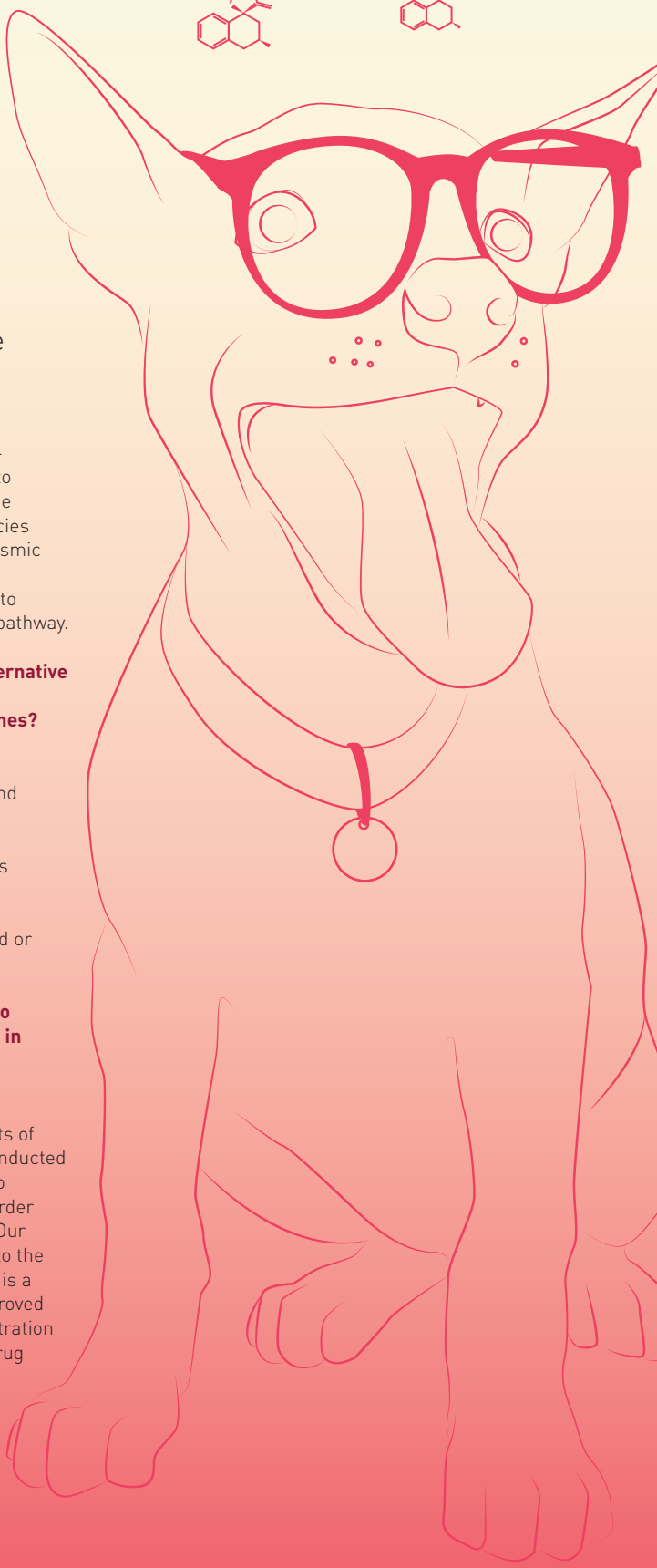
Kinostat® could be man's best friend

Professor Peter F Kador has developed topical Kinostat® to ameliorate the development and progression of cataracts in dogs with diabetes mellitus. He discusses the significance of this work, which has the potential for translation to human treatment



Could you reveal how you came to focus your research on diabetes mellitus and its effects on ocular health?

I started my scientific career at the National Eye Institute of the US National Institutes of Health (NIH), working under Dr Jin Kinoshita, who discovered the adverse effects of aldose reductase (AR) and the polyol pathway while at Harvard in the early 1960s. As my career there advanced, I worked on the development of aldose reductase inhibitors (ARIs) and how control of this enzyme affected the different parts of the eye.

Why is it important to be able to control hyperglycaemia to reduce diabetes' impact on ocular tissues?

Many cells require insulin in order for glucose to enter and be converted to energy. Diabetes is the name for a group of metabolic diseases that are characterised by the presence of high blood sugar levels over a prolonged period of time because glucose cannot adequately enter the cells to be utilised for energy production. This is either due to the lack of insulin production – as in the case of Type 1 – or a combination of reduced insulin production and failure of insulin present to be recognised by cells.

The excess glucose goes into cells that do not require insulin for glucose uptake, where it adversely alters the cells. In the eye, this includes select cells in the cornea, lens, iris and retina. Changes in these cells lead to corneal problems, difficulties in accommodating light changes and irreversible blindness due to cataract formation and retinopathy.

To what extent does AR contribute to diabetes-linked ocular disease?

AR is the rate-limiting step in the two-step polyol pathway where glucose is converted to fructose. AR catalyses the conversion of glucose to sorbitol – and this process has been linked to the induction of osmotic stress, the generation of reactive oxygen species through osmotic-induced endoplasmic reticulum stress, the induction of apoptosis and redox changes due to increased flux through the polyol pathway.

Why is it necessary to find an alternative to surgery for reversing the development of cataracts in canines?

Approximately 80 per cent of dogs develop cataracts and become blind within the first year of developing diabetes. If left untreated, the presence of cataracts often results in the development of glaucoma and uveitis. At that point, the dog must either have the eyes removed or be euthanised.

Will your research on ARIs lead to new therapies for ocular disease in the future?

While animal studies have clearly demonstrated the beneficial effects of ARIs, most of the clinical trials conducted on humans in the 1980s through to 2000 failed due to low dosing (in order to prevent potential side effects). Our aim is to translate the use of ARI to the veterinary market where diabetes is a major problem for pets. Once approved by the US Food and Drug Administration (FDA), we plan to transition this drug back to humans for the treatment of keratopathy, which affects up to 70 per cent of human diabetics, and then to young diabetics who also develop cataracts and retinopathy.

A cost-effective cataract treatment for canines

Researchers from the **University of Nebraska Medical Center** and **Therapeutic Vision, Inc.** have made an important breakthrough in inhibiting the onset of ocular complications relating to diabetes in dogs. Their development of Kinostat® to enable application through eye drops could lead to an effective treatment for humans with diabetes

DIABETES MELLITUS IS a condition that afflicts approximately 347 million people around the world. It is characterised by an inability to use the energy found in food due to the body not producing enough insulin, not using the insulin it does produce, or a combination of the two. If the condition is not treated properly, it can lead to hyperglycaemia – high blood sugar levels that last for a long period of time. Hyperglycaemia can cause a wide range of problems including changes to the cells in the various parts of the eye. Such changes can lead to the formation of cataracts and retinopathy, both of which are causes of sight loss.

Diabetes also afflicts animals and, as with humans, can lead to eye problems. Indeed, a high proportion of dogs become blind following development of diabetes, which requires cataract surgery to restore vision. This surgery is often expensive and rarely covered with insurance policies; as such, a team of researchers has been investigating the efficacy of an alternative treatment, one which costs significantly less than surgery and has the potential to be translated to use in humans.

COMBATING OCULAR COMPLICATIONS

The team, led by Founder of Therapeutic Vision, Inc. and University of Nebraska Medical Center's Professor Peter F Kador, has studied Kinostat®, an aldose reductase inhibitor (ARI) first developed in the early 1980s. The enzyme aldose reductase (AR) is known to be linked to the rapid onset of diabetic ocular complications, so finding a means of inhibiting AR is of huge benefit in combating such complications. However, when Kinostat® was initially developed it was used orally, which caused problems.

"The drug has a very short half-life in dogs which lowers its overall activity to the point where it is not commercially feasible," explains Kador. "To bypass this metabolism, I modified the drug to be delivered as an eye drop, which wasn't easy; tear flow in dogs is far higher than in humans so no standard eye drop formulations worked." Kador therefore developed a new formulation – Kinostat® – named in honour of Dr Jin Kinoshita, the scientist who first discovered the adverse effects of AR and Kador's mentor at the US National Institutes of Health (NIH).

CLEAR RESULTS

The team investigated whether Kinostat® was effective in dogs once cataract formation had commenced. They found that while the lenses of the eye would never become clear again, the progression of early cortical cataracts was significantly reduced so vision could be maintained. Next, they conducted a proof-of-concept study to determine if owners administering the drug to their pet would be effective. Remarkably, the answer was an emphatic yes, with some diabetic dogs living up to eight years without developing cataracts.

Once these results had been collected, the team conducted a US Food and Drug Administration (FDA) sanctioned placebo-controlled clinical trial at 12 sites across the US, with initial analysis indicating that there is a significant drug effect with over 80 per cent of all clear-eyed dogs with no lens changes receiving the drug.

TRANSLATION TO HUMANS

Excitingly, Kinostat® also appears to have the potential to become a safe and effective treatment for humans with diabetes. Toxicity tests have indicated that the eye drops are non-toxic and, once approved by the FDA, Kador and his team plan to transition them to humans. "The use of these drops for cataracts is controversial and would be difficult to conduct because it takes years for cataracts to develop in humans," explains Kador. "The first target will therefore be the cornea."

That up to 70 per cent of diabetics develop corneal problems highlights the importance of what Kador is proposing. While ARIs have repeatedly been shown to prevent corneal changes, companies have never before developed them as the costs were thought to be too high compared with the potential profit margins. Kador and his team's new eye drop application method removes this problem and, with it, problems associated with retinopathy and the formation of cataracts.

KINOSTAT®

OBJECTIVES

- To investigate the effectiveness of the aldose reductase inhibitor Kinostat® in preventing cataract formation in diabetic dogs
- To modify Kinostat® for translation to an effective treatment for humans with diabetes

KEY COLLABORATOR

Milton Wyman, DVM, MS, DAVCO, Veterinary Ophthalmologist, Therapeutic Vision, Inc. and Professor Emeritus, Ohio State University College of Veterinary Medicine, USA

FUNDING

US National Institutes of Health (NIH): R43EY018013-01A; R44 EY018013-02A1; R44 EY018013-2b

State of Nebraska Small Business Innovation Research Initiative Phase 2 Grant No. 16-01-054

CONTACT

Dr Peter F Kador
Professor of Pharmaceutical Sciences

College of Pharmacy
University of Nebraska Medical Center
Omaha
Nebraska 68198 6025
USA

T +1 402 740 4397
E pkador@unmc.edu / pkador@therapeuticvision.com

www.therapeuticvision.com

http://bit.ly/LI_PK

PETER F KADOR received a PhD in Medicinal Chemistry from the Ohio State University and, after a 25-year career at NIH, retired as the Chief of the Laboratory of Ocular Therapeutics from the National Eye Institute. For the past 14 years, he has served as a professor at the College of Pharmacy and adjunct professor in the Departments of Ophthalmology and Veterinary Sciences at the University of Nebraska Medical Center. He founded Therapeutic Vision, Inc. and under a US Food and Drug Administration (FDA) minor use/minor species designation is developing the topical Kinostat®. His work on diabetes and age-related eye diseases has been recognised with numerous national and international awards. He is a fellow of the American Association of Pharmaceutical Scientists and the Association for Research in Vision and Ophthalmology. He serves as the Executive Vice-President for the National Foundation for Eye Research and has served as President, Trustee and currently Treasurer of the Association for Ocular Pharmacology and Therapeutics. He has organised or co-organised over 28 national and international workshops and conferences and has over 240 publications and patents.