway, have been observed in discs of patients with DDD, indicating increased Wnt signaling.[6] This increase in Wnt signaling triggers the production of enzymes that break down the intervertebral extracellular matrix and promote disc degradation.[6] As shown by *in vitro* studies, Wnt signaling also inhibits the proliferation of nucleus pulposus cells, which reside in the disc and are responsible for providing cushioning to the joint.[7,8] These lines of evidence suggest that targeted inhibition of the Wnt pathway might preserve disc integrity and potentially lead to disc regeneration in patients with DDD.

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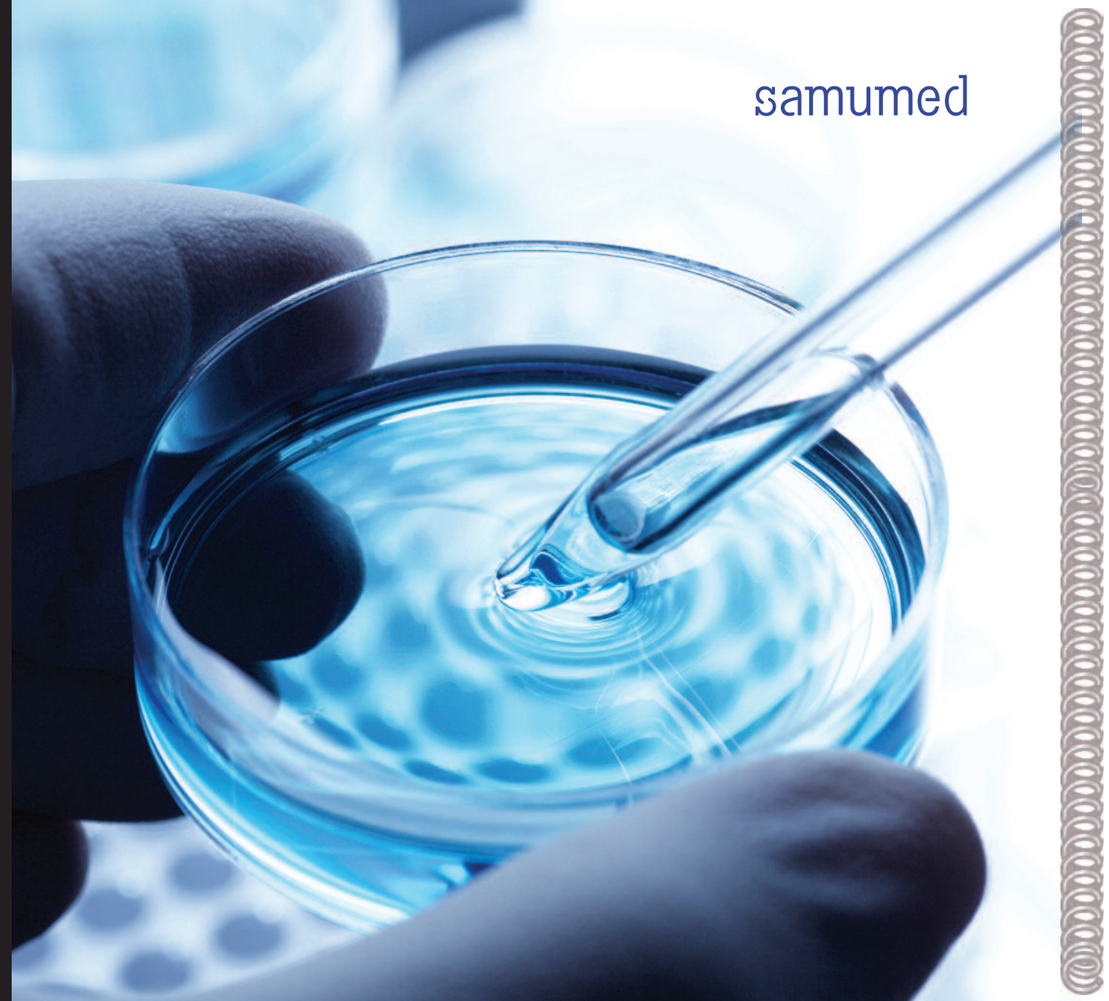

IDIOPATHIC PULMONARY FIBROSIS (IPF)

IPF is a chronic, progressive, fibrotic disorder of the lower respiratory tract that typically affects adults over the age of 40.[1] It is the most common interstitial lung disease seen by pulmonologists. In the US, the prevalence of IPF ranges from 13.2-27.9 per 100,000 for women and 20.2-63.0 per 100,000 for men.[1] As a result of progressive fibrosis, patients with IPF experience deteriorating lung function and severe dyspnea, which can take on a slow, rapid, or mixed clinical course that ultimately ends in death.[2] The median survival for patients is estimated to be between 2.5 and 3.5 years from diagnosis.[2] Several pulmonary and non-pulmonary comorbidities are associated with IPF, including emphysema, lung cancer, cardiovascular disease, gastroesophageal reflux disease, and depression.[3] Because age is a major risk factor and predictor of IPF, the disease prevalence is expected to rise with the aging population.[2] There is no cure for IPF and therapeutic options currently remain limited.[3]

The exact cause of IPF is not known, but it is thought to be the result of abnormal repair of alveolar injury.[2] Results from several studies suggest that the Wnt signaling pathway is involved in the processes that drive lung inflammation and fibrosis. Wnt signaling is essential for lung development, but in healthy adult lungs Wnt signaling is inactivated.[4] However, in the lungs of IPF patients, overexpression of Wnt proteins and activated Wnt signaling have been found in the alveolar epithelium and fibroblasts.[2,5] This activation of Wnt signaling may represent an abnormal reactivation of developmental stem cell pathways that lead to inappropriate tissue remodeling[2], and suggests that targeted inhibition of the Wnt pathway in the lungs of patients with IPF may have a therapeutic benefit.

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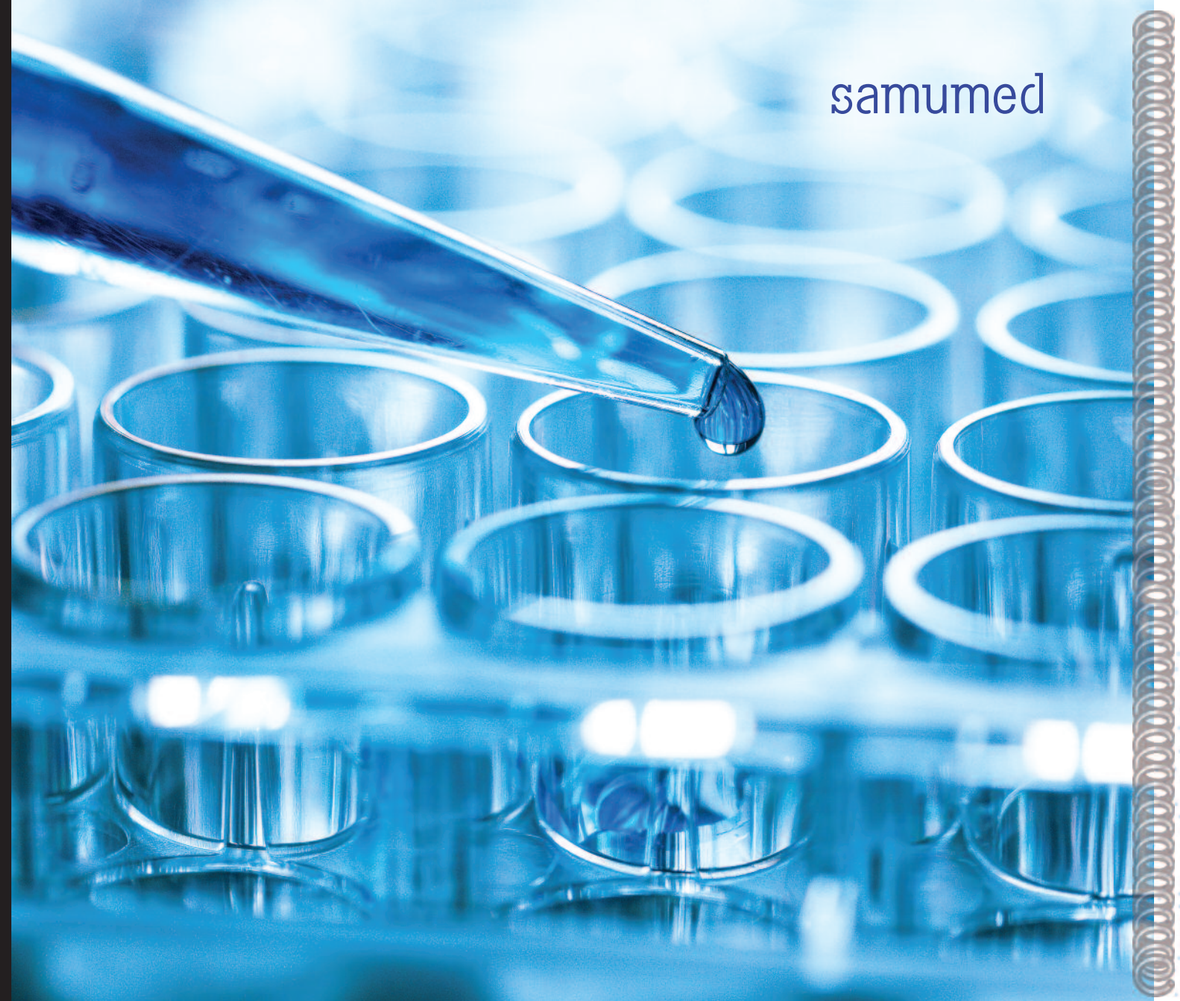

PSORIASIS (PSO)

PSO is the most common chronic, immune-mediated skin disorder, affecting up to approximately 3% of the US population, varying by family history, race, and geographic location.[1] Plaque psoriasis, the most prevalent type, is characterized by thickened epidermal layers resulting from the abnormal growth, differentiation, and apoptosis (cell death) of keratinocytes, producing raised, well-demarcated, erythematous, and frequently pruritic/painful plaques with silvery scales. In addition to the physical and psychological impact of disease, PSO is associated with specific comorbidities, including psoriatic arthritis, obesity, diabetes, cardiovascular disease, metabolic syndrome, and inflammatory bowel disease.[2] Current treatment is determined by disease severity, which is generally established by the body surface area involvement. While mild disease can be treated with topical therapy, moderate to severe disease frequently requires systemic medications, such as biologic agents.

The Wnt signaling pathway has been shown to play an essential role in the self-renewal and proliferation of keratinocytes.[3] Studies in patients with PSO have shown that Wnt protein expression is increased, and inhibitory proteins are decreased in biopsies of psoriatic lesions. This indicates that there is increased Wnt signaling and a reduction of intrinsic factors that moderate Wnt signaling involved in the disease process.[4,5] Results from a recent study using samples from psoriatic lesions suggested that inhibition of a Wnt protein lead to a reduction in keratinocyte proliferation and induced apoptosis.[6] These lines of evidence suggest that targeted Wnt inhibition is a potential therapeutic option for patients with plaque psoriasis.

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TENDINOPATHY (TEN)

TEN is the clinical diagnosis of pain, swelling, and impaired performance of the tendon, the tissue that connects muscle to bone.[1,2] TEN can encompass both inflammation of the tendon (tendinitis) and degeneration of the tendon (tendinosis). Epicondylitis, or pain in the wrist extensor tendons in the elbow, affects 1-3% of the population, with 10% of cases refractory at 6 months progressing to surgery.[3] The Achilles tendon at the ankle and the patellar tendon of the knee are also frequently affected.[2]

The Wnt pathway may play a role in the disease process of TEN. In human studies and animal models of the disease, overexpression of Wnt proteins has been demonstrated.[4,5] The Wnt pathway is involved in the processes that determine if mesenchymal stem cells become tendon cells. Activated Wnt signaling has been shown to direct tendon-derived stem cells away from a tendon cell fate.[4] Additionally, activated Wnt signaling may lead to increased production of degradative proteases that contribute to the breakdown of tendon tissue.[5] Inhibition of the Wnt pathway is a potential therapeutic target for the treatment of TEN.

Long-term vision pursued with principles

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