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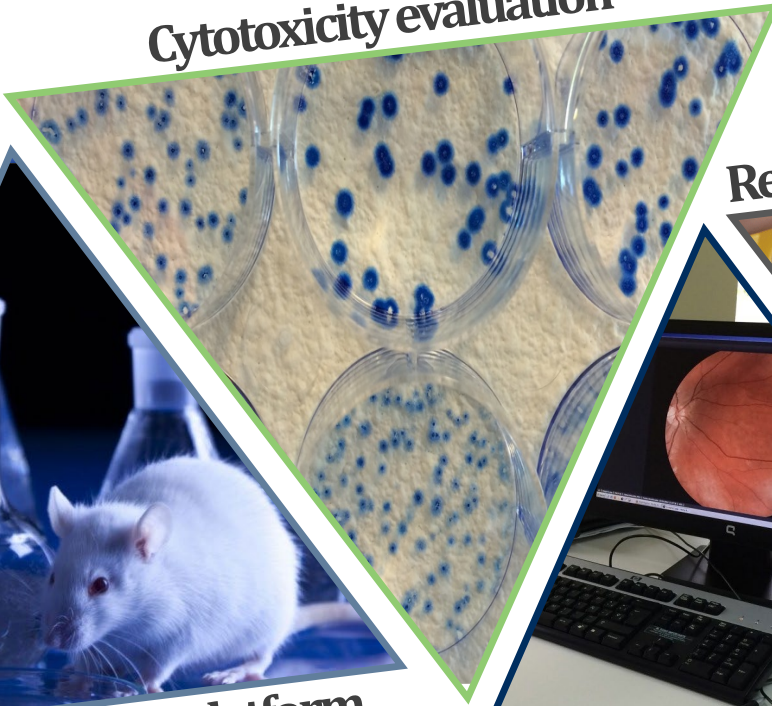
VISION R&D

state of the art solutions

Spin-off company from IOBA, University of Valladolid (2002)

Our Services

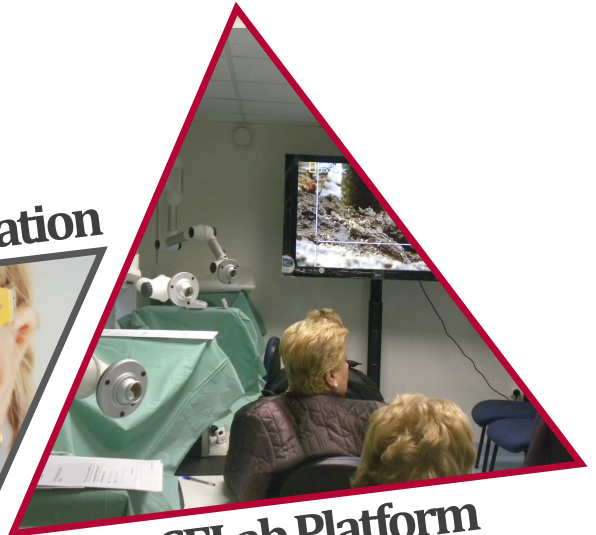
Cytotoxicity evaluation



Rehabilitation



CELab Platform
*Controlled Environment
Laboratory*



Preclinical testing platform



Tele-ophthalmology



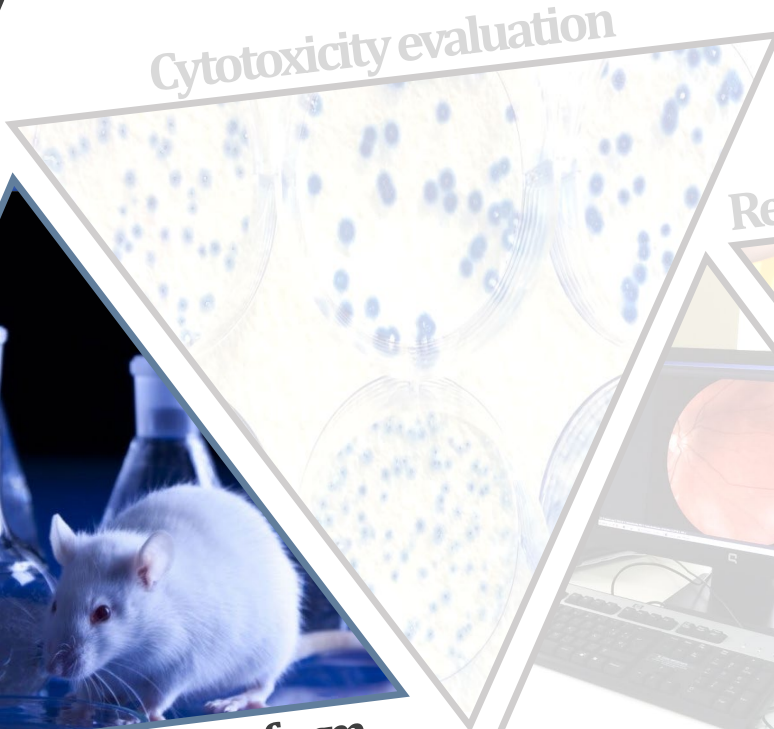
VISION R&D *state of the art solutions*

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Preclinical testing platform



Cytotoxicity evaluation



Tele-ophthalmology

Rehabilitation



CELab Platform
*Controlled Environmental
Laboratory*

Preclinical Platform

In vitro

**3D &
*Ex vivo***

In vivo

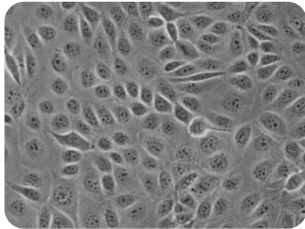
Research lines:

Advanced Therapies
& Nanomedicine

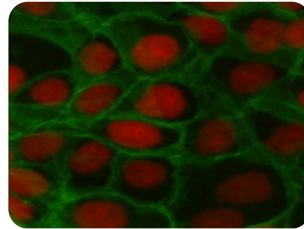
Inflammation &
Biomarkers

Immortalized Human Cell Lines

- Corneal Epithelial Cells
- Conjunctival Epithelial Cells



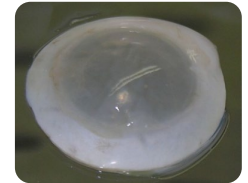
IOBA-Cell Culture Lab



IOBA-Cell Culture Lab

Primary Cultures: Human Ocular Surface Tissues

- Corneal, Conjunctival and Limbal Epithelial Cells
- Corneal, Conjunctival and Limbal Fibroblasts
- Conjunctival Goblet Cells



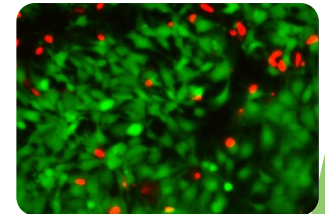
IOBA

In vitro Models

- ❖ Corneal Inflammation
- ❖ Conjunctival Inflammation
- ❖ Corneal Oxidative Stress
- ❖ Conjunctival Oxidative Stress
- ❖ Corneal Wound Healing
- ❖ Corneal Apoptosis and Inflammation
- ❖ Conjunctival Apoptosis and Inflammation

Assays in Cell Monolayer

- ✓ Cell Viability
- ✓ Cell Proliferation
- ✓ Permeability
- ✓ Intracellular Location
- ✓ Transepithelial Resistance (TER)
- ✓ Scratch Assay
- ✓ Protein/mRNA Expression



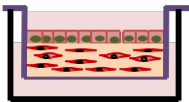
IOBA-Cell Culture Lab

3D Model of Human Conjunctiva

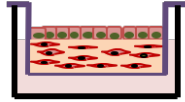
Inflammatory Diseases:

- Dry Eye Disease
- Allergy

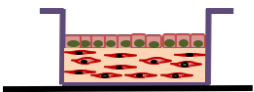
Submerged



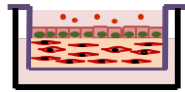
Air-lifted



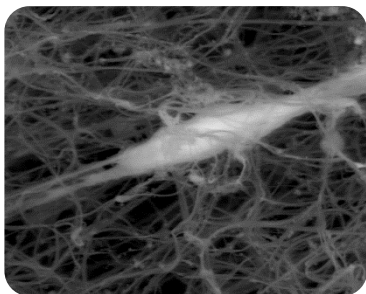
Desiccation



IL-13

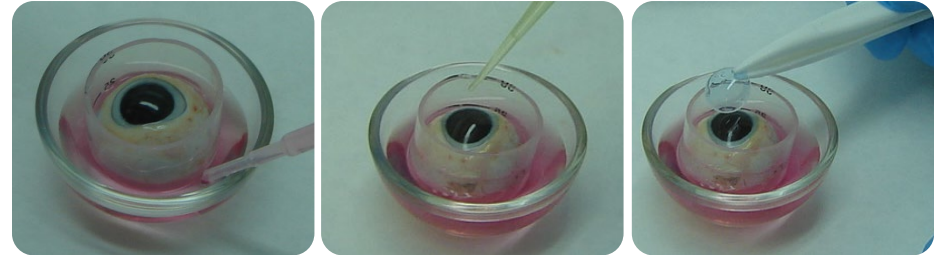


García-Posadas et al.
PLoS One 2017 (IOBA)

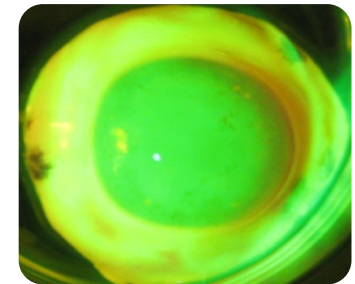


García-Posadas et al.
PLoS One 2017 (IOBA)

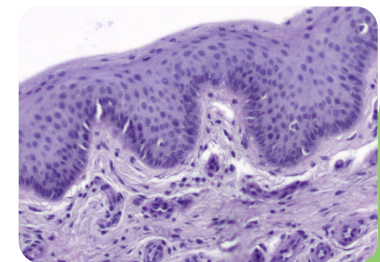
Ex vivo Culture of Porcine Ocular Surface



IOBA-Cell Culture Lab



IOBA-Cell Culture Lab



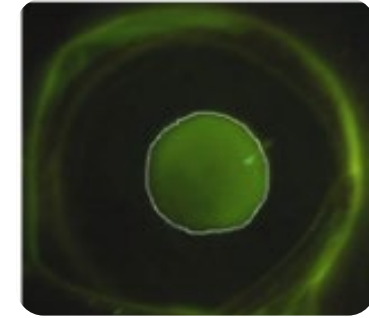
IOBA-Cell Culture Lab

Assays in 3D & Ex vivo Models

- Tolerability
- Permeability
- Tissue Location
- Wound Healing
- Protein/mRNA Expression
- Functional Assays (efficacy)

Corneal Epithelial Wound Healing Model

- New Zealand Rabbits (*Oryctolagus cuniculus*)



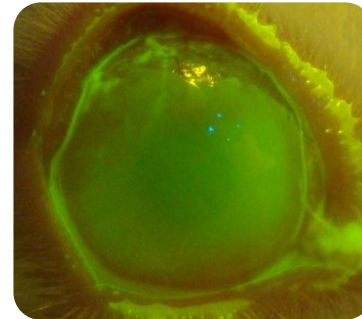
IOBA

Partial Limbal Stem Cell Deficiency Model

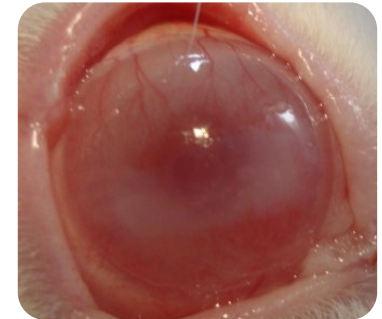
- New Zealand Rabbits

Total Limbal Stem Cell Deficiency Model

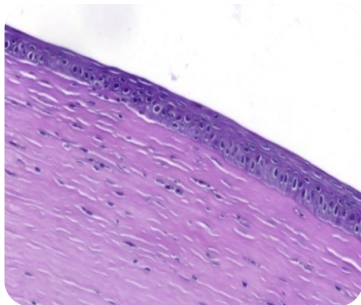
- New Zealand Rabbits
- Pigs (*Sus scrofa*)



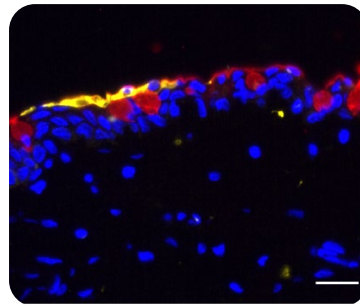
IOBA



IOBA



Galindo et al.
Stem Cells 2017 (IOBA)



Galindo et al.
Stem Cells 2017 (IOBA)

Assays in *In vivo* Models

- ✓ Tolerability
- ✓ Wound Healing
- ✓ Histopathology
- ✓ Protein/mRNA Expression

Our Experience

Recent years

1. Galindo S, Herreras JM, López-Paniagua M, Rey E, de la Mata A, Plata-Cordero M, Calonge M, Nieto-Miguel T. **Therapeutic Effect of Human Adipose Tissue-Derived Mesenchymal Stem Cells in Experimental Corneal Failure Due to Limbal Stem Cell Niche Damage.** Stem Cells. 2017;35:2160-74.
2. García-Posadas L, Soriano-Romaní L, López-García A, Diebold Y. **An engineered human conjunctival-like tissue to study ocular surface inflammatory diseases.** PLoS One. 2017;12:e0171099.
3. López-Paniagua M, Nieto-Miguel T, de la Mata A, Dziasko M, Galindo S, Rey E, Herreras JM, Corrales RM, Daniels JT, Calonge M. **Comparison of functional limbal epithelial stem cell isolation methods.** Exp Eye Res. 2016;146:83-94.
4. Soriano-Romaní L, García-Posadas L, López-García A, Paraoan L, Diebold Y. **Thrombospondin-1 induces differential response in human corneal and conjunctival epithelial cells lines under in vitro inflammatory and apoptotic conditions.** Exp Eye Res. 2015;134:1-14.
5. Abengózar-Vela A, Calonge M, Stern ME, González-García MJ, Enríquez-De-Salamanca A. **Quercetin and Resveratrol Decrease the Inflammatory and Oxidative Responses in Human Ocular Surface Epithelial Cells.** Invest Ophthalmol Vis Sci. 2015;56:2709-19.
6. Abengózar-Vela A, Arroyo C, Reinoso R, Enríquez-de-Salamanca A, Corell A, González-García MJ. **In Vitro Model for Predicting the Protective Effect of Ultraviolet-Blocking Contact Lens in Human Corneal Epithelial Cells.** Curr Eye Res. 2015;40:792-9.
7. Arranz-Valsero I, Soriano-Romaní L, García-Posadas L, López-García A, Diebold Y. **IL-6 as a corneal wound healing mediator in an in vitro scratch assay.** Exp Eye Res. 2014;125:183-92.
8. García-Posadas L, Arranz-Valsero I, López-García A, Soriano-Romaní L, Diebold Y. **A new human primary epithelial cell culture model to study conjunctival inflammation.** Invest Ophthalmol Vis Sci. 2013;54:7143-52.
9. Benito MJ, Calder V, Corrales RM, García-Vázquez C, Narayanan S, Herreras JM, Stern ME, Calonge M, Enríquez-de-Salamanca A. **Effect of TGF- β on ocular surface epithelial cells.** Exp Eye Res. 2013;107:88-100.

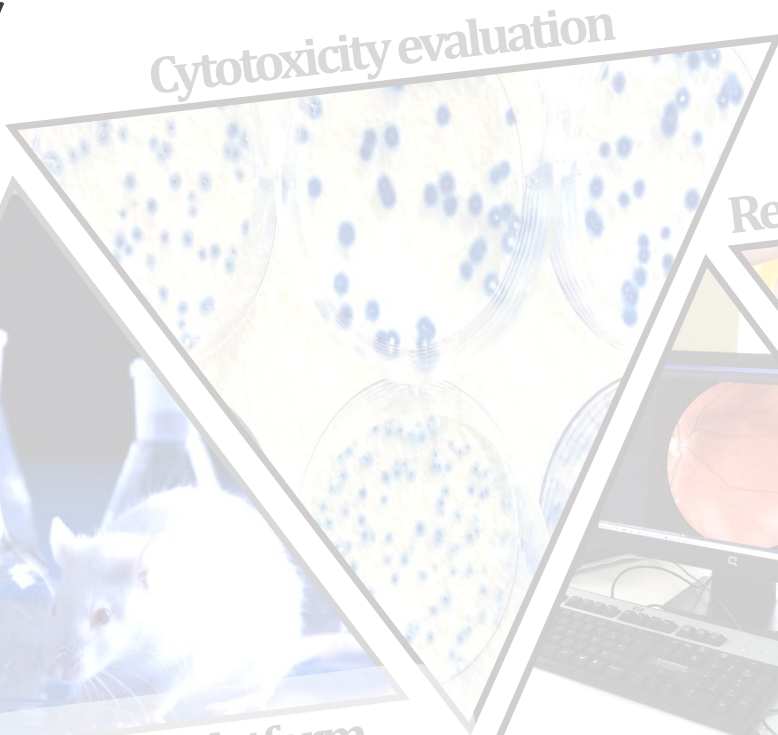
VISION R&D *state of the art solutions*

Spin-off company from the University of Valladolid (2002)

Our Services



Preclinical testing platform



Cytotoxicity evaluation



Tele-ophthalmology

Rehabilitation



CELab Platform
Controlled Environment
Laboratory



About us...

Controlled **Environment** Lab:

1



 Environment Chamber

3



Parque Científico
Universidad de Valladolid **i+d**

 External Laboratories

2



 Associated laboratories

Molecular Biology Laboratory
Ocular Pathology Laboratory

 Clinical Trials Unit

 Research groups: Ocular Surface Research Group

 Clinical Units

Ocular Immunology
OculoFacial Pain Unit (UniDOF)

 Statistical Unit

 Quality Control Unit

CELab

What can we do?



**Therapeutic
clinical trials /studies**

*Drugs
Medical devices*



**Non-therapeutic
clinical trials /studies**

*Contact lenses
Lubricant solutions*



Other uses

*Inflight simulation
Sport and training*

...



Technical features

EVALUATION ROOM



EXPOSURE ROOM



Our Facilities

EXPOSURE ROOM

- Capacity: 8 patients
- Personal computers
- Screen monitor TV
- Near distance activities



Pressure range

940 mbar
450 mbar
(1 mbar steps)



Air flow

None – Turbulent



Luminance

50 – 1000 lux
(1 lux steps)



Temperature

15°C – 30°C
(1°C steps)



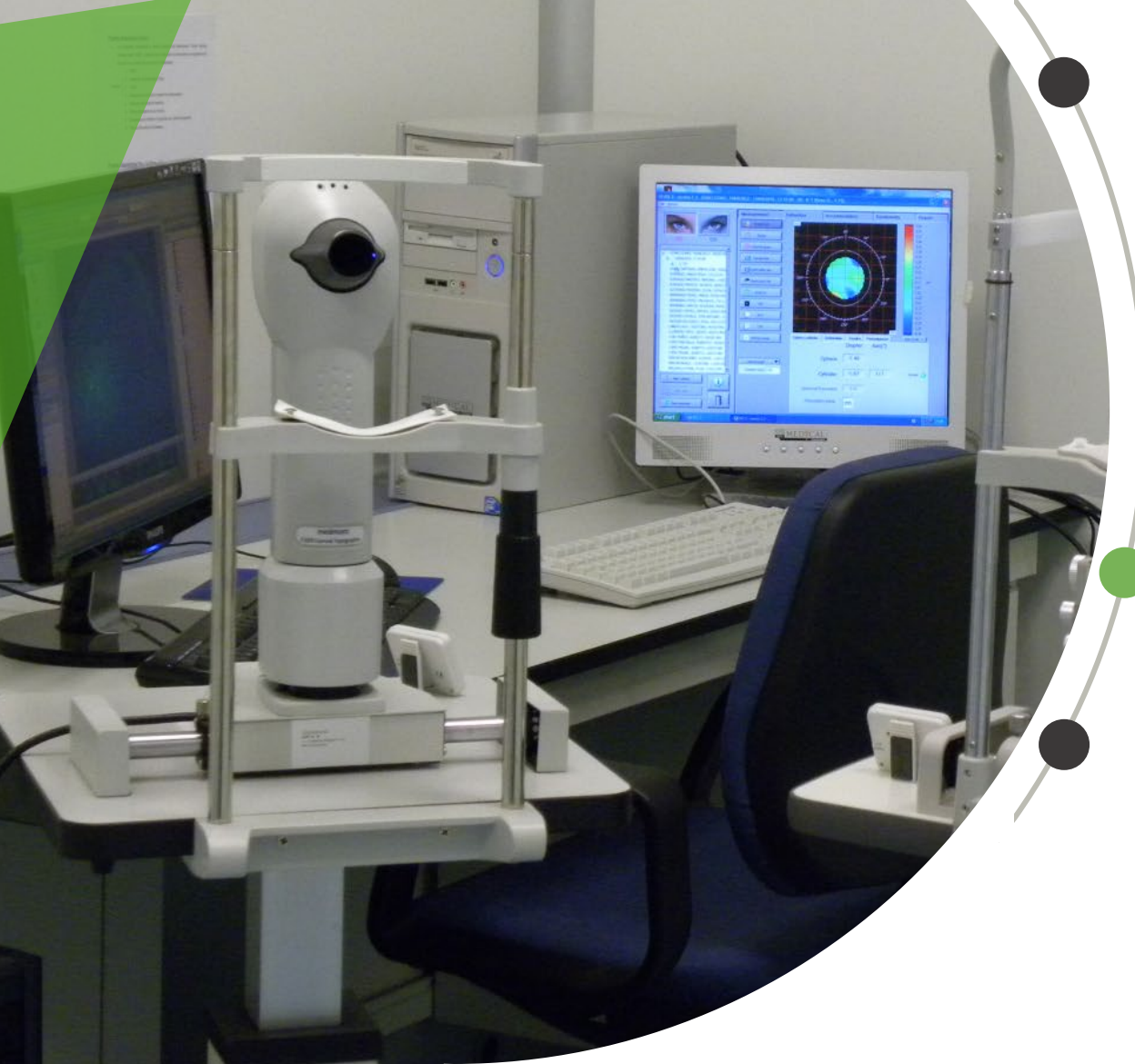
Relative humidity

5% – 80%
(1% steps)

CUSTOMIZED CLINICAL STUDIES

Our Facilities

EVALUATION ROOM



Confocal in vivo Microscopy

Easy Tear View Plus

Esthesiometer (Belmonte)

Osmometers

Slit-Lamp

ETDRS chart

Visual A Charts

Corneal topographer

Aberrometer Hartmann-Shack

Other ...

Our Facilities

EVALUATION ROOM



Symptoms and QoL assessment

Non-contact esthesiometry

Tear film evaluation

Tear Osmolarity

Ocular aberrometry

Corneal topography

In vivo confocal microscopy

Oculo facial pain assessment

High and low contrast visual acuity

Others ...



Our Facilities

EVALUATION ROOM

SAMPLES



Tears



**Ocular surface
epithelial cells**



Saliva



Blood

**Molecule/Molecular
Analysis**

DNA SNPs

MicroRNA

Gene expression

Proteins

Lipids

**Exposure to controlled
“normal” environment (NCE)
to normalize each patient in
order to avoid bias and
misleading results due to
external conditions**



**Exposure to adverse
controlled environment (ACE)
(desiccating stress) to elicit an
acute worsening
(inflammatory)**



Our Value

CELab

What are the advantages?

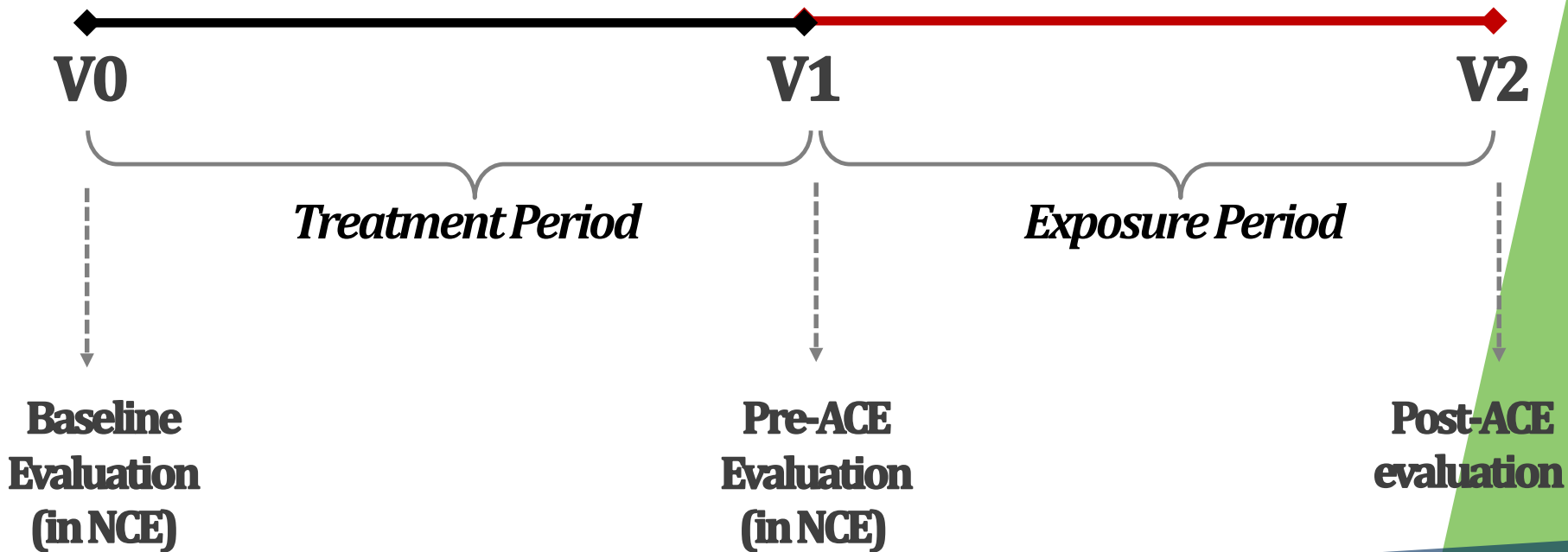
Clinical Trial

(Traditional Design)

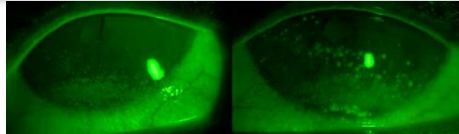


Clinical Trial

CUSTOMIZED DESIGN



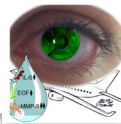
**Controlled adverse environment
(desiccating stress) for 2h worsens Dry Eye
by provoking an inflammatory response in
the lacrimal functional unit**



Investigative Ophthalmology & Visual Science, March 2013, Vol. 54, No. 3

**Influence of a Controlled Environment Simulating an
In-Flight Airplane Cabin on Dry Eye Disease**

Marisa Tesón,¹ María J. González-García,^{1,2} Alberto López-Miguel,³ Amalia Enríquez-de-Salamanca,^{1,2} Vicente Martín-Montañez,¹ María Jesús Benito,¹ María Eugenia Mateo,¹ Michael E. Stern,⁴ and Margarita Calonge^{1,2}



Am J Ophthalmol 2014;157:788–798

**Dry Eye Exacerbation in Patients Exposed to Desiccating
Stress under Controlled Environmental Conditions**

ALBERTO LÓPEZ-MIGUEL, MARISA TESÓN, VICENTE MARTÍN-MONTAÑEZ,
AMALIA ENRÍQUEZ-DE-SALAMANCA, MICHAEL E. STERN, MARGARITA CALONGE,
AND MARÍA J. GONZÁLEZ-GARCÍA

Am J Ophthalmol 2016;161:133–141

**Clinical and Molecular Inflammatory Response
in Sjögren Syndrome–Associated Dry Eye
Patients Under Desiccating Stress**

ALBERTO LÓPEZ-MIGUEL, MARISA TESÓN, VICENTE MARTÍN-MONTAÑEZ,
AMALIA ENRÍQUEZ-DE-SALAMANCA, MICHAEL E. STERN, MARÍA J. GONZÁLEZ-GARCÍA, AND
MARGARITA CALONGE

The Ocular Surface, <https://doi.org/10.1016/j.jtos.2019.03.009>

Response profiles to a controlled adverse desiccating environment based on clinical and tear molecule changes

Itziar Fernández^{a,b}, Alberto López-Miguel^{b,c,*}, Amalia Enríquez-de-Salamanca^{a,b}, Marisa Tesón^b, Michael E. Stern^{b,d}, María J. González-García^{a,b}, Margarita Calonge^{a,b,d}

^a Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Valladolid, Spain
^b IOBA (Institute of Applied Ophthalmobiology), Universidad de Valladolid, Valladolid, Spain
^c Red Temática de Investigación Colaborativa en Oftalmología (OftaRed), Instituto de Salud Carlos III, Madrid, Spain
^d ImmunEyez LLC, CA, USA



**Therapeutic approaches prevent this
Dry Eye inflammatory-mediated
worsening**

Ophthalmology 2016;123:141–153



**Topical Fluorometholone Protects the Ocular
Surface of Dry Eye Patients from Desiccating
Stress**

A Randomized Controlled Clinical Trial

José Pinto-Fraga, MSc,^{1,2} Alberto López-Miguel, PhD,^{1,3} María J. González-García, PhD,^{1,2} Itziar Fernández, PhD,^{1,2} Alberto López-de-la-Rosa, MSc,¹ Amalia Enríquez-de-Salamanca, PhD,^{1,2} Michael E. Stern, PhD,⁴ Margarita Calonge, MD^{1,2}

The Ocular Surface 16 (2018) 368–376

**Severity, therapeutic, and activity tear biomarkers in dry eye disease: An
analysis from a phase III clinical trial[☆]**

José Pinto-Fraga^a, Amalia Enríquez-de-Salamanca^{a,b,*}, Margarita Calonge^{a,b,c},
María J. González-García^{a,b}, Alberto López-Miguel^{a,d}, Alberto López-de la Rosa^a,
Carmen García-Vázquez^a, Virginia Calder^e, Michael E. Stern^{c,f}, Itziar Fernández^{a,b}

[☆]IOBA (Institute of Applied Ophthalmobiology), University of Valladolid, Valladolid, Spain
^aCIBER-BBN (Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine), Spain
^bImmunEyez LLC, USA
^cVISION R&D, Valladolid, Spain
^dUniversity College London, UCL, London, UK
^eBaylor College of Medicine, Houston, TX, USA



The Ocular Surface 16 (2018) 84–92

**Topical fluorometholone treatment and desiccating stress change
inflammatory protein expression in tears**

Janika Näntinen^{a,b,*}, Antti Jylhä^{a,1}, Ulla Aapola^d, Amalia Enríquez-de-Salamanca^{c,d},
José Pinto-Fraga^{c,d}, Alberto López-Miguel^{c,e}, María J. González-García^{c,d},
Michael E. Stern^f, Margarita Calonge^{c,d}, Lei Zhou^{h,j,k}, Matti Nykter^h, Hannu Uusitalo^a,
Roger Beuerman^{a,h,i,j,k}

^aSILK, Department of Ophthalmology, University of Tampere, Finland
^bBioMediTech Institute, Tampere, Finland
^cIOBA (Institute of Applied Ophthalmobiology), University of Valladolid, Valladolid, Spain
^dCIBER-BBN (Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine), Spain
^eVISION I + D, SL, Valladolid, Spain
^fAllergan, Inc., Irvine, CA, USA
^gToys Eye Center, Finland
^hSingapore Eye Research Institute, Singapore
ⁱDuke-NUS Neuroscience, Singapore
^jDuke-NUS Medical School Ophthalmology and Visual Sciences Academic Clinical Program, Singapore
^kOphthalmology, Yong Loo Lin Medical School, National University of Singapore, Singapore



**Effect of Controlled (Normal or Adverse)
Environment in Contact Lens Discomfort –
Biomarkers**



JOURNAL OF BIOMEDICAL MATERIALS RESEARCH B: APPLIED BIOMATERIALS | MAY 2014 VOL 102B, ISSUE 4

**Influence of environmental factors in the *in vitro* dehydration of
hydrogel and silicone hydrogel contact lenses**

Vicente Martín-Montañez,^{1,2} Alberto López-Miguel,^{2,3} Cristina Arroyo,¹ María E. Mateo,¹
José M. González-Méijome,⁴ Margarita Calonge,^{1,2} María J. González-García^{1,2}

¹Ocular Surface Group, IOBA, Universidad de Valladolid, Spain

²CIBER-BBN (Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine), Spain

³VISIÓN I+D, SL, Valladolid, Spain

⁴Clinical and Experimental Optometry Research Laboratory, Center of Physics, University of Minho, Braga, Portugal

Cornea • Volume 35, Number 9, September 2016

**Effect of Environmental Conditions on the Concentration of
Tear Inflammatory Mediators During Contact Lens Wear**

Vicente Martín-Montañez, PhD,*† Amalia Enríquez-de-Salamanca, PhD,*†
Alberto López-de la Rosa, MSc,* Alberto López-Miguel, PhD,* Itziar Fernández, PhD,*†
Margarita Calonge, MD,*† José M. González-Méijome, PhD,‡ and María J. González-García, PhD*†

Ophthalmic & Physiological Optics 37 (2017) 60–70

**Ocular response to environmental variations in contact lens
wearers**

Alberto López-de la Rosa^{1,*}, Vicente Martín-Montañez^{1,*}, Alberto López-Miguel¹, Itziar Fernández^{1,2},
Margarita Calonge^{1,2}, José M. González-Méijome³ and María J. González-García^{1,2}

¹Ocular Surface Group, IOBA, University of Valladolid, Valladolid, Spain, ²Networking Research Center on Bioengineering, Biomaterials and
Nanomedicine (CIBER-BBN), Valladolid, Spain, and ³Clinical and Experimental Optometry Research Laboratory, Center of Physics, University of Minho,
Braga, Portugal

The Ocular Surface 18 (2020) 829–840

**Inflammatory status predicts contact lens discomfort under adverse
environmental conditions**

Itziar Fernández^{a,b}, Alberto López-Miguel^{b,c,*}, Vicente Martín-Montañez^b,
Amalia Enríquez-de-Salamanca^{a,b}, Margarita Calonge^{a,b}, José M. González-Méijome^d,
María J. González-García^{a,b}

^a Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Valladolid, Spain

^b IOBA (Instituto de Oftalmobiología Aplicada), Universidad de Valladolid, Valladolid, Spain

^c Red Temática de Investigación Collaborative en Oftalmología (OftaRed), Instituto de Salud Carlos III, Madrid, Spain

^d Clinical and Experimental Optometry Research Laboratory, Center of Physics, University of Minho, Braga, Portugal





1. More reliable diagnostic test values = Reducing the number of subjects necessary to obtain statistically significant results
2. By running a large amount of evaluation tests and biomarkers, the efficacy of the potential therapeutic candidate is widely defined.
3. The most valid end-points can be selected for further multicenter clinical trials, eliminated those that showed no signal.
4. Ability to obtain a “yes/no” answer before running a large sample of patients for multicenter clinical trials with registration purposes.
5. Increases speed and saves economical resources in drug development/registration/commercialization programs.