Alcohol abuse drug can be repurposed to treat a blinding disorder

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New research from University College London, Moorfields Eye Hospital and Duke University School of Medicine has identified a gene that drives scarring, together with a rapidly translatable therapy, for the UK's most common cause of blinding conjunctivitis. The results demonstrate that the drug disulfiram, licensed for the control of alcohol abuse, normalises human and mouse scar making cell (fibroblast) functions and inhibits mouse ocular mucosal (conjunctival) scarring. Fight for Sight, UCL Business, and Moorfields Eye Charity funded the study, which is published in the *Journal of Clinical Investigation Insight* on 4 August.

Scarring conjunctivitis is a major cause of chronic pain and sight loss. The conjunctiva is the membrane that lines the eyelid and covers the eye . In health, it helps lubricate and protect the eye, but in conditions such as ocular mucous membrane pemphigoid (ocular pemphigoid), severe eye allergy, Stevens-Johnson syndrome, and trachoma inflammation trigger rapid pathological scarring, which often persists after the inflammation has gone destroying the protective functions of the conjunctiva.

Ocular mucous membrane pemphigoid was chosen for current investigations because mucous membrane pemphigoid is a prototypical immune mediated mucosal scarring disorder (that affects other mucosal sites at the orifices as well as the conjunctiva). It is also the most common immune mediated scarring conjunctival disease in the UK. Standard treatment for both mucous membrane pemphigoid and its ocular form is to suppress the immune system. This controls

inflammation when it works, but there are unpleasant side effects and it has little effect on scarring. Approximately 1 in 5 people with the ocular form go blind.

In the current study, the research team screened for genetic activity linked to scarring in conjunctival tissue, and in the scar making cells (fibroblasts) grown from this conjunctiva. The aim was to identify potential therapeutic target molecules and provide a test bed for treatment.

Professor John Dart and Professor Julie Daniels, both of NIHR Moorfields Biomedical Research Centre and the UCL Institute of Ophthalmology, were joint research leads, together with Professor David Abraham at UCL Royal Free Campus.

Results show that the aldehyde dehydrogenase 1 (ALDH1) family of enzymes is more active in tissue and fibroblasts from people with ocular mucous membrane pemphigoid compared to controls. ALDH1 is an enzyme that's critical for one step in the process of turning vitamin A into retinoic acid - a key protein in immunity, inflammation and scarring.

Conjunctival scarring like that seen in ocular pemphigoid arises in a mouse model of severe allergic conjunctivitis previously developed by study co-author Dr Daniel Saban's team at Duke University School of Medicine. Following the ALDH1 results in tissue and fibroblasts, these mice were treated daily with eye drops containing disulfiram for 7 days after the induction of immune mediated conjunctivitis.

Disulfiram is a drug that's licensed for treating alcohol abuse. It works by blocking ALDH activity, including ALDH2, which processes alcohol. Treatment reduced eye surface inflammation in the mice and prevented scarring compared to controls.Ocular pemphigoid fibroblasts were

treated with disulfiram to test its effect on ALDH inhibition in these human scarring cells. In keeping with the in vivo results, disulfiram treatment of human ocular pemphigoid fibroblasts, significantly inhibited their abnormal behaviour in a range of tests.

Dr Sarah Ahadome at UCL Institute of Ophthalmology is the study's first author. She says: "Our results have demonstrated that inhibiting ALDH1 activity with disulfiram effectively reduces inflammation and prevents scarring in vivo, and significantly reduces the signs of scarring in vitro, in human ocular pemphigoid fibroblasts. It may be that this approach will be more effective at scar prevention when there is active inflammation, but this is an important proof-of-concept that currently untreatable scarring conjunctivitis may respond to eye drops or other topical application of a drug that can be repurposed."

A companion study from Dr Saban's lab at Duke University, in collaboration with Dr Virginia Calder's lab at the UCL Institute of Ophthalmology, is being published at the same time. Professor Dart commented on results from both studies: "Collectively there is evidence from our data, and from that of Dr Saban's team, that aldehyde dehydrogenase has critical roles in inflammation and conjunctival fibrosis, and is produced by the dendritic cells of the immune system and by fibroblasts. We suggest that progressive scarring in ocular pemphigoid results from fibroblast self-regulation, mediated by ALDH, through its metabolite retinoic acid (Vitamin A). These findings suggest that the repurposing of disulfiram, for the topical treatment of mucosal scarring in ocular pemphigoid and similar disorders such as severe eye allergy, may result in effective anti-scarring therapy and provide justification for a randomised controlled trial of disulfiram therapy for scarring in OMMP"

Fight for Sight's Director of Research, Dr Dolores M Conroy said: "This is very important work given the devastating impact of progressive

scarring on the eye and other organs. There is currently just one licensed drug for fibrosis and that is for lung disease. Mucous membrane pemphigoid affects the eye in 7 in 10 people with the condition, with 1 in 5 going blind. The potential for disulfiram as an effective treatment is very exciting, particularly as we know that it may be closer to the clinic than a drug developed from scratch, and especially if it can also find an application in trachoma, which affects 40 million people around the globe.

Professor Phil Luthert, Director of the UCL Institute of Ophthalmology stated:"Scarring remains a major problem in eye disease, and in many other conditions, and uncontrolled conjunctival fibrosis is terrible to live with. This breakthrough offers new hope and is a great example of how discovery science can come together with smart repurposing of existing drugs to reach a solution for patients."

More information: Sarah D. Ahadome et al, Aldehyde dehydrogenase inhibition blocks mucosal fibrosis in human and mouse ocular scarring, *JCI Insight* (2016). DOI: 10.1172/jci.insight.87001

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