Therapeutic evaluation of anti-fibrotic agents for thyroid eye disease (TED) in a preclinical mouse model

Abstract for the general public

Autoimmune diseases develop when the immune system fails to distinguish its own cells from foreign ones and therefore starts to attack its own organs. The frequency of autoimmune disorders has been rising steadily for several decades. These diseases often affect the thyroid gland, particularly in women. The most common are Hashimoto's thyroiditis (HT) and Graves' disease (GD).

Both HT and GD are inflammatory thyroid disorders, but their manifestations are different. **HT leads to damage of the thyroid gland and a lack of its hormones** (hypothyroidism). Effective treatment of HT is available and consists in supplementation of thyroid hormones. Meanwhile, **GD is associated with uncontrollable stimulation of the thyroid gland and production of an excess of hormones** (hyperthyroidism). This results in enlargement of the thyroid gland and an increased susceptibility to cancer development. GD treatment is difficult, and many patients require surgical removal of the thyroid or its destruction with radioactive iodine.

In patients with GD, the inflammation can also develop in tissues located behind the eyeball. This condition is called thyroid eye disease (TED), also referred to as Graves' orbitopathy. Inflammation and swelling in the eye socket cause the eyeball to bulge forward (proptosis). In extreme cases, this might cause vision loss. After the inflammation has withdrawn, the tissues become fibrotic, often leading to restricted eye movement and squint. TED treatment is unsatisfactory, and some patients need surgical operations to restore the correct eye socket anatomy.

Even though fibrosis is an irreversible phenomenon, there are anti-fibrotic drugs, pirfenidone and nintedanib, which can impede its development. They are commonly used for the treatment of idiopathic pulmonary fibrosis, but they have also been proven effective in other disorders associated with fibrosis. We hypothesize that anti-fibrotic drugs will also display activity in TED.

The aim of the project is to gain a better understanding of TED development in a mouse model, and to evaluate how anti-fibrotic drugs modify the course of this disease. **To our best knowledge, this will be the first study of pirfenidone and nintedanib in an animal model of TED**.

We will use the mouse model of GD/TED, where immunization leads to the production of autoantibodies, reflecting the course of the disease in humans. After the disease is established, the animals will receive chow containing pirfenidone or nintedanib. Afterwards, we will analyze the severity of GD and TED. We plan to evaluate eye socket tissues for signs of TED, especially fibrosis. We will also assess the level of factors responsible for the development of fibrosis, to provide more insight into the mechanism of TED development and the influence of anti-fibrotic drugs on this process.

We expect the proposed study to provide new data regarding the course of TED and the underlying mechanisms. We hope to prove the beneficial effects of anti-fibrotic therapy on TED development. We believe that, in case of positive results, studies on the efficacy of the proposed therapy will be continued in clinical trials in the future, which may provide direct benefit for patients.