REDEFINING CLINICAL TRIALS

Glaucoma | AMD

NOVAI

ABOUT NOVAI

NOVAI IS A BIOTECHNOLOGY COMPANY COMMERCIALISING DARC TECHNOLOGY

Novai is establishing DARC (Detection of Apoptosing Retinal Cells) as the market leading biomarker in the clinical development of treatments for glaucoma and Age-related Macular Degeneration (AMD).

Novai's proprietary DARC platform, comprising of a biologic combined with Artificial Intelligence (AI), enables immediate categorisation of disease severity, cohort enrichment, and prompt detection of efficacy-based-failure. This can accelerate your clinical development programs, and provide significant cost and time savings.

Our vision is for DARC to become the biomarker of choice for drug development in the ophthalmic space.

SAVE
TIME & MONEY

IMPROVE
PATIENT COHORTS

OPTIMISE
DRUG DEVELOPMENT

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DISRUPTING OPHTHALMOLOGY DEVELOPMENT

Render of DARC Molecule

DARC is changing ophthalmology clinical trials. It is proven to identify "at-risk" patients and provide efficacy readouts of intervention in weeks (rather than years). DARC has been recognized as an exploratory ophthalmic biomarker by the FDA, MHRA and TGA.

Save time and money by implementing better designed studies/trials by incorporating DARC into your designs.

Please see our website for the full range of original publications.

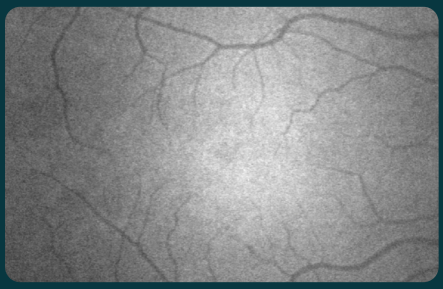


Figure 1: AI algorithm optimised baseline of human subject

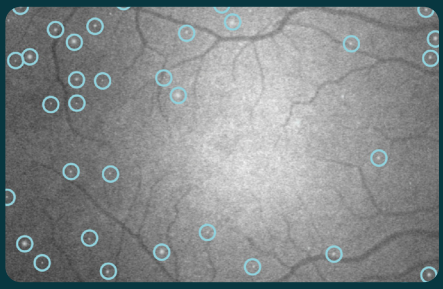


Figure 2: A DARC image of same subject with glaucoma, illustrating white DARC Spots identified using AI algorithm

(teal circles)

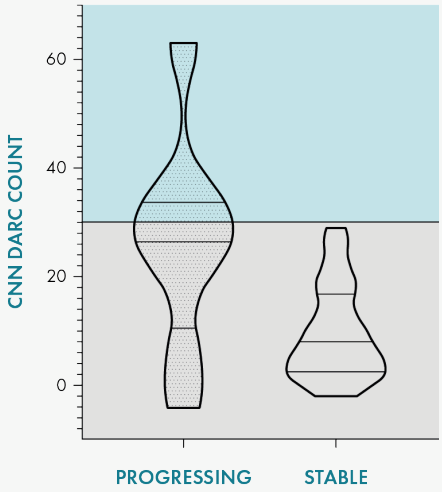
HOW DARC WORKS

The DARC biomarker binds to individual cells undergoing stress (or apoptosis) in diseased retina. This means the readout identifies, as white spots, the earliest changes of cellular damage.

In human AMD and glaucoma trials, the AI-driven DARC algorithm has provided objective data regarding predicting damage some 18-36 months ahead of standard of care measures.

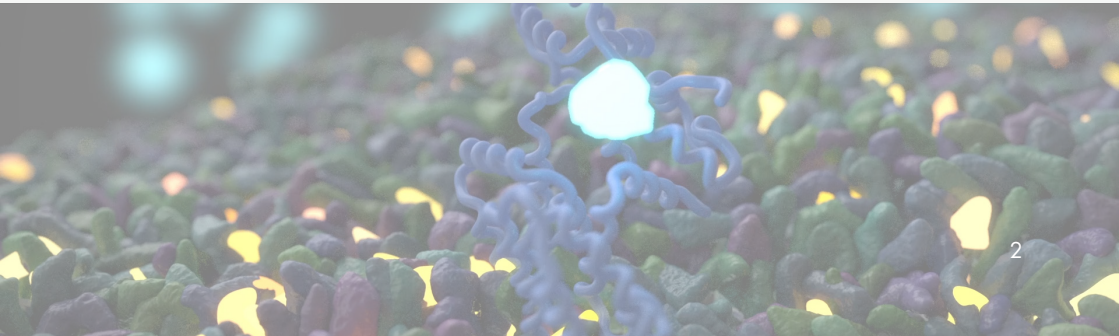
Thus, DARC allows implementation of trials with a more consistent patient population (enrichment) as well as provide more acute measures of disease progression and intervention outcome.

	CNN	2 AGREE
AUC	0.89	0.79
SENSITIVITY	0.86	0.71
SPECIFICITY	0.92	0.88



The Positive Predictive Value (PPV) of DARC is 100% for predicting glaucoma Progression

All glaucoma patients with DARC Counts > 30 went on to progress with OCT RNFL at 18 months



HOW DARC WORKS FOR **YOUR** TRIALS...

Novai's DARC biomarker comprises a protein connected with a fluorescent dye, with a reassuring safety record demonstrated in preclinical and clinical phase I and phase II trials, giving you confidence to utilise it in your drug development studies.

Using Novai's patented AI algorithm, the number and pattern of distribution of these cells (flourescent spots) can be quantified, allowing the patients with active disease and at a high risk of progression to be identified.

Patients identified with a higher DARC count who are more likely to progress to more severere disease

DARC can enrich your patient pool to maximise clinical outcomes

Selected patients are split. Half are given new therapeutic; half are given no drug.

Successful candidates show a reduction in DARC count. This can be identified within weeks.

Mitigate the risk of efficacy related clinical failure.

CHALLENGES IN THERAPEUTIC DEVELOPMENT

According to a 2016 report from the Biotechnology Innovation Organisation (BIO), the likelihood of a therapeutic making it from Phase I to approval was just 9.6% over the previous decade. [REF 1]

One of the biggest challenges in ophthalmology trials is the ability to effectively triage patients.

Traditional end points such as visual field, best corrected visual acuity, and intra-ocular pressure (IOP) fail to provide sufficient detail of patients' rate of progression and active disease state.

While OCT provides a reliable indication of patients' disease state, this is still measuring damage at the tissue, not cellular level. This is measuring damage AFTER it is irreversible, rather than identify it pre-emptively, in time for a potential intervention.

REF 1: Thomas D. W, Burns J., Audette J., Carrol A., Dow-Hygelund C. and Hay M. (2016). Clinical Development Success Rates 2006–2015. San Diego: Biomedtracker.

THE VALUE OF BIOMARKERS

BIO's report highlights the benefits of using selection biomarkers across the clinical development timeline.

Trials using biomarkers to enhance their selection criteria were far more likely (almost 26%) to result in FDA approval than those without (8%).

Only 0.5% of ophthalmology trials between 2005-2015 incorporated a selection biomarker.

The need for an effective biomarker in ophthalmology is therefore particularly acute.

HOW DARC CAN ASSIST IN THE TIMELY AND ACCURATE CONCLUSIONS TO YOUR PRE-CLINICAL AND CLINICAL DEVELOPMENT PORTFOLIO

DARC will allow early identification and monitoring, and enable active disease management in glaucoma and AMD using existing and commonly available imaging technology.

Novai has established a proven pathway from pre-clinical candidate to early phase clinical trials, using the power of DARC as an exploratory and translatable end point.

SERVICES:
PRE-CLINICAL

We offer a full service model, right from helping you plan the protocols through to conducting the studies with your asset in well-established laboratories and then providing you with a comprehensive report of the result.

Novai also offers to work with a number of preferred CRO partners, for whom Novai provides extensive training on the incorporation of DARC administration protocols and image capture.

PRE-CLINICAL: GLAUCOMA & AMD

- Test your new asset in animal models using well-established disease models - *DARC has already demonstrated efficacy for several glaucoma assets within days to weeks using these models.*
- Investigate whether treatments can ameliorate cell stress and apoptosis in vivo.
- Evaluate the dose dependent response.
- Generate a translatable DARC end point.
- Determine efficacy, reliably informing your decision to advance to a clinical trial.

SERVICES: CLINICAL

Once your asset is ready for clinical study, Novai can offer DARC as a key component of your trial strategy, and assist with trial design if required, working alongside yourselves and your CRO to improve and accelerate the trial.

SUPERIOR PATIENT COHORT ENRICHMENT.

We've proven that an increased DARC count is indicative of likely disease progression, meaning you can identify enhanced cohorts that are most likely to demonstrate the efficacy of your drug.

EFFICIENT PoC CLINICAL TRIALS

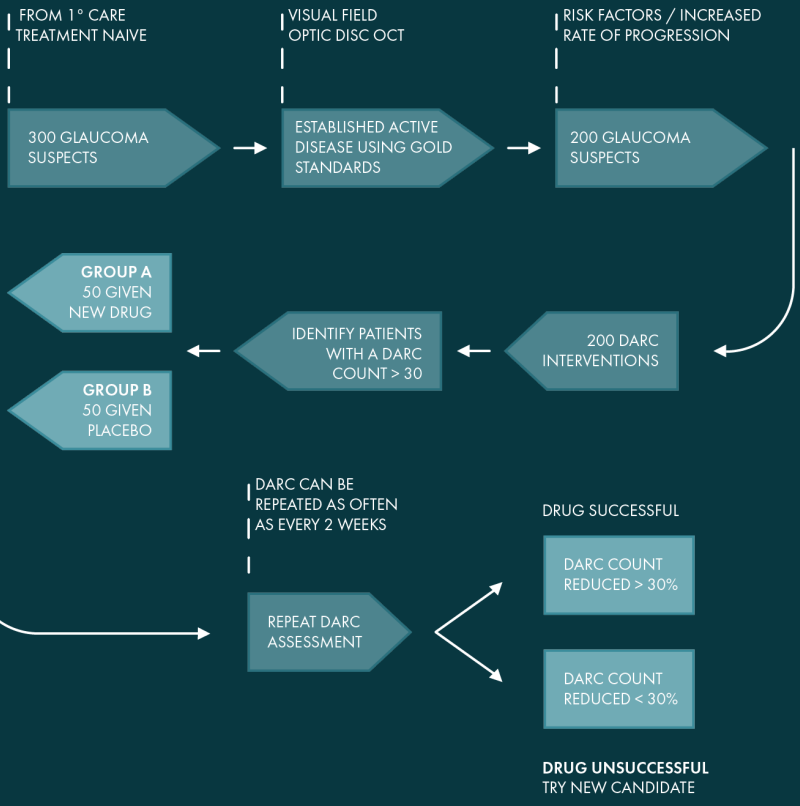
Once a PoC (Proof of Concept) study has commenced, DARC is used as a surrogate end point, indicating in just a matter of weeks whether the candidate is going to be successful - saving both time and money compared to just relying on the gold standards.

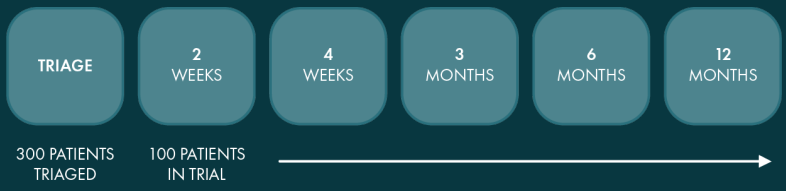
CLINICAL: GLAUCOMA & AMD

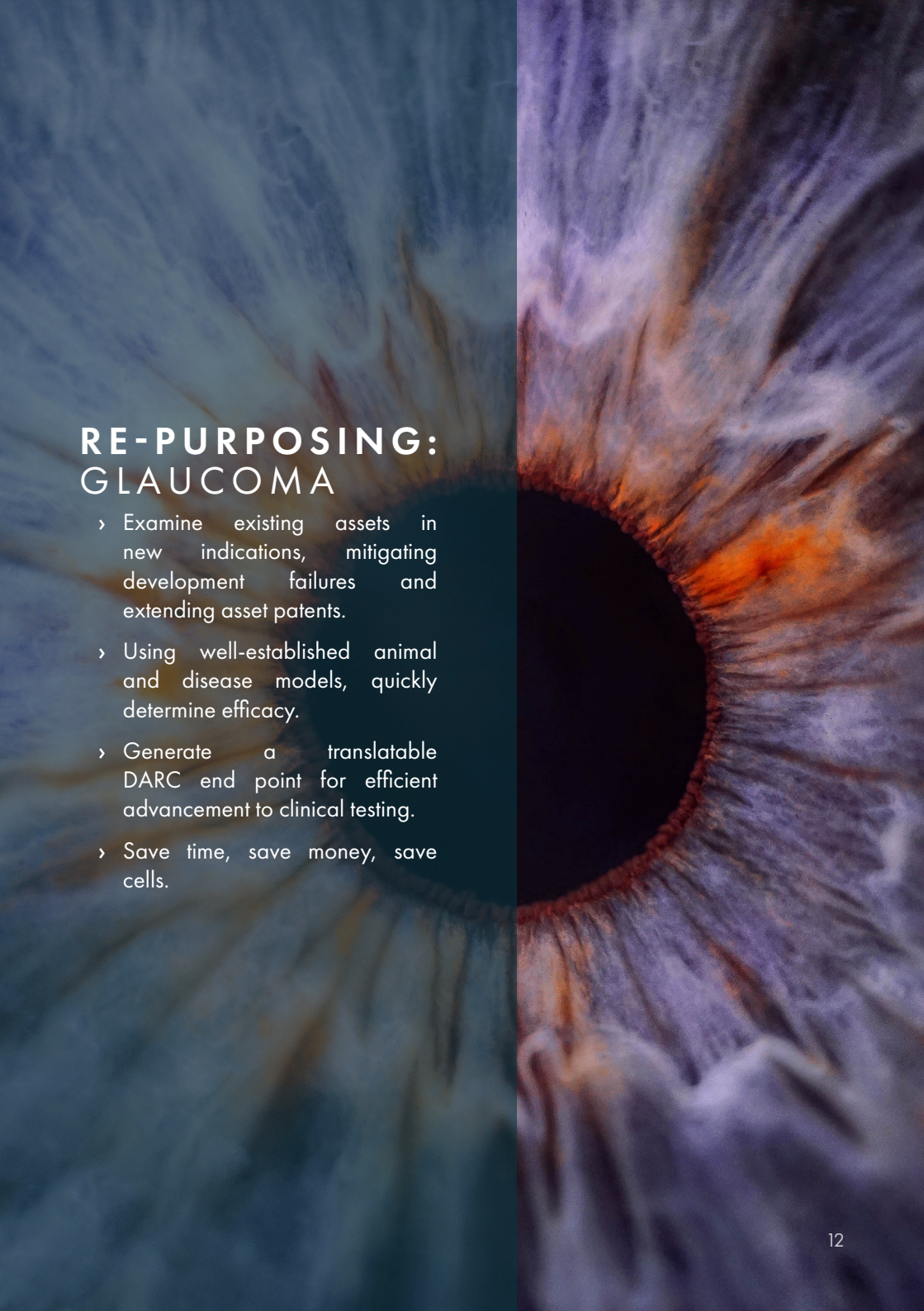
DARC has proven able to identify risk of progression in glaucoma, wet AMD and dry AMD in humans - affording study enrichment and acting as a surrogate end point.

- High DARC Count is indicative of more active disease and a greater risk of progression.
- Enrich your patient cohorts by using DARC to identify more likely progressors, potentially reducing the required sample size.
- Effective therapeutics show a reduction in DARC Count within weeks. Combining enriched cohorts and accelerated findings maximises the chance of success.

REPRESENTATIVE EXAMPLE OF DARC USAGE IN GLAUCOMA CLINICAL TRIAL

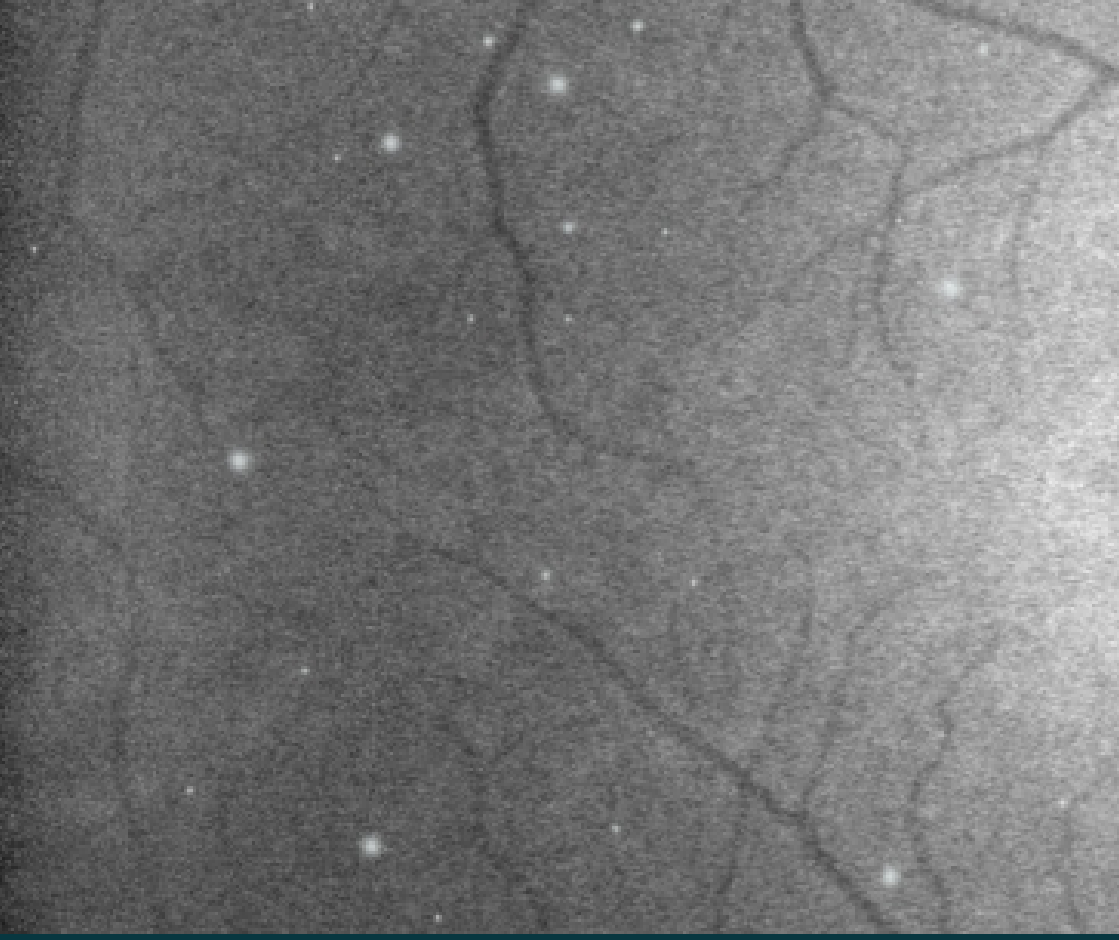






RE-PURPOSING: GLAUCOMA

- Examine existing assets in new indications, mitigating development failures and extending asset patents.
- Using well-established animal and disease models, quickly determine efficacy.
- Generate a translatable DARC end point for efficient advancement to clinical testing.
- Save time, save money, save cells.



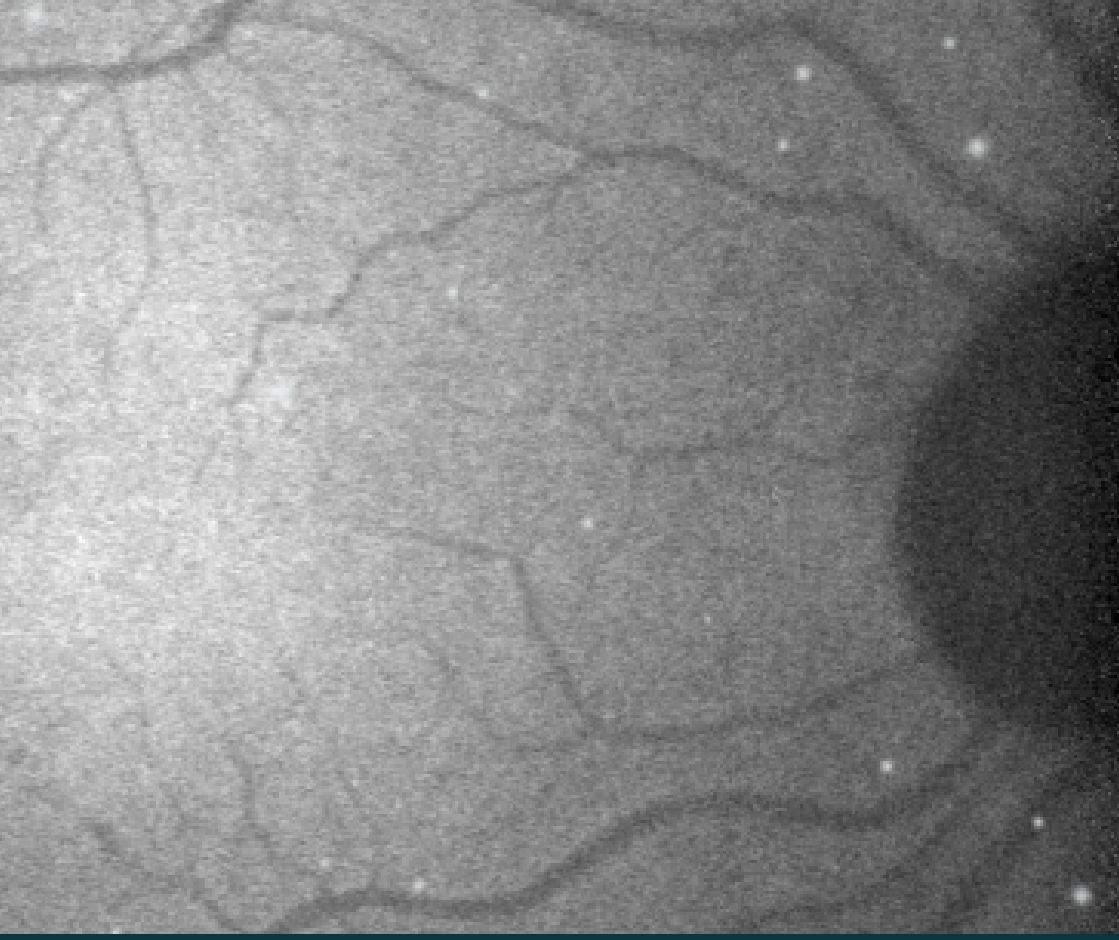
SUMMARY

DARC CAPABILITY

1. Establish translatable pre-clinical end points.
2. Identify patients with more active disease.
3. Rapid determination of efficacy.

CLIENT BENEFITS

1. Reduce risk of advancing an underperforming asset to clinical trial.
2. Enrich patient groups based on disease activity.
3. Test drugs in weeks rather than years.



DARC CAPABILITY

- MHRA,TGA & FDA - approved exploratory biomarker.
- Proven to identify early efficacy-based failure.
- Proprietary AI forms an integral part of the technology platform.
- The only available method of detecting retinal cell stress in-vivo.

USING DARC CAN SIGNIFICANTLY DE-RISK AND ACCELERATE DEVELOPMENT OF THERAPEUTICS

DARC: FROM LAB TO CLINIC SUMMARY

Detecting retinal cell stress & apoptosis with DARC: Progression from lab to clinic.
Cordeiro MF, Hill D, Patel R, Corazza P, Maddison J, Younis S.
Prog Retin Eye Res. 2021 Jun 5:100976

Cells that are under stress can undergo programmed cell death (Apoptosis). When under stress or Apoptosing, they express a molecule called Phosphotidylserine on their surface. DARC (Detection of Apoptosing Retinal Cells) is a retinal imaging technology that has been developed within the last 2 decades from lab to Phase 2 clinical trials. It uses ANX776 (fluorescently labelled Annexin A5) in-vivo to bind Phosphotidylserine, thereby identifying stressed and apoptotic cells in the living eye. Thus DARC identifies cells under stress in-vivo before they are lost permanently; and therefore can be potentially rescued.

Phosphotidylserine expression, and therefore DARC signal, can change within hours allowing for very rapid detection of cellular response to intervention. DARC imaging is performed using existing equipment used to perform ICG angiography, obviating the need for custom equipment.

Cordeiro et al's work has demonstrated three key abilities of the technology:

- Repeatable administration
- Precise quantification of cell stress
- Sensitivity to a broad range of apoptotic stages

ABILITY	USE IN DISEASE ASSESSMENT, DIAGNOSIS, AND MANAGEMENT	USE IN ASSESSMENT OF NEW TREATMENTS
ABILITY TO REPEAT MEASUREMENTS	Disease can be tracked as it evolves, revealing insights such as changes in rate of progression. Response to treatment can also be measured.	Allows more subtle investigation of potential therapies, which for example may change in effectiveness based on treatment length or initial severity of disease.
GRANULAR 'DOSE' RESPONSE	The severity of the disease can be estimated with a high degree of precision, revealing details regarding treatment dose requirements and response to treatment.	Small changes to disease state can be detected, allowing more accurate statistical comparisons to be made in the assessment of treatment effectiveness.
SENSITIVE TO PS EXTERNALISATION	By capturing early apoptotic stages, and continuing through to late apoptosis, a broad range of cell stress can be observed, potentially detecting pathological changes sooner.	Capturing a broad range of apoptotic events allows more data regarding retinal cell stress to be captured in a single DARC image, making subtle treatment effects easier to detect.

During development, DARC has undergone biochemistry optimisation, scale-up, GMP manufacture and extensive pre-clinical evaluation in glaucoma, AMD and optic neuropathy models as well as Alzheimer's, Parkinson's and Diabetic models. Within these pre-clinical models, it has been used successfully to assess efficacy of therapies and levels of disease activity.

In human trials, ANX776 has to date been found to be safe and well-tolerated in 129 patients, including 16 from Phase 1 and 113 from Phase 2. These established optimal dose to be 0.4 mg with half-life of 20.7 minutes and confirmed good safety profile with no recorded serious adverse effects and no patients withdrawing from the study.

Results on glaucoma and AMD patients have been recently published, and show DARC with an AI-aided algorithm can be used to predict disease activity as follows:

- Glaucoma cohort: DARC counts are significantly higher in progressing glaucoma patients compared to stable patients. The Positive Predictive Value (PPV) of DARC, using a DARC Count >30, was 100% at predicting glaucoma progression 18 months later indicating that DARC technology can be used as a predictive biomarker of glaucoma disease progression.
- AMD cohort: Baseline DARC count of >5 predicted wet AMD eyes which went on to form new areas of subretinal fluid up to 36 months later. The PPV was over 70% at predicting new SRFs at all time points indicating that DARC technology can be used as a biomarker of wet AMD disease progression by predicting new SRF formation.
- Geographic atrophy cohort: Baseline DARC count of >10 predicted expansion of geographic atrophy (GA) and the expansion of GA was detectable 36 months later by OCT imaging; indicating that DARC technology can be used as a biomarker of dry AMD disease progression by predicting larger areas of expanding GA.

FUTURE DIRECTIONS: Even as further studies are being done to validate these findings, there is clear evidence for DARC technology to be used as a biomarker now. Much larger subsequent clinical studies are planned to establish DARC as a diagnostic. Nasal route of administration allowing for acceptability in the future as a screening tool.

The review published in the journal Progress in Retinal and Eye Research in 2021 chronicles DARC development and its progression into Phase 2 clinical trials from lab-based research. It discusses hypotheses and approaches to challenges and regulatory hurdles in translating technology.

READ OUR FULL RANGE OF ORIGINAL RESEARCH & PUBLICATIONS

SAVE
TIME & MONEY

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CURRENT **END POINTS** IN **OPHTHALMIC** CLINICAL TRIALS DETECT **VISUAL & STRUCTURAL** CHANGES IN PATIENTS AFTER **18 MONTHS OR LONGER**

THERE ARE **NO** EARLY DETECTION DISEASE **BIOMARKERS** TO DETECT AND MEASURE **CELL** HEALTH

DARC IS CHANGING ALL THAT

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- Identify patients with more active disease
- DARC enables rapid drug testing
- Enrich patient group based on disease activity
- Test drugs in weeks rather than years

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Glaucoma | AMD

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