

ASX RELEASE

Ellex Medical Lasers Limited (ASX:ELX)

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Topic: 2RT to Feature at European Laser Innovation Forum 2018



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**Adelaide, Australia 23 March 2018** – Ellex Medical Lasers Limited (ASX:ELX), a global leader in medical devices for the diagnosis and treatment of eye disease, today announced the agenda for a panel discussion on the Company's proprietary 2RT<sup>®</sup> Retinal Rejuvenation Therapy at the European Laser Innovation Forum to be held in Nice, France on 24 March 2018.

2RT<sup>®</sup> is Ellex's breakthrough laser therapy which has the potential to positively influence the lives of millions of people suffering from age-related macular degeneration (AMD) in its early stages. An interventional treatment, 2RT<sup>®</sup> may allow physicians to treat patients at a stage of the disease for which there is no alternative therapy. It may also defer or eliminate the need for expensive, invasive pharmaceuticals that are currently used in the late stage of the disease.

Sponsored by Ellex, the forum will enlist a panel of world-renowned faculty, including John Marshall, PhD, FRCPath, to share their collective experiences and latest updates for 2RT<sup>®</sup>. Ellex believes that this is an important initiative given the expected completion of the 2RT<sup>®</sup> LEAD clinical trial in mid 2018.

Topics to be discussed at the forum include:

**"Early to intermediate AMD: Where are we today?"**

Moderators: Prof. John Marshall and Dr. Isabelle AKNIN

Speaker: Dr. Isabelle AKNIN

**"2RT: The Mechanism of Action"**

Moderators: Prof. John Marshall and Dr. Isabelle AKNIN

Speaker: Prof. John Marshall

**"2RT: Publications and Research"**

Moderators: Prof. John Marshall and Dr. Isabelle AKNIN

Speaker: Prof. Andrea Cusumano

**"Clinical Experience and Case Reports with 2RT and AMD and CSME"**

Moderators: Prof. John Marshall and Dr. Isabelle AKNIN

Speaker: Dr. Ann Swiech-Zubilewicz

**"Clinical Experience and Case Reports with 2RT and AMD and CSME"**

Moderators: Prof. John Marshall and Dr. Isabelle AKNIN

Speaker: Dr. Alain Mayeras

## **“Clinical Experience and Case Reports with 2RT and AMD and CSME”**

Moderators: Prof. John Marshall and Dr. Isabelle AKNIN

Speaker: Dr. Hakan Kaymak

The Laser Innovation Forum coincides with the publication of a white paper addressing the 2RT® method of action by Professor Marshall. The paper, entitled “Rejuvenating Bruch’s Membrane” (attached), describes the scientific and clinical history of 2RT®.

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### **ABOUT THE SPEAKERS**

Prof. John Marshall (United Kingdom)

Professor John Marshall is an internationally recognised expert on laser and light bio-effects in the field of ophthalmology. He is a Fellow of the Academy of Medical Sciences, Emeritus Professor of Ophthalmology at King’s College London and an honorary distinguished Professor in Visual Science at the University of Cardiff. He is also honorary Professor of Ophthalmology in the Institute of Ophthalmology, University College London. Professor Marshall is the co-inventor of the world’s first diode laser for ophthalmology and the inventor of excimer laser technology for refractive surgery. During the past 30 years, his research has shed light on the mechanism underlying age-related, diabetic and inherited retinal disease, and on the development of lasers for use in ophthalmic diagnosis and surgery. Professor Marshall served as Chairman of Ellex’s Medical Advisory Board and has over 40 years of ophthalmology experience.

Dr. Isabelle Aknin (France)

Dr. Isabelle Aknin specializes in retinal diseases and ocular aging pathologies. She is currently appointed at Oxford Private Hospital in Cannes and is also associated with the Hospital of La Fontonne in Antibes. Dr. Aknin is an angiography Consulting Member of the SFO (Société Française d’Ophtalmologie), the French Society of Retina, the American Diabetes Association, the ARVO, the American Academy of Ophthalmology (AAO) and the International Ocular Inflammation Society. She also co-founded the independent association “ARMD – Mediterranean Retina Association” in 2008 with Dr. Melki (France). A winner of the 2009 Prize of the French Society of Retina, she is an expert in retinal disease management and treatment.

Prof. Andrea Cusumano - Rome Vision Clinic – Rome (Italy)

Prof. Anna Swiech-Zubilewicz - University Hospital of Lublin – Lublin (Poland)

Dr. Roxana Fulga- Brayer, Kaymak, Klabe Privatpraxis – Düsseldorf (Germany)

Dr. Alain Mayeras - Ophtalliance Centre d’Ophtalmologie – Challans (France)

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## ABOUT 2RT

A non-thermal laser therapy, Retinal Rejuvenation Therapy, 2RT<sup>®</sup>, stimulates a natural, biological healing response in the eye and in a pilot study on 50 patients has demonstrated potential as an intervention which may positively influence early Age-Related Macular Degeneration. 2RT<sup>®</sup> offers the potential to apply treatment earlier in the disease process with the aim of slowing retinal degeneration, thereby eliminating or delaying the risk of vision-threatening complications associated with the late-stage of retinal disease.

## ABOUT ELLEX

Ellex designs, develops, manufactures and sells innovative products that help eye surgeons around the world to effectively and efficiently treat eye disease. Ellex is a world leader in this field. Headquartered in Adelaide, Australia, Ellex has ophthalmic lasers and devices that treat glaucoma, retinal disease primarily caused by diabetes, secondary cataract and vitreous opacities, as well as age-related macular degeneration. Manufacturing is carried out in Adelaide, Australia and Fremont, California. Sales and service directly to eye surgeons is conducted via subsidiary offices in Fremont, Minneapolis, Lyon, Berlin and Tokyo. A network of more than 50 distribution partners around the world services other markets.

**For additional information about Ellex and its products, please visit [www.ellex.com](http://www.ellex.com)**

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### **For further information on Ellex please contact:**

Tom Spurling, CEO  
Ellex Medical Lasers Limited  
3 Second Avenue, Mawson Lakes, SA, 5095  
W +61 8 7074 8200 | M +61 417 818 658  
[tspurling@ellex.com](mailto:tspurling@ellex.com)

Mark Lindh, Investor Relations & Corporate  
W +61 8 87074 8200 | M +61 414 551 361  
[mlindh@ellex.com](mailto:mlindh@ellex.com)

Maria Maieli, CFO & Company Secretary  
Ellex Medical Lasers Limited  
3 Second Avenue, Mawson Lakes, SA, 5095  
W +61 8 7074 8200  
[mmaieli@ellex.com](mailto:mmaieli@ellex.com)

# REJUVENATING BRUCH'S MEMBRANE

JOHN MARSHALL PhD, FRCPATH FMedSci

Frost Professor of Ophthalmology, Institute of Ophthalmology, University College, London  
Emeritus Professor of Ophthalmology, Kings College, London

**Deterioration of transport processes across Bruch's membrane has been implicated in development of age-related macular degeneration. Fortunately, a breakthrough laser therapy, 2RT, may help improve Bruch's membrane function and delay the development of the disease.**

Bruch's membrane, located between the retinal pigment epithelium (RPE) and the choroidal capillaries, is a complicated five-layer, sieve-like structure that allows reciprocal exchange between the general circulation and the RPE/retina. Specifically, it allows metabolites vital for the proper functioning of the rods and cones to pass from the choroidal circulation towards the RPE/retina, and waste products to pass from the RPE/retina back into the choroidal vasculature.<sup>1</sup>

For the first 30 years of an individual's life, the exchange of waste and nutrients across Bruch's membrane occurs very efficiently. However, as the eye ages, the permeability of Bruch's membrane is reduced, inhibiting its ability to remove and exchange fluid and waste deposits. Current data suggests that by age 40, the flow is reduced to approximately 50 per cent of what it is in childhood. By age 80, it is reduced to a small fraction.<sup>2</sup> Age-related deterioration of Bruch's membrane is an important phenomenon as it is a high risk factor implicated in the onset and progression of early age-related macular degeneration (AMD).<sup>3</sup>

## THE PATHOLOGY OF BRUCH'S MEMBRANE AGING

General aging of Bruch's membrane is characterized by progressive thickening, and accumulation of lipid-rich extracellular matrix (ECM) deposits, and glycation- and lipid-end products. In advanced aging of Bruch's membrane, such as that associated with AMD, these changes are excessive and lead to the death of RPE cells and photoreceptor cells.

An increased accumulation of ECM material as Bruch's membrane ages is indicative of a problem with the degradation pathway. The degradation pathway for ECM turnover comprises the family of matrix metalloproteinases (MMPs) together with their inhibitors, i.e., tissue inhibitors of metalloproteinases (TIMPs). There are several MMPs; however, MMP-2 and MMP-9 appear to degrade both ECM components and non-ECM molecules allowing matrix turnover. Most MMPs are secreted by the RPE as latent zymogens, some are processed intracellularly, and a few are processed at the cell membrane into fully active enzymes.

Studies undertaken in Bruch's membrane-choroid preparations by my colleagues and I showed that the level of inactive proenzymes increased with age; there were also a low or undetectable level of active forms of MMPs.<sup>4</sup> Further findings revealed that advanced ageing in AMD was also associated with significantly reduced levels of active MMP-2 and MMP-9<sup>5</sup> and sequestration of the latent forms with existing debris, thereby exacerbating the problem. Research by Kamei and Hollyfield also found that during normal aging, TIMP-3 content in Bruch's membrane of the macula increases significantly;<sup>6</sup> an increase in TIMP along with a decrease in active forms of MMPs likely explains the reduced degradation of ECM deposits in aged eyes. These observations suggest that increasing the level of activated MMPs within Bruch's membrane may help to improve transport

# REJUVENATING BRUCH'S MEMBRANE

of metabolites and catabolites and slow the development of (or even potentially reverse) this risk factor for AMD.

## THE EFFECTS OF LASER INTERVENTION

In 2012, my team and I published findings from a study showing that treatment with a specific laser, known as 2RT (Ellex, Adelaide, Australia), activates the RPE leading to the release of activated MMPs.

The 2RT laser is a specially designed Q-switched, frequency-doubled, green Nd:YAG with a wavelength of 532 nm designed specifically for the purposes of safe and effective retinal rejuvenation. One of the key differences between 2RT and other pulse-generating lasers is that instead of using millisecond or microsecond treatment times and thermal damage processors, 2RT utilises extremely fast nanosecond pulse resulting in a non-thermal disruptive damage mechanism. The device has a pulse duration of three nanoseconds with an energy of approximately 200  $\mu$ J per pulse. It also features a large 400  $\mu$ m spot size, instead of the traditional top-hat or Gaussian-shaped laser beam and 50- $\mu$ m spot size commonly used for retinal laser treatments. This larger spot size prevents Bruch's membrane from "popping" and haemorrhaging; however, using a 400  $\mu$ m spot could potentially destroy the photoreceptors as a result of killing off a large area of RPE cells, resulting in an inability to supply metabolites. Consequently, 2RT features a speckled beam profile which exclusively targets selected, individual cells within the RPE, such that only 10-20 per cent of cells within the spot are randomly raised above damage threshold and subsequently degenerate. All of the laser energy is designed to stay within the targeted RPE cells and does not extend to neighbouring cells, thus avoiding damage to the overlying photoreceptors and underlying Bruch's and choroidal structures (and thereby reducing the risk of secondary choroidal neovascularisation). In contrast, a conventional laser will damage photoreceptor cells which would clearly defeat the object of laser treatment. The approach taken with micro-pulse laser systems is to use a pulse frequency of 100 to 300 microseconds followed by an off interval of 1,700 to 1,900 microseconds.<sup>11</sup> Initial studies with this approach have demonstrated efficacy similar to argon lasers, with reduced thermal damage compared to conventional photocoagulation. However, micro-pulse still produces similar laser/tissue reactions as conventional photocoagulation, due to the thermal spread of energy outside of the target site.

In our study, we irradiated human RPE-Bruch's choroid explants with an early model 2RT using a 400  $\mu$ m spot size with a discon-

tinuous energy distribution and a total irradiation of 240 mJ/cm<sup>2</sup>. The RPE-Bruch's choroid explants were then returned to the incubator for 14 days. Subsequently, RPE cellular dynamics were assessed using confocal laser scanning, conventional microscopy, cell viability, and proliferation assays. MMPs were quantified by gelatine zymography and densitometry.

Findings showed that within four hours of laser intervention, 47 per cent  $\pm$  8 per cent of the RPE cells within the treatment zone displayed clear signs of injury. By post-treatment days 10 to 14, most of the injured beds were repopulated by migrating RPE cells from regions surrounding the lesion. The results also showed profound changes in activated MMP-2 and MMP-9 with levels increasing by  $6.7 \pm 2.6$ -fold and  $4.4 \pm 1.1$ -fold, respectively, above controls at day seven post laser.<sup>7</sup>

## DELAYING AMD PROGRESSION

Our findings suggest that the nanosecond laser pulse modality provides an avenue for transiently increasing the RPE-mediated release of active MMP enzymes. Although the likely impact of this enzymatic release on the structural and functional aspects of aging Bruch's membrane requires further assessment, early clinical findings indicate that laser treatment may delay pathological and molecular changes in AMD.<sup>7</sup>

In a 12-month prospective, non-randomised, pilot intervention study, conducted at the Centre for Eye Research Australia by Professor Robyn Guymer, 50 patients with bilateral intermediate AMD (drusen > 125 $\mu$ m) were treated with a single application of 2RT to assess the ability of the laser to delay the progression of early AMD. Findings showed that a single application of the 2RT laser produced bilateral improvements in macular function (as measured by flicker perimetry) and appearance.

In a follow-up to the 12-month pilot study, 24-month clinical data showed that no patient had progressed to the advanced 'wet' form of AMD. Further, no patients had developed choroidal neovascularization.<sup>8,9</sup>

A multi-center, randomised trial known as LEAD (Laser Intervention in Early Age-Related Macular Degeneration) is currently underway to investigate the safety and efficacy of 2RT nanosecond microsurgical laser intervention in early AMD<sup>10</sup>. The trial, which began in 2012, includes 292 patients with bilateral high-risk intermediate AMD (drusen >125 $\mu$ m). Patients

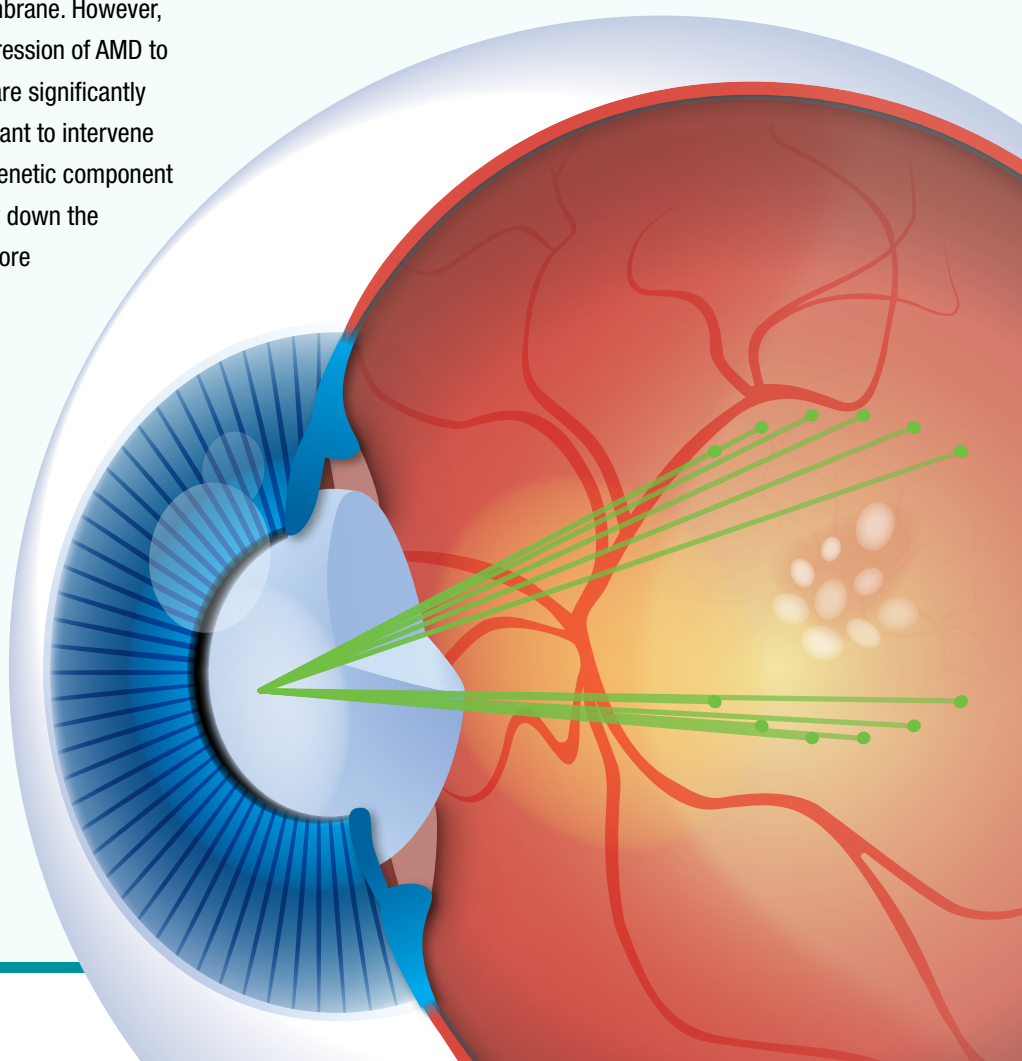
in the treatment group will undergo the 2RT procedure in one eye, with treatment to be repeated at six-monthly intervals. Patients in the control group will undergo a sham procedure. The primary endpoint is progression to advanced AMD in the treated eye, as assessed by ocular examination, colour fundus photography, ocular coherence tomography and fluorescein angiography at 36 months post initial intervention. The secondary endpoint is progression to advanced AMD in the non-treated eye.

Of course one of the main challenges associated with studying the effects of 2RT in AMD is that treatment is prophylactic. If you treat a patient with reasonably good vision in a trial, it is difficult to determine if the laser has achieved anything. Consequently, we need to use more sophisticated tests, such as focal flash recovery times, whereby you flash the patient before treatment and measure photoreceptor recovery time and then repeat three months after treatment. If there is a faster flash recovery time after treatment, it suggests that transport processes have improved;<sup>11,12</sup> however, we don't have this information yet. Using a test known as fundus reflectometry which measures the visual pigment before and after treatment would also be useful, but again, we don't yet have this data.

Overall, treatment with 2RT should help to improve early-stage AMD by cleaning up the debris in Bruch's membrane. However, the ultimate goal of 2RT is to prevent the progression of AMD to its late stages. Since the transport processes are significantly depleted in most people by age 40, it is important to intervene sooner rather than later. There is of course a genetic component to the development of AMD, but if we can slow down the basal rate of Bruch's membrane aging and restore function to what it was when the patient was in their teens, we should be able to significantly delay AMD onset.

**“All of the laser energy is designed to stay within the targeted RPE cells and does not extend to neighbouring cells, thus avoiding damage to the overlying photoreceptors and underlying Bruch's and choroidal structures - and thereby reducing the risk of secondary choroidal neovascularisation.”**

**“...if we can slow down the basal rate of Bruch's membrane aging and restore function to what it was when the patient was in their teens, we should be able to significantly delay AMD onset.”**



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[ellex.com](http://ellex.com)

### Head Office

3 Second Avenue  
Mawson Lakes, SA, 5095 AUSTRALIA  
+61 8 7074 8200

### Registered Office

82 Gilbert Street  
Adelaide, SA, 5000 AUSTRALIA  
+61 8 7074 8200

### Ellex Inc. (USA)

7138 Shady Oak Road  
Minneapolis, MN, 55344 USA  
800 824 7444

### Ellex iTrack

41316 Christy Street  
Fremont, CA, 94538 USA  
800 391 2316

### Ellex Inc. (Japan)

3F, 3-2-22 Harumi Chuo-ku  
Tokyo 104-0053 JAPAN  
+81 3 5859 0470

### Ellex France SARL

La Chaufferie - 555 chemin du bois  
69140 Rillieux la Pape FRANCE  
+33 4 8291 0460

### Ellex Deutschland GmbH

ZPO floor 1, Carl-Scheele-Str.16  
12489 Berlin GERMANY  
+49 30 6392896 00

### Ellex Australia

3 Second Avenue  
Mawson Lakes, SA, 5095 AUSTRALIA  
+61 8 7074 8200