Potential new treatment for severe dry eye disease, RCSI research 'miR-744-5p contributes to ocular inflammation in patients with primary Sjogrens Syndrome'

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The Ocular Immunology Research Group focus on conditions where the body's immune system, which normally protects us from infection and disease, becomes uncontrolled and begins to target our healthy cells or tissues instead of foreign material, bacteria, viruses or diseases.

Our research program currently focusses understanding what is happening on the surface of the eye for patients with autoimmune conditions that leads to severe dry eye disease. While dry eye sounds relatively minor, these patients suffer from dry irritated eyes that significantly impact not only their vision but also their day to day activities and quality of life. In the disease we primarily focus on Sjogrens Syndrome the cells of the immune system begin to travel in increased numbers to the glands of the body which produce tears, saliva or mucus called exocrine glands. Here the immune cells release large amounts of soluble protein mediators or messenger molecules, that normally signal the immune system to attack bacteria, virus or damaged cells. These molecules cause inflammation and fibrosis of the glands which ultimately stop them from working leading to the severe dry eye and dry mouth symptoms these patients have. Researchers have been interested in figuring out what is happening with the immune system in these patients that causes the cells to attack the glands and effect the surface of the eye. Recently a network of regulators was discovered that controls all of the processes within our cells. These regulators or controllers are small pieces of genetic material termed micro RNAs. In other autoimmune diseases states the balance of these controllers has been shown to be important in causing disease symptoms. We were interested in looking at the levels of these controller in ocular epithelial cells from patients and healthy controls to see if the levels were different and if we could find a controller that we could manipulate to halt the damage and destruction caused by the immune system.

We found that patients with autoimmune dry eye disease had different amounts and types of regulatory micro RNAs or controllers in their cells compared to ocular epithelial cells from healthy controls. This suggested that changes in the amounts of these regulators could be causing the increased production of inflammation-triggering messenger molecules from our immune cells ultimately leading to dry eye disease in Sjogren Syndrome patients.

Micro RNAs control messenger molecules by stopping them from being made or causing them to be destroyed in the cell so they are not released. Changes in the amounts of micro RNA controllers within our cells will therefore cause too much or too little of the important messenger molecules to be made and alter the message that is delivered to our immune cells. One such regulator that we found at high levels in patient cells was called micro RNA-744. This was particularly interesting to us as one of the messenger molecules it could potentially control, Pellino 3, had previously been shown to be an important protein required to limit inflammatory messenger production. As the amount of micro RNA-744 was very high in the patient cells it suggested to us that amount of the regulatory messenger molecule Pellino 3 could be very low which could cause uncontrolled amounts of inflammatory messenger molecules to be released from cells and destroy the glands and damage the surface of the eye. Indeed our studies did show that when large quantities of the controller micro RNA-744 were found in patients they had a dramatically lower level of the essential controller of inflammation, Pellino 3, in their cells.

We next looked at ways to restore or increase the amount of Pellino 3 in patient cells. We speculated that if we could restore or increase Pellino 3 levels in eye cells from Sjogren Syndrome patients then we could perhaps limit or stop the inflammatory process that is responsible for disease symptoms by helping to limit the amount of inflammatory messenger molecules present within eye cells from autoimmune patients. Using commercially available synthetic genetic sequences, that can copy or

stop the function of micro RNA controllers we were able to lessen the amount of micro RNA-744 within cells, this increased Pellino 3 levels and reduced the levels of inflammation causing messenger molecules.

Our studies have found a list of micro RNA controllers that are present in different amounts in patient cells compared to healthy controls. This is useful as this panel can be used to help diagnose patients with Sjogrens Syndrome. At present diagnosis takes a long time due to the fact that patients have symptoms like an array of other autoimmune conditions including lupus and rheumatoid arthritis. We can also use the list of micro RNA controllers that we found to be altered in patients to help make new drugs to treat the disease. There are currently no effective treatments for Sjogren Syndrome related dry eye disease. In common with other dry eye conditions patients rely on anti -inflammatory drugs and ocular tear replacements which treat the symptoms but do not target what is driving the disease. We believe that if we can copy or stop the function of micro RNA controllers using synthetic genetic sequences, that limit inflammation, we can stop exocrine glands being destroyed, restore tear production and normal eye function.

Overall we believe that this is a first step toward a potential new treatment, and much more pre-clinical testing is needed before we can develop it into something that is ready for patients. However, our research provides the opportunity to possibly treat the root cause of the disease rather than just the symptoms

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News

Innovative new Left Bundle Branch Pacing (LBBP) treatment

Dr Jonathan Lyne, Director of Cardiac Electrophysiology at Beacon Hospital

Beacon Hospital marked Irish Heart Month this past September, by announcing a ground-breaking and innovative new cardiac pacemaker treatment, called Left bundle branch pacing (LBBP), for patients with Left bundle branch block (LBBB).

The new procedure is being pioneered in Ireland by Dr Jonathan Lyne, Director of Cardiac Electrophysiology at Beacon Hospital. Dr Lyne is a world leading expert in cardiac rhythm abnormalities and is operating at Ireland's only Heart Rhythm Centre at Beacon Hospital.

Where an irregular heartbeat is discovered a pacemaker may be required, and in Ireland around 4,000 people get a pacemaker every year.

The new Left bundle branch pacing (LBBP) treatment involves the pacing lead being fixed deep into the left side of the intraventricular septum to allow capture of the left bundle.

It is a newer technique compared with His Bundle Pacing (HBP). Dr Jonathan Lyne points out that the positive aspects of HBP are somewhat offset by its limitations when compared to myocardial pacing such as high thresholds, small R waves, long fluoroscopy times and higher failure rates.

LBBP has had an impressive rate of accumulation of early evidence and holds promise as a method for physiological conduction system pacing that overcomes some of the fixation, threshold and sensing challenges of HBP. LBBP is also able to resynchronise patients with LBBB and is very promising for cardiac resynchronisation therapy due to its ability to correct block within the cardiac conduction system beneath the His and proximal left bundle. In published trials LBBP in patients with LBBB has resulted in very impressive improvements in left ventricular structure and function.

Dr Weijang Huang and his team from the First Affiliated Hospital of Wenzhou in China pioneered LBBP, have performed over 1000 cases and published widely on the topic. Dr Jonathan Lyne spent time learning and perfecting the technique with Dr Huang in China.

Since returning Dr Lyne has carried out the procedure in over 50 patients and is the first and only cardiologist carrying out this procedure in Ireland. Dr Lyne has organised the first worldwide educational event at Beacon Hospital to teach interested colleagues how to perform this novel technique. To allow a wider audience to access the event it is being recorded and placed in webinar format to achieve a broader and wider global audience.

Dr Lyne, Director of Cardiac Electrophysiology at Beacon Hospital said, "The science and technology behind treatments with pacemakers is constantly evolving, and I want to always offer patients the best and most effective solutions. I strongly believe, based on evidence, that this new LBBP procedure is the way of the future for many pacemaker procedures and in particular treating heart failure and LBBB, with many benefits compared to other procedures. As growing evidence accumulates that this physiological form of conduction system pacing will translate to tangible clinical benefits for patients, this modern technique will be sought by an increasing number of patients and cardiologists. To this end, I'm happy to be able to bring the procedure to Ireland, to Beacon and to actively engage with other consultants to teach them the technique.

"I'm currently working with the medical device industry to develop adequate delivery devices and I'm planning clinical trials to follow and confirm the clinical improvements seen following LBBP."