Santen's Global R&D

2021

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Santen's Global R&D Network

Addressing global unmet medical needs by networking around the world

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CONTENTS

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Patient Focused R&D

We put people at the center of working towards living happy lives through vision. By starting In Service of Patients as our innovative pilot program, we seek out ways to understand the patient and caregiver experience, utilizing every opportunity to learn from, and listen to, them. Our project is a holistically designed, top-down, bottom-up approach to adopt a People Centric behavior and transform the culture of Santen.

Global R&D has implemented a dynamic approach to change management through participating in roundtable discussions, learning modules, and guiding principles. We are working to actively transform Santen's approach to prioritizing patient and caregiver insights in early development, clinical trials, and late-stage global R&D activities. As we establish an innovative framework within global R&D, that knowledge will ultimately be used to train all employees on how to collect meaningful patient and caregiver insights from their community, further strengthening the development of People Centricity at Santen. Our ultimate goal is to make lives easier by delivering the right products to the right people in a more efficient manner.

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Message from the Head of Ophthalmology Innovation Center

For the innovation in ophthalmology we are facing many challenges and opportunities. However, I am confident that we can get over these, because Santen is the global leader in ophthalmology and its long history of addressing the entire spectrum of patient needs. Our wealth of experience, our visionary leadership, our unparalleled skillset and our extraordinary vision make Santen uniquely qualified to shepherd new technologies through to approval across the globe. And we are confident that we will achieve that as a specialty company in ophthalmology that has been polishing for 130 years.

Santen works with various partners in seeking to enable that change in patient management based on our therapeutic area strategy, and will continue to do so across the entire spectrum of patient needs. Patients deserve better, and we should be at the forefront of the conversation about delivering relevant and meaningful benefits to our community.

In addition, Santen has built strong relationships with academia around the world as a result of the global expansion promoted under Vision 2020. Based on the strong partnerships, we are conducting aggressive discussions everyday with Singapore Eye Research Institute, University College London, and many other universities and specialists, as well as startup companies about cutting-edge treatment technologies such as gene therapy and cell therapy, and new therapeutic modalities around the globe. Under the COVID-19 pandemic we are accelerating these discussions without borders by working remotely.

We are also focusing on technologies which exceed current conventional pharmacotherapy. We will achieve innovation in ophthalmology through an open innovation in which we combine the strengths of Santen with those of other companies.

By doing so, we will contribute to Happiness with Vision for patients worldwide through the Best Vision Experience.

Reza Haque, MD, Ph.D.

Head of Ophthalmology Innovation Center

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Early Pipelines: Front of the Eye

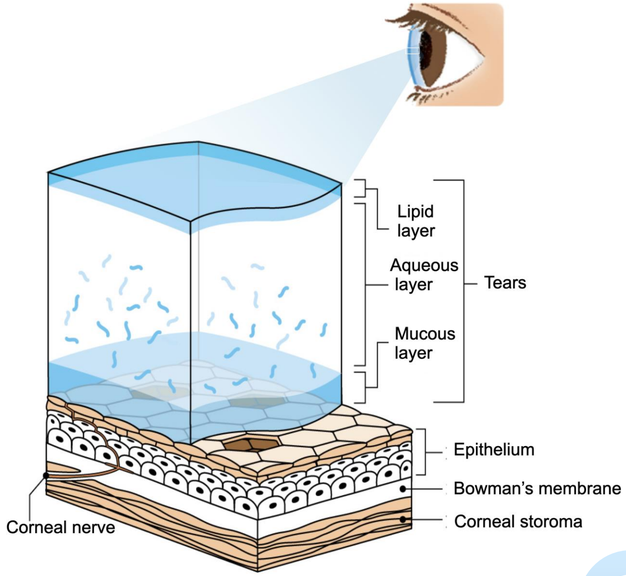
In the Ocular Surface & Anterior Segment Therapeutic Area, Santen is working on unmet medical needs in corneal & conjunctival diseases and refractive disorders. Dry Eye and Myopia are described below.

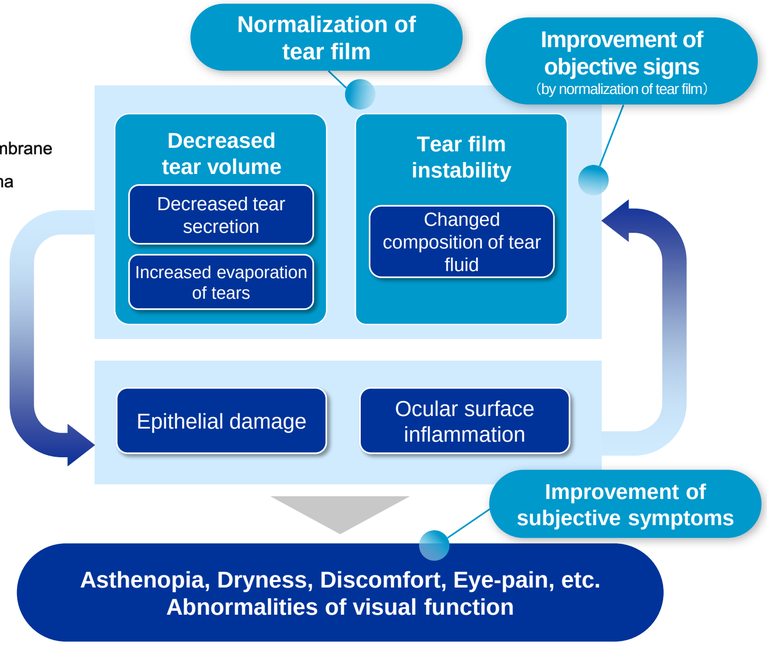
Dry eye

Dry eye is one of the most common eye diseases that can cause dryness, eye fatigue, severe sensations, cornea and conjunctiva damage. Further progression of dry eye may result in blurred vision, poor vision, and other abnormalities in vision. This disease decreases work productivity and quality of life significantly. The number of dry eye patients is on the rise with the aging population and the increasing use of digital devices.

Dry eye is a multifactorial disease and development of the disease is largely related to tear film instability and inflammation. The tear film is as thin as 7 micro meters and composed of a lipid layer, an aqueous layer and a mucous layer. Several factors such as aging, autoimmune diseases, air conditioning, long time use of digital devices may lead to imbalance of the tear film layers and may cause inflammation on the ocular surface resulting in a vicious circle.

Santen provides treatments for all of the three tear film layers and inflammation. We are working on next generation products to enhance tear fluid secretion and to normalize increased evaporation for tear film stabilization. We are also working on new mechanisms of action for inflammation and nerve dysfunction to relieve subjective symptoms.





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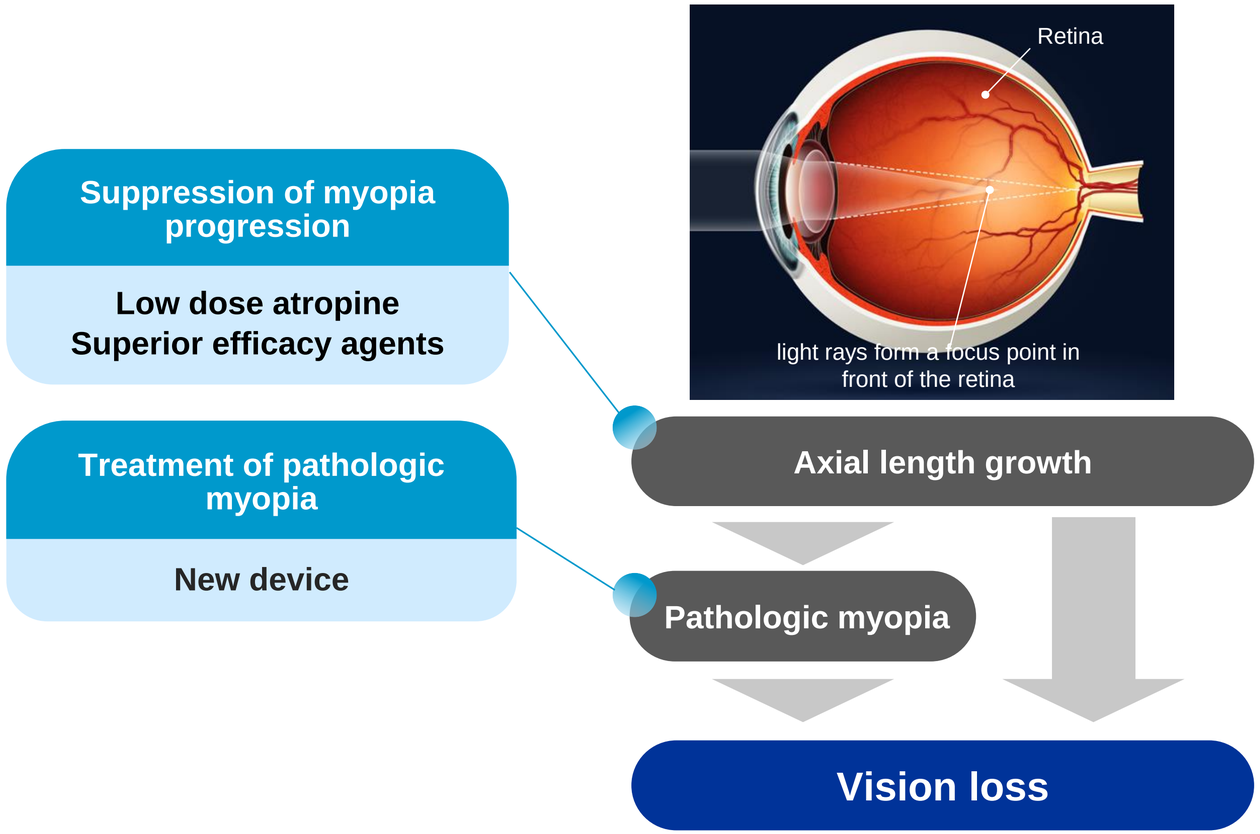
Early Pipelines: Front of the Eye

Myopia

Myopia denotes a vision condition where unadjusted incoming light focuses in on the front of the retina. This condition is thought to be mainly caused by the extension of the eyeball from the front to the rear. Prevalence of myopia is increasing and expected to reach 50% worldwide in 2050. The prevalence is especially high in Asian countries dues to genetic and environmental reasons. People may think that myopia can be corrected with eye glasses, contact lens etc. and may not feel the needs for further treatments, however advanced myopia increases the risk of pathologic myopia that can lead to vision loss.

Low-dose atropine has been reported to reduce progression of myopia in children and used off-label. Our goal is to launch STN1012700 (low-dose atropine) in the most fastest possible way. Santen is also working on a second generation anti-myopia drug to achieve superior efficacy over the low-dose atropine as well as a new device to find a cure for pathologic myopia.



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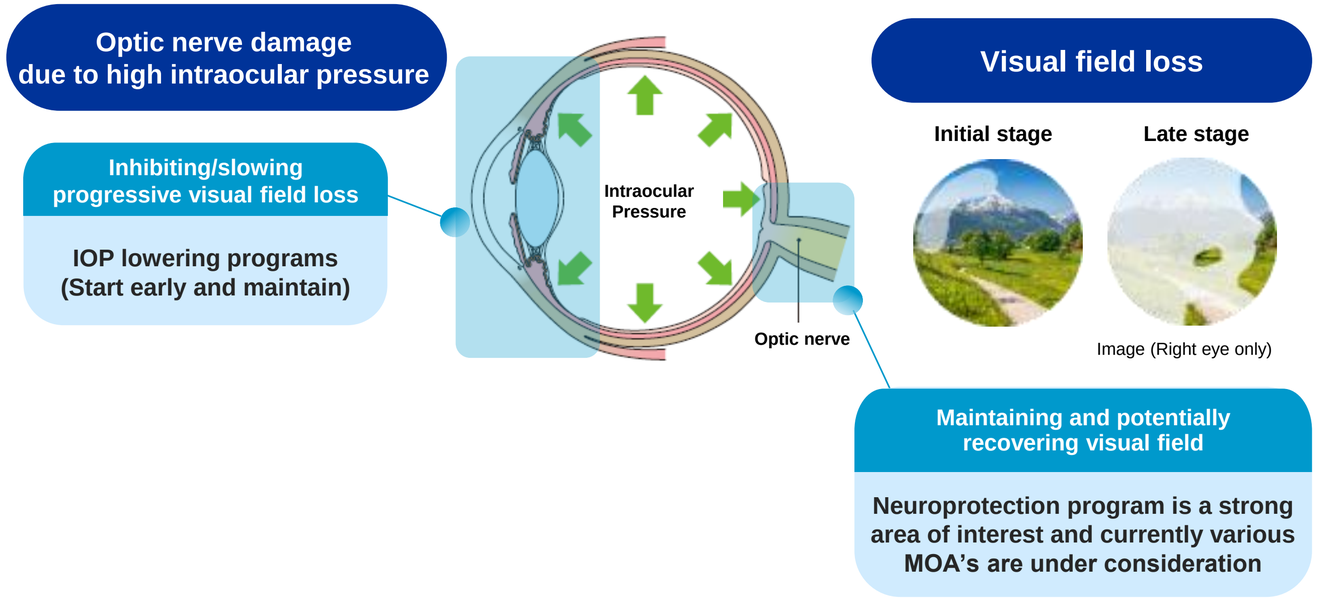
Early Pipelines:
Glaucoma & Neuroprotection

Glaucoma is a group of conditions in which there is progressive irreversible loss of the visual field which can lead to blindness. It is the second leading cause of blindness worldwide after cataracts. Damage occurs to the retinal ganglion cells and to the optic nerve that transmits visual information to the brain, thereby gradually diminishing the visual field. Elevated intraocular pressure (IOP) is the main modifiable risk factor of optic nerve damage, and reducing IOP is considered to be the most effective treatment for preserving visual function. The treatment usually must be continued throughout the remainder of life.

We are developing a variety of products to help eliminate anxiety and burden to patients, so that we can provide treatments for every stage of their glaucoma progression. Santen produces several IOP-lowering drugs, including the first-line drug "FP agonist" Tapros. Also produced is the “EP2 agonist” Eybelis ophthalmic solution which has a novel mechanism of action as well as a differentiated side-effect profile. Furthermore, STN1012600 (Sepetaprost), an FP/EP3 dual agonist ocular hypotensive agent with a novel combination of mechanisms of action is currently under development. STN1012600 has an exploratory clinical study under consideration for FY2021 to further elucidate a differentiated profile from what is currently available to patients.

For patients with primary open angle glaucoma where IOP is uncontrolled, despite maximally tolerated medical therapy, or where the progression of the disease warrants surgery, Santen is also developing STN2000100 (PRESERFLO MicroShunt), a novel, minimally-invasive, ab-externo surgical device.
Also as part of the company’s patient-centric focus, Santen continues to evolve the eyedrop administration systems to be more user-friendly and address areas of unmet need.



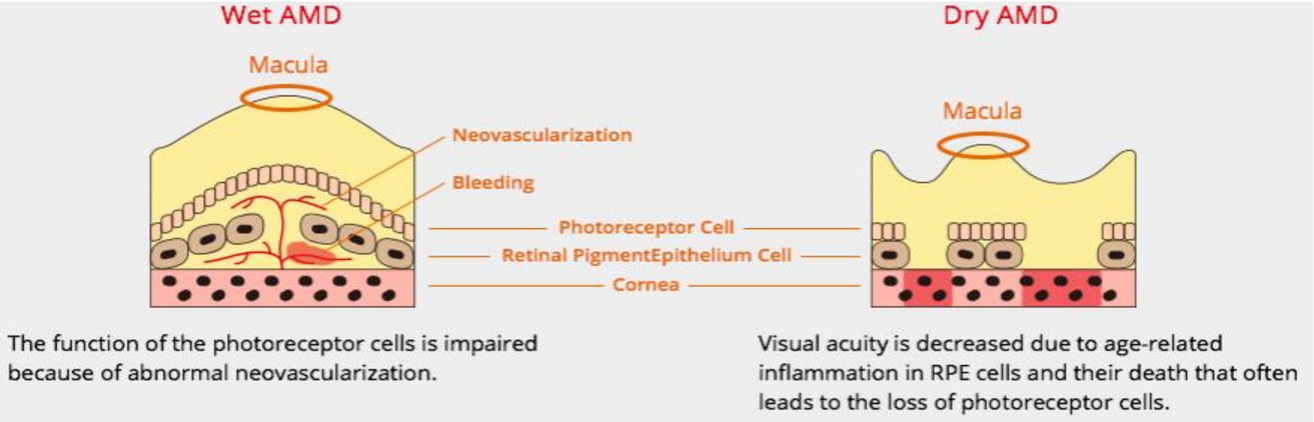
Early Pipelines: Back of the Eye

In the Retina and Vitreous Therapeutic Area, Santen is working on addressing unmet medical need, as well as working to improve on the current standard of care. Wet Age-related Macular Degeneration and Inherited Retina Diseases are two of many retina diseases that Santen is working on.

Wet Age-related Macular Degeneration (wet AMD)

AMD is a slowly progressing disease that accounts for one of the main causes of irreversible blindness in developed nations. The most acute, vision-threatening form of AMD is the exudative (wet) type. Wet AMD is characterized by the formation of subretinal choroidal neovascularization, leading to sudden and severe visual loss. Research has identified vascular endothelial growth factor (VEGF) as an important pathophysiological component in neovascular AMD and its intraocular inhibition as one of the most effective therapies for treating the disease. The introduction of anti-VEGF as a standard treatment in wet AMD has led to a great improvement in the prognosis of patients, allowing recovery and maintenance of visual function in most cases. However, the therapeutic benefit of anti-VEGF therapy is accompanied by a difficulty in maintaining the treatment schedule, addressing patients that do not respond well to therapy, as well as the associated economic burden.

Santen is advancing the development of novel therapeutics to address unmet need in wet AMD and should be entering the clinical stage for these programs in the near future.



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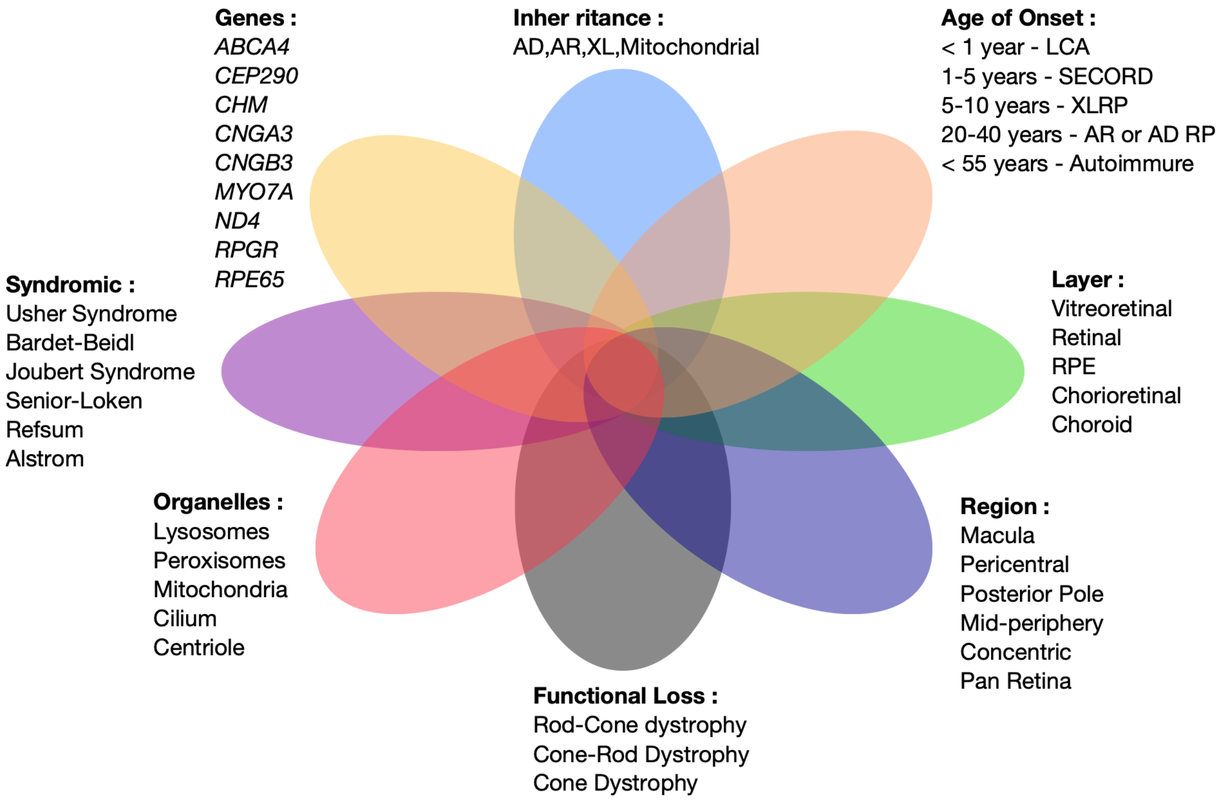
Early Pipelines: Back of the Eye

Inherited Retinal Diseases (IRDs)

Inherited retinal diseases (also called inherited retinal dystrophies) are a group of rare eye disorders that are caused by an inherited gene mutation. Although IRDs encompass several diseases, such as retinitis pigmentosa and Leber congenital amaurosis, in most cases they share a common end result of progressive photoreceptor death leading to vision loss and blindness. Over 250 genes have been implicated in causing IRDs and genetic testing is becoming the standard of care for these patients. The identification of these causative genes, gene-based classification, and the clinical description of the diseases they cause has changed the way IRDs are treated. Importantly, for a little more than a decade, retinal gene therapy has brought the possibility of treating these previously untreatable diseases closer to reality.

Santen has solidified its commitment to fighting blindness caused by IRDs by entering into a licensing agreement with jCyte for their first-in-class investigational therapy currently in clinical development for retinitis pigmentosa, as well as other internal programs designed to address the vast unmet needs in the IRD space.

The Spectrum of Inherited Retinal Disease



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External Collaboration

Santen R&D seeks, evaluates, triages and recommends early-stage scientifically validated opportunities in small molecules, peptides, antibodies, cells, devices, combination products, diagnostics/biomarkers and platform technologies to enrich Santen R&D and future product pipeline. This is accomplished by establishing and maintaining long term robust alliances, partnerships and collaborations with companies and high caliber universities and research institutions, including research Foundations. We also enhance Santen's global visibility by key presentations at conferences and by organizing targeted symposia, seminars, think-tanks and workshops on a worldwide basis. Examples of partnerships include those with Boehringer Ingelheim, PeptiDream, and jCyte through which we are addressing drug discovery/development for treatment of eye diseases. We established a multi-year research collaboration with the Singapore Eye Research Institute (SERI), a top Asian ophthalmology Institute, including a joint fully functional research laboratory. The myopia drug candidate STN1012700 (low-dose atropine) resulted from this collaboration and has entered clinical trials. Many other diseases are being addressed through this collaboration with SERI.

Likewise, Santen R&D has signed a joint research collaboration with Harvard University and University of Ulster (Northern Ireland) in drug candidate research for glaucoma treatment using a novel technology to aid neuroprotection. Many other strategic alliances and research collaborations are also under way in Europe, for example at University College London Institute of Ophthalmology, where we are managing and supporting long term PhD Studentship programs and establishing long term research collaborations with world renowned ophthalmology experts working in many diverse fields. One key area of interest is in the development of surrogate end-point biomarkers for glaucoma.

Efficient Product Development with Partners

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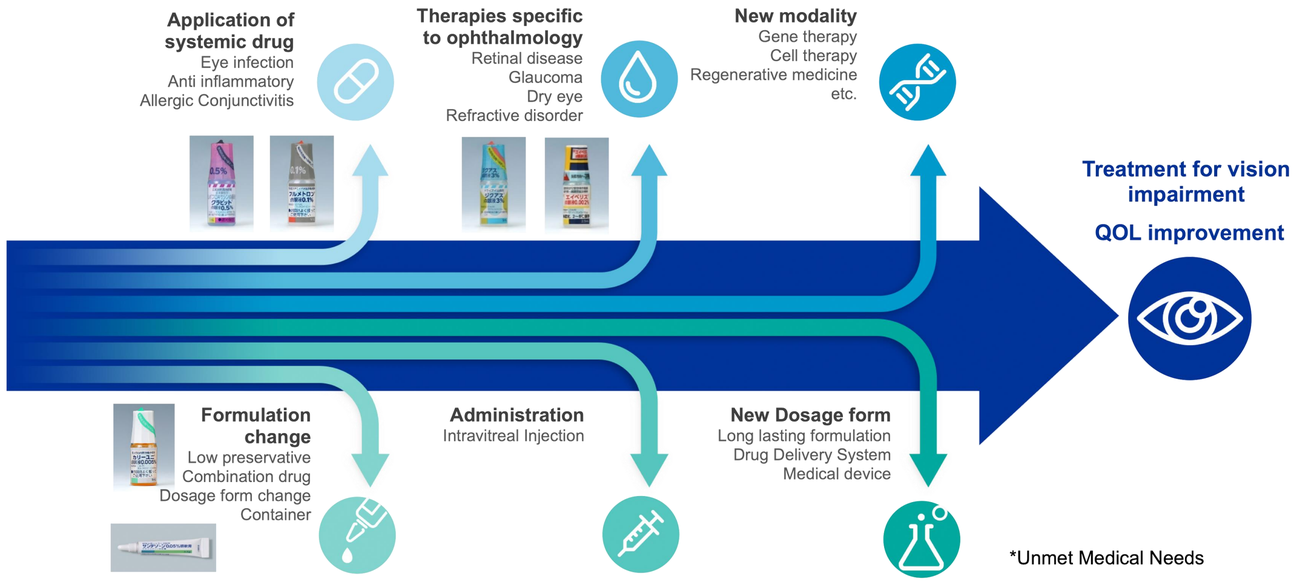
Modality Innovation

In the field of ophthalmology, the first approach was the application of systemic drugs to ophthalmology. Ophthalmic treatments are based on ophthalmic solutions.

We have been continually improving quality of life, including improving the usability, by reducing preservatives, developing preservative-free formulations, developing combination formulations, changing dosage forms, and developing easy-to-use ophthalmic containers. In addition, ophthalmology-specific therapeutic agents have been developed such as Diquas for dry eye and Eybelis for glaucoma.

We are continuing to address retinal diseases, glaucoma, dry eye, and refractive disorders in order to launch first drug in the world. Intravitreal injections have also emerged as a treatment for the retina back of the eye. In the future, innovative therapies with new modalities such as new innovative biologics, and regenerative medicine that includes cell and gene therapy are expected, and new therapeutic agents are expected to be incorporated into better therapies by utilizing long lasting formulations, drug delivery systems, and medical devices as pharmaceutical technology. We work closely with highly talented personnel across Santen to identify and develop best in class modality.

Bring Out Joy “to be Able to See” by Fulfilling UMNs*



*Unmet Medical Needs

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Message from the Head of Product Development Division

One of the key focus areas of Santen is to transform ourselves to be the leading entity of people and patient centricity. I believe that at the end of the day our task is to help guide patients by providing all the needed information and insights related to eye diseases and treatments. In order to achieve that, as a first step we in Product Development Division (PDD) think we need to build a method for patients to feel value and ownership not only after delivering the final product to them, but during clinical trials. We think it is important to build a system that allows easier entry and participation in clinical trials without having to go and see the investigator to complete an Informed Consent or needing to go to the hospital for a simple blood draw for successful development of the candidates from proof of concept (POC) onwards. By utilizing digital technology at all levels, we believe we can create a system that allows greater ownership and participation from the start. Improving the environment in which patients can easily participate will improve the success rate of our clinical trials.

As we have already seen with the recent impact of COVID-19, the shift towards remote clinical trials has begun. The digitalization of clinical trials is therefore expected to accelerate in the future. As in real life, having everything at your fingertips will become standard for clinical trials. The other point we wish to mention briefly is new end point settings. By searching for new biomarkers and incorporating the technology of imaging functional and structural changes in the eye as part of end points evaluations, we aim to accelerate and develop products to meet the needs of patients as soon as possible. Such kind of technics will be utilized across PDD including Medical Affairs. We are on a quest to re-envision ophthalmology development, all with the aim of helping our patients have a happy life through improved vision.

Peter Sallstig, MD, MBA
Corporate Officer
Head of Product Development Division

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Upcoming Pipelines

	Code	Indication	Region	Status
Omidenepag isopropyl **EYBELIS**	**STN1011700**	Glaucoma / ocular hypertension	US	Filed Plan: FY2021 approval
			Japan	Launched
			Asia	Launched in February 2021 in Korea
Sepetaprost	**STN1012600**	Glaucoma / ocular hypertension	US	P2 Plan: FY2022 additional P2 completion
			Japan	P2b (dose finding study completed)
Glaucoma implant device **PRESERFLO MicroShunt**	**STN2000100**	Glaucoma	US	Completed PMA rolling submission Discussion with FDA on-going Plan: under consideration
			Japan	Plan: FY2021 filing
			Europe	Launched
			Asia	Filed Plan: FY2021 approval
			Others	Apptoved in March 2021 in Canada Plan: FY2021 Launch
Netarsudil dimesylate **Rhopressa**	**STN1013900** AR-13324	Glaucoma / ocular hypertension	Japan	Started P3 in November 2020 Plan: FY2023 P3 completion
Atropine sulfate	**STN1012700**	Myopia	Japan	P2/3 Plan: FY2023 P2/3 completion
			China	Plan: FY2021 P1 start
			Asia	P2 (met primary endpoin)
AFDX0250BS	**STN1013400**	Myopia	Japan	Plan: FY2021 P1 start
Diquafosol sodium (long-lasting) **Diquas**	**STN1008903**	Dry eye	Japan	P3 (met primary endpoint) Plan: FY2021 filing
Sirolimus (intravitreous injection)	**STN1010900**	Uveitis	US	P3 Plan: FY2022 P3 completion
			Japan	P3
			Europe	P3
			Asia	Filed

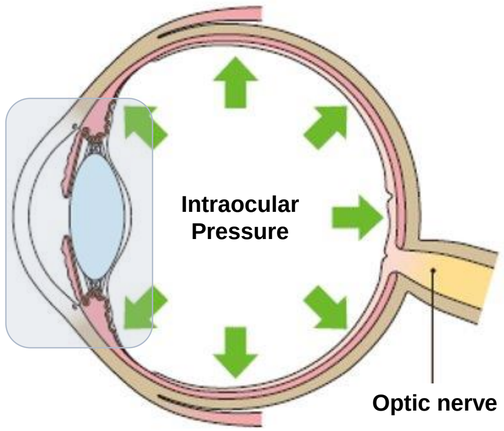
	Code	Indication	Region	Status
Tafluprost / timolol maleate (combination) **TAPCOM / TAPTIQOM**	**STN1011101**	Glaucoma / ocular hypertension	China	P3 Plan: FY2023 P3 completion
Latanoprost	**STN1013001** Catioprost	Glaucoma / ocular hypertension	Europe	P3 Plan: FY2021 P3 completion
			Asia	
Intraocular lens **Lentis Comfort**	**MD-16**	Cataract	Japan	Launched in November 2020

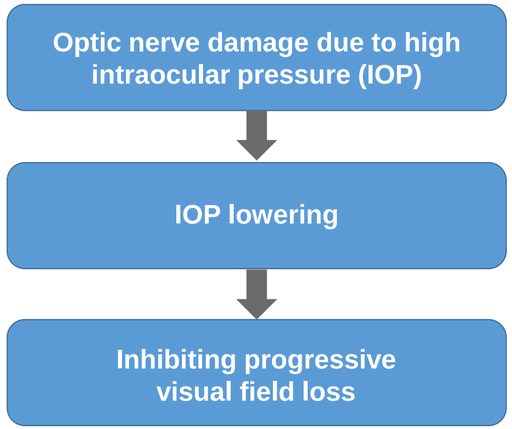
- STN1013800 (RVL-1201); The company is planning to start clinical trials for blepharoptosis in FY2021 in Japan and also considering the filing in Asia with data used for US approval. Licensing region / Japan, China, Asia and Europe
- STN6000100 (jCell); The company is planning to start clinical trials for retinitis pigmentosa in FY2021. Licensing region / Japan, China, Asia and Europe

STN1012600

Glaucoma is a disease in which the optic nerve that transmits visual information to the brain is damaged, thereby gradually diminishing the visual field. Elevated IOP is believed to be the main cause of optic nerve damage, and reducing IOP is considered to be the most effective treatment for preserving visual function.

STN1012600 (sepetaprost) is an ocular hypotensive FP/EP3 agonist, a new mechanism of action. An additional Phase 2 study in US has been started after December 2020, in parallel with the preparation for Phase 3 studies. In this Phase 2 study, the STN1012600 differentiated profile from the existing drug will be looked for.





STN1012700

STN1012700 is a proprietary novel ophthalmic formulation of low-dose atropine, developed jointly by Santen and Singapore Eye Research Institute. We started developing STN1012700 targeting the first regulatory approved product in Asia for reducing myopia progression.

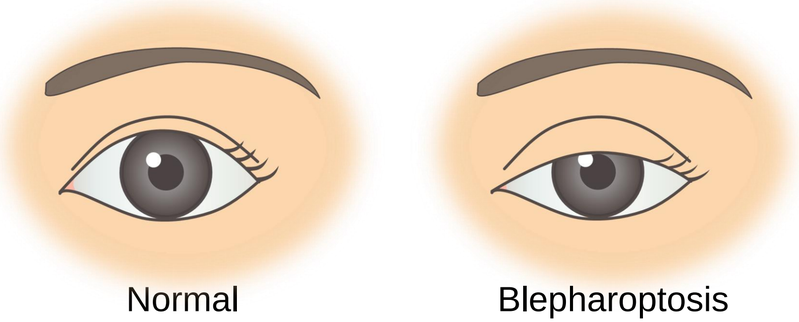
We completed APPLE Study, a Phase 2 clinical trial in Singapore. The study met its primary endpoint; changes in the objective spherical equivalent after 12 months of drug administration, and no severe adverse events were observed throughout the treatment period. We have conducted ORANGE Study, a Phase 2/3 clinical trial in Japan since 2019. We plan to apply for approval of manufacturing and marketing in the future.

High myopia has been reported to be associated with increased risk of pathologic myopia, glaucoma and cataract. Recent large population-based studies reported that the prevalence of myopic maculopathy are correlated with the degree of myopia (diopter) even in low myopia. Therefore, reducing myopia progression during childhood can reduce the future risk for myopic maculopathy. We hope STN1012700 will contribute to protect people from evitable eye diseases and visual impairment.

STN1013800

Acquired blepharoptosis, also known as ptosis or droopy eyelid, is a unilateral or bilateral drooping of the upper eyelid that usually occurs from a partial or complete dysfunction of the muscles that elevate the upper eyelid. It can lead to loss of visual field and cosmetic concerns for patients. While precise prevalence of the condition is unknown, tens of millions of adults are believed to suffer from ptosis globally.

STN1013800 (RVL-1201) is a novel, once-daily ophthalmic formulation of oxymetazoline, a direct-acting alpha adrenergic receptor agonist, which when administered to the eye, is believed to selectively target Müller's muscle and elevate the upper eyelid. RVL-1201, was approved on July 8, 2020 under the brand name UPNEEQ™ by Osmotica Pharmaceuticals in the US. Santen will be responsible for further development of RVL-1201 and regulatory approvals as well as commercialization in its licensed territories under the agreement.



STN1013900 / STN1014000

STN1013900 (Rhopressa, netarsudil ophthalmic solution 0.02%), a once-daily eye drop approved by the US Food and Drug Administration (FDA) for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension, was launched in the US in April 2018. STN1014000 (Rocklatan, netarsudil/latanoprost ophthalmic solution 0.02%/0.005%), the first and only fixed-dose combination of Rhopressa and the widely-prescribed prostaglandin analog latanoprost, was approved by the FDA and was launched in the US in the second quarter of 2019.

Preparations for the first Phase 3 study in Japan for STN1013900 are ongoing and the study is expected to commence early 2021. Santen will be responsible for all development and commercialization related to the products in Japan and several other Asian countries.

STN2000100

STN2000100 (PRESERFLO MicroShunt) is an unique glaucoma drainage device designed to treat all stages of primary open angle glaucoma (POAG), the most prevalent form of glaucoma. We believe that it will enable to mitigate burden of patients and medical professionals according to its merit that it is safer and shorter operation time than the invasive procedures such as trabeculectomy and tube shunt surgery.

We have entered into an expanded collaboration in the development and commercialization with Glaukos Corporation for the product development, commercialization, and sales of STN2000100 in the Americas (North, Central and South America), Australia, and New Zealand. By offering the rights to product development, commercialization, and sales in said regions, we transfer to Glaukos all STN2000100-related regulatory affairs, clinical development activities tailored to obtaining approval for the surgical device, and all commercialization endeavors including marketing. We continue to develop and commercialize STN2000100 in regions other than the Americas, Australia and New Zealand. We submitted a Premarket Approval to the FDA, which was accepted in July 2020. After receiving the FDA’s feedback in February 2021 about the review, we went into discussions with Glaukos over the development and commercialization of STN2000100. We discussed how to obtain approval as early as feasible, and in turn decided to collaborate in the development and commercialization endeavors in the Americas, Australia, and New Zealand by leveraging Glaukos’s expertise in glaucoma surgery.

STN6000100

Retinitis pigmentosa, a disease caused by genetic mutations, causes wide-ranging degeneration of retinal photoreceptor cells and retinal pigment epithelial cells. It often strikes people in their teens, with many patients rendered blind by middle age. Worldwide, approximately 1.9 million patients suffer from the disease.

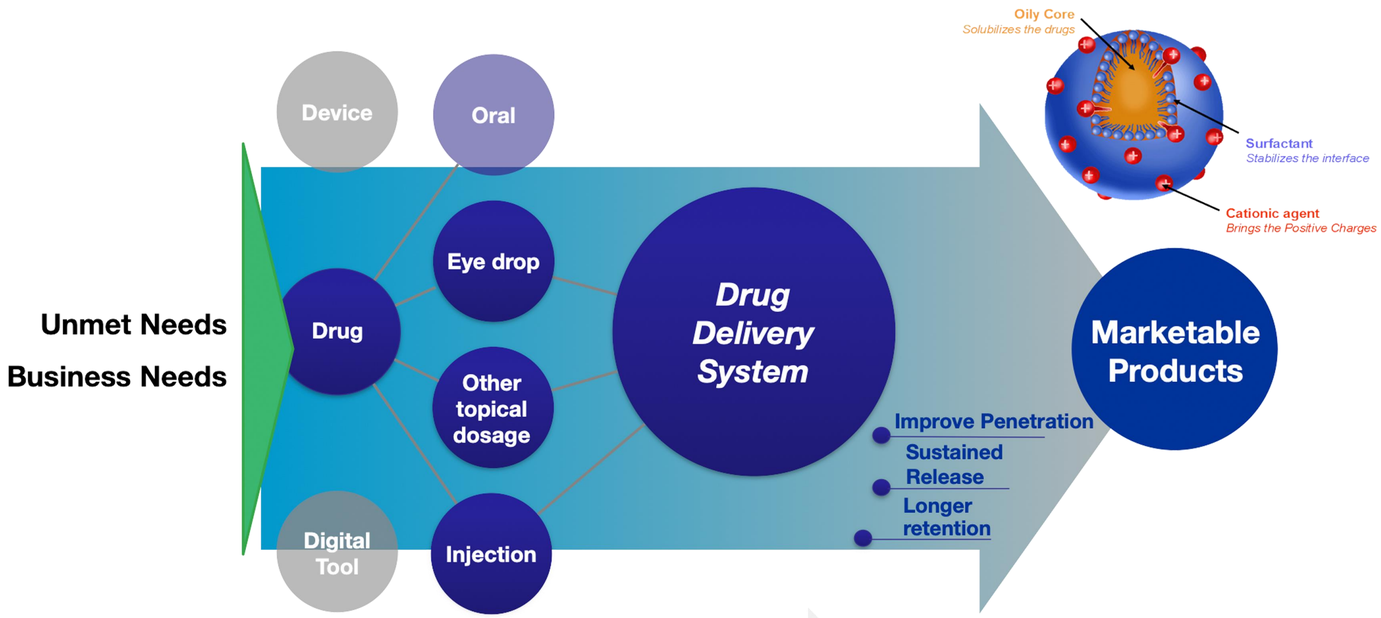
STN6000100 (jCell) is a cell therapy product, and its principal component is retinal progenitor cells. The product is administered through intravitreal injection, a procedure that is minimally invasive in comparison to the standard method of direct retinal injection used for other genetic and cell therapies. The cells introduced into the eye release cell growth and protection factors that activate and protect retinal cells. Such mechanism of action is believed to have the potential to be applied to all types of retinitis pigmentosa irrespective of the condition's genetic causes.
In the US, the evaluable portion of a Phase 2b clinical trial of jCell for the treatment of retinitis pigmentosa has been completed, and the crossover portion continues. jCell therapy has been administered in over 100 patients.

Drug Delivery System (DDS)

Why DDS?

Instillation is the most general administration route and has been used for a long time for ocular treatment. However, instillation is not sufficient to fill out the future unmet needs in ophthalmology.

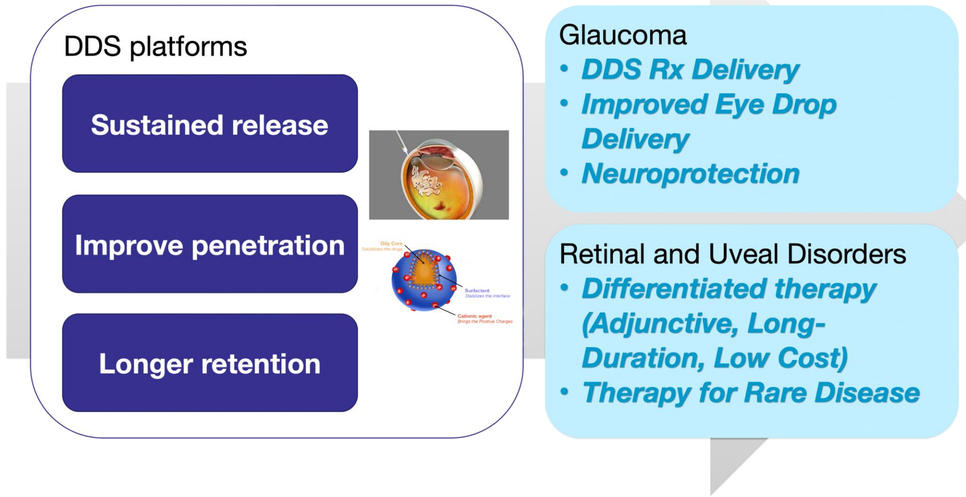
Santen R&D will develop the most desirable DDS platform internally or by collaborating with an external partner company based on the experience of numerous ophthalmic medical expertise.



Ocular DDS causing a paradigm shift

Our policy on DDS development would be that we quickly deliver the desirable DDS in ophthalmology having high safety and quality to patients.

We believe that our DDS could bring many benefits to patients currently suffering from various eye diseases, because there are many eye diseases for which there is no cure due to lack of duration and/or the poor drug penetration.



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China R&D

China is one of the priority countries for the growth of Santen. We are going to enhance and reconstruct the functions of China R&D and strongly accelerate development pipelines. As started in the “Current status of pipeline”, we are planning to develop STN2000100 and STN1007603, in addition to STN1012700 and STN1011101. Surgeries using STN2000100 were conducted in the China International Medical Tourism Pilot Zone as part of a program to initiate unapproved medical device use. We expect these experiences will boost development in China. STN1007603 (Verkazia), eye drops for vernal keratoconjunctivitis is already available in Europe and Asia and has been listed in “The Third Batch of Urgent Unmet Clinical Needs List”. We have confirmed that will get clinical trial waiver from the China agency. In addition to the existing pipeline, we will accelerate the development of new drugs that will meet the needs of patients in China.

	Code	Indication	Status
Atropine sulfate	**STN1012700**	Myopia	Plan: FY2021 P1 start
TAPCOM/ TAPTIQOM	**STN1011101**	Glaucoma / ocular hypertension	Plan: FY2023 P3 completion
PRESERFLO MicroShunt	**STN2000100**	Glaucoma	Initiate unapproved medical device use program at Boao Super Hospital in the Boao Lecheng International Medical Toursim Pilot Zone Successful first surgeries operated on January 9, 2021
Verkazia	**STN1007603**	Vernal keratoconjunctivitis	China FDA accepted the NDA for the treatment of vernal keratoconjunctivitis in April 2021.

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