PRESS RELEASE

Alcohol abuse drug can be repurposed to treat a blinding disorder

- Disulfiram prevents scars forming in a mouse model of scarring conjunctivitis
- Human scar making cells, from patients with scarring conjunctivitis, are returned to normal by disulfiram
- Disulfiram is currently licensed to treat alcohol abuse (sold as Antabuse)
- Disulfiram works by blocking the pathway that generates Vitamin A.

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.”

Ends

NOTES TO EDITORS

Publications

- Ahadome et al. Aldehyde dehydrogenase inhibition blocks mucosal fibrosis in human and mouse ocular scarring. JCI Insight. 2016;1(12):e87001
  Pre-publication URL: http://insight.jci.org/articles/view/87001?key=8a651b204e228f66cb72
  Final URL: http://insight.jci.org/articles/view/87001
  DOI: 10.1172/jci.insight.87001

  Pre-publication URL: http://insight.jci.org/articles/view/87012?key=5af8c5a9762ed12a91e2
  Final URL: http://insight.jci.org/articles/view/87012
  DOI: 10.1172/jci.insight.87012

Commercialisation

UCL Business has a patent behind this technology and is seeking commercial partners. See: http://www.uclb.com/technologies/treatment-of-fibrosis-with-aldh-inhibitors

Fast facts

- Mucous membrane pemphigoid is a severe autoimmune disorder in which the skin and mucous membranes blister and scar.
- OMMP affects an estimated 1 in 1 million people. Women and men are equally affected.
• Conjunctival scarring can also be caused by other conditions including Stevens-Johnson syndrome, trachoma and atopic keratoconjunctivitis.

**Fight for Sight** is the leading UK charity dedicated to funding pioneering research to prevent sight loss and treat eye disease. Fight for Sight is funding research at leading universities and hospitals throughout the UK.

Major achievements to date include: saving the sight of thousands of premature babies through understanding and controlling levels of oxygen delivery; restoring sight by establishing the UK Corneal Transplant Service enabling over 52,000 corneal transplants to take place; providing the funding for the research leading to the world’s first clinical trial for choroideremia; bringing hope to children with inherited eye disorders by co-funding the team responsible for the world’s first gene therapy clinical trial; and identifying new genes responsible for glaucoma, retinitis pigmentosa, keratoconus and other corneal disorders, and Nance-Horan syndrome.

Fight for Sight’s current research programme is focusing on preventing and treating age-related macular degeneration, diabetic retinopathy, glaucoma, cataract and corneal conditions. We are also funding research into the causes of childhood blindness and a large number of rare eye disorders.

For more information, contact: Ade Deane-Pratt on 020 7264 3907 or ade@fightforsight.org.uk

www.fightforsight.org.uk

**Moorfields Eye Charity** raises vital extra funds that allow Moorfields Eye Hospital to remain the world’s leading centre for eye care, research and education. We provide targeted funds, beyond those provided by the NHS, to educate the researchers and clinicians of tomorrow, invest in state-of-the-art equipment, and research cures and treatments for diseases that affect millions. With the support of our donors, we fund exceptional facilities and research breakthroughs that bring hope to people around the UK and the world.

Blindness and sight problems are a growing global challenge. Moorfields Eye Hospital, together with our research partner the UCL Institute of Ophthalmology, is the world’s best hope of meeting it. Moorfields Eye Charity is a registered charity in England and Wales. Its registered charity number is 1140679.

**About UCL (University College London)**

UCL was founded in 1826. We were the first English university established after Oxford and Cambridge, the first to open up university education to those previously excluded from it, and the first to provide systematic teaching of law, architecture and medicine. We are among the world’s top universities, as reflected by performance in a range of international rankings and tables. UCL currently has over 35,000 students from 150 countries and over 11,000 staff. Our annual income is more than £1 billion.

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Moorfields Eye Hospital NHS Foundation Trust is one of the world’s leading eye hospitals, providing expertise in clinical care, research and education. Moorfields has provided excellence in eye care for more than 200 years and continues to be at the forefront of new breakthroughs and developments. Along with their academic partners at the UCL Institute of Ophthalmology, Moorfields is recognised as a leading centre of excellence in eye and vision research. Together, they form one of the largest ophthalmic research sites in the world.

The National Institute for Health Research (NIHR) is funded by the Department of Health to improve the health and wealth of the nation through research. The NIHR is the research arm of the NHS. Since its establishment in April 2006, the NIHR has transformed research in the NHS. It has increased the volume of applied health research for the benefit of patients and the public, driven faster translation of basic science discoveries into tangible benefits for patients and the economy, and developed and supported the people who conduct and contribute to applied health research. The NIHR plays a key role in the Government’s strategy for economic growth, attracting investment by the life-sciences industries through its world-class infrastructure for health research. Together, the NIHR people, programmes, centres of excellence and systems represent the most integrated health research system in the world. For further information, visit the NIHR website (www.nihr.ac.uk).

NIHR Biomedical Research Centre at Moorfields Eye Hospital and UCL Institute of Ophthalmology: established in April 2007 and awarded a second five-year term by the NIHR from April 2012, its purpose is to conduct 'translational research' that is designed to take advances in basic medical research from the laboratory to the clinic, enabling patients to benefit more quickly from new scientific breakthroughs. Our centre is currently one of 11 Biomedical Research Centres that were awarded in 2012 to NHS/university partnerships with an outstanding international reputation for medical research and expertise, and experience of translating that research into the clinical setting. For further information, please visit www.brcophthalmology.org

UCL Business PLC (UCLB) is a leading technology transfer company that supports and commercialises research and innovations arising from UCL, one of the UK’s top research-led universities. UCLB has a successful track record and a strong reputation for identifying and protecting promising new technologies and innovations from UCL academics. UCLB has a strong track record in commercialising medical technologies and provides technology transfer services to UCL’s associated hospitals; University College London Hospitals, Moorfields Eye Hospital, Great Ormond Street Hospital for Children and the Royal Free London Hospital. It invests directly in development projects to maximise the potential of the research and manages the commercialisation process of technologies from laboratory to market. For further information, please visit: www.uclb.com Twitter: @UCL_Business