

Research

Key Issues in the 2003–2005 Medium-term Management Plan

- Emphasize promising research themes in allocating resources
- Strengthen drug discovery in the field of ophthalmology
- Seek alliances to maximize the potential of rheumatoid arthritis and osteoarthritis treatments



Santen's research staff combines a variety of compounds to synthesize compounds with novel mechanisms of action.

Concentrating Resources on R&D Themes that Allow Santen to Display Its Strengths

Santen strives to create pharmaceuticals that will address unmet medical needs and contribute to enhanced quality of life of patients by making full use of its expertise in ophthalmology and rheumatism/osteoarthritis.

The key strategies to achieve this goal include:

- 1) Determine unmet needs and understand research and development trends among competitors in order to concentrate resources on themes that will allow us to display our strengths;
- 2) Emphasize prescription ophthalmics, both discovered in-house and in-licensed, to strengthen our product pipeline with therapeutically superior new products;
- 3) Out-license or form strategic alliances for our rheumatoid arthritis and osteoarthritis drug candidates to maximize their potential; and
- 4) Maintain our competitive advantages by accelerating research and development.

We will determine our research themes by evaluating the anticipated future needs in ophthalmology and rheumatism/osteoarthritis over the next ten to fifteen year time frame and prioritize resources on areas with unmet needs and good business potential.

In the field of rheumatism/osteoarthritis, we have already narrowed our focus to three promising themes. Our prior investments in ophthalmic research have yielded numerous results; we have set milestones for each research theme and will continue to focus our efforts on those with the most promise.

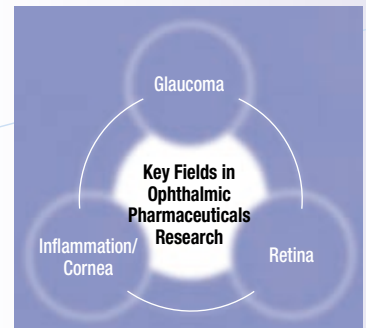
Enhancing Ophthalmic Discovery Research

In the past, Santen's research efforts focused on developing ophthalmic formulations of systemic drugs. In recent years, however, in-licensing of compounds from other companies has become difficult. We believe that technological innovation is needed to attain future growth. Strengthening our ability to create innovative ophthalmic pharmaceuticals is therefore one of the most important tasks in the 2003-2005 Medium-term Management Plan.

We will leverage the know-how we have acquired through our research on rheumatoid arthritis treatment to strengthen our in-house ophthalmic discovery research. Rheumatoid

arthritis shares common etiological and pathological symptoms, such as angiogenesis, inflammation and edema, with retinal and other diseases in the posterior segment of the eye. By focusing on these common symptoms, we will establish novel, efficient drug discovery techniques to create innovative ophthalmic pharmaceuticals.

In November 2002, we completed an expansion of the Nara Research and Development Center and integrated the research functions of ophthalmology and rheumatism there. We expect this move to stimulate research into themes shared by ophthalmology and rheumatism.



Focus on Next-generation Treatments for Glaucoma and Retinal Disorders

Unmet needs in ophthalmologic diseases have shifted from the anterior segment (cornea and conjunctiva) to the posterior segment (retina and optic nerve).

Glaucoma is a progressive optic neuropathy that causes optic disc and nerve fiber layer damage, usually associated with loss of visual function. Intraocular pressure¹ is the most important risk factor for the disease, although a significant proportion of patients do not have elevated intraocular pressure. Today, glaucoma treatment is the largest segment of the global ophthalmics market. An aging population and advances in diagnostic technology indicate that the number of glaucoma patients will continue to increase. We see glaucoma treatment as a field with great market potential, both now and in the future, and we are increasing research on glaucoma treatments such as those that reduce intraocular pressure with novel action mechanisms. Research efforts to date have added three new glaucoma drug candidates to our product pipeline.

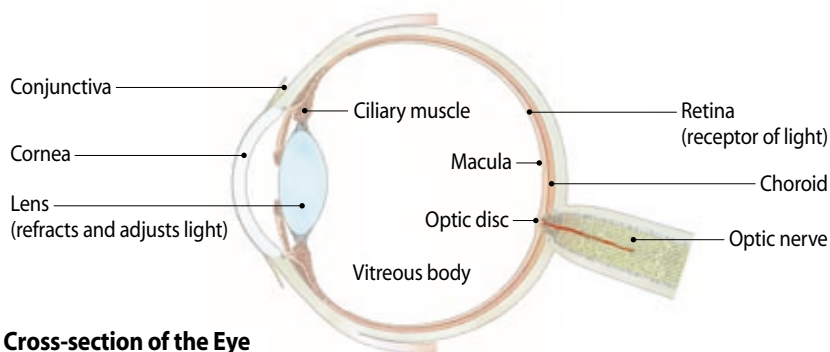
The number of patients suffering from retinal disorders such as age-related macular degeneration² and diabetic retinopathy³ is also increasing as the population ages. These disorders are accompanied by angiogenesis from the choroid and retina as they progress. We are conducting research on new drugs by applying our knowledge of angiogenesis suppression

Notes

1. Intraocular pressure: The pressure retained within the eye. The eye must keep an adequate degree of turgidity in order for us to see objects. Secretion and excretion of aqueous humor through ciliary bodies control the balance of intraocular pressure.
2. Age-related macular degeneration: A disease caused by age-induced disorders in the macula, which is a component of the retina essential for seeing objects.
3. Diabetic retinopathy: A complication of diabetes in which defects in the capillaries of the retina damage the retina. Diabetic retinopathy can lead to bleeding in the back of the eye and detachment of the retina, and is the primary cause of vision loss.

The Mechanism of Vision

Our eyes allow us to see by receiving light reflected off objects. The eye is constructed much like a camera. External light passes through the cornea and then refracts through the lens of the eye, which is like the lens of a camera, onto the retina. The retina is similar to the film in a camera because it registers an image of the object. The optic nerve transmits the image to the brain, which perceives what the object is.



Cross-section of the Eye



The Nara Research and Development Center, which was expanded to twice its previous size in 2002, features a unique "free address" system that allows researchers to select seats according to the needs of their jobs.

obtained through research into rheumatoid arthritis. Moreover, we have also developed our own drug delivery system (DDS) technologies for the efficient delivery and sustained release of active ingredients to affected areas in the posterior segment, and are now examining the possibility of applying these technologies to actual drug production. Presently, there are almost no effective treatments for retinal diseases, and therefore the development of a breakthrough, next-generation treatment will be extremely significant.

We are also conducting research on allergies, dry eye and other diseases of the surface of the eye, with a particular focus on patients with severe conditions that current treatments cannot cure. At the same time, with the aim of further improving the quality of life of patients, we have developed innovative DDS technologies that reduce administration time, increase absorption and alleviate discomfort when administering eye drops.

Unique Compounds Being Developed for Rheumatoid Arthritis

Rheumatoid arthritis causes inflammation in the knees, elbows and other joints, gradually breaking down bone and cartilage until it eventually deforms the joints. People who suffer from this disease bear excruciating pain, and no treatment that addresses the underlying cause of rheumatoid arthritis has yet been discovered because little is known about its mechanisms. In recent years, work has gained momentum on the development of a new type of treatment called TNF inhibitors. These new drugs block the activity of tumor necrosis factor (TNF), a type of endogenous protein called a cytokine⁴ that is associated with immune reaction and joint degeneration. This development is expected to significantly improve the quality of life of patients.

We have narrowed our target in rheumatoid arthritis research to focus on stopping the degeneration of bones and cartilage by suppressing cytokine secretion or regulating the proliferation of synovial cells. Research in this area has already led to the discovery of DE-096, an oral TNF inhibitor, and DE-098, an anti-APO-1 antibody.

The majority of other TNF inhibitors, either already on the market or in the late development stage, are injectable biological agents. However, DE-096, discovered by Santen, is a compound with a low molecular weight that can be administered orally. Basic research has demonstrated effectiveness against rheumatoid arthritis comparable to injectable biological agents. Once we develop a commercially viable formulation of DE-096, patients will no longer have to visit medical centers for their scheduled injections. Moreover, DE-096 will involve lower manufacturing costs, which will lighten the financial burden on patients.

One pathological condition of rheumatoid arthritis is the excessive proliferation of synovial cells, which causes bone and cartilage degeneration. The injectable anti-APO-1 antibody, DE-098, induces apoptosis (death) of synovial cells within damaged joints. We have already established a pilot manufacturing process for DE-098.

The launch of TNF inhibitors and other new treatments for rheumatoid arthritis is likely to make this field more competitive in the near future. Rather than limiting our scope for new drug development to rheumatoid arthritis, we are exploring a broad array of target markets covering all facets of bone and joint disease. To make the best use of our management resources, we will seek joint development, marketing alliances or out-licensing for our candidate compounds in these fields to maximize their potential.

Note

4. Cytokine: A type of protein with low molecular weight secreted by various kinds of cells. Cytokines involved in the pathogenesis of rheumatoid arthritis regulate the extent and length of immune reaction and mediate the exchange of information among cells. Tumor necrosis factor (TNF) is a type of cytokine.