

# CORNEA



Project no: COOP-CT-2005-017905

Project acronym: **CORNEA**

Project title:  
**Development of an Artificial Cornea for the Human Eye**

Instrument: Specific Projects for SMEs

Thematic Priority: Co-operative Research Projects (CRAFT)

## Final Activity Report

Period covered: from 2005-08-12 to 2008-08-11

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Duration: 36 months

Project coordinator name: Dr. Wolfgang G.K. Müller-Lierheim  
Project coordinator organization name: CORONIS

Revision: **R00**



## Development of an Artificial Cornea for the Human Eye

**CRAFT-Project supported by the European Commission**  
**Project Nr.: COOP-CT-2005-017905**

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### Project Objectives

The cornea is the entrance window of the eye. It shields the eye from dust and germs, and at the same time acts as the eye's outermost lens contributing about 75 percent of the eye's focusing power.

Opacification of the cornea of the human eye results in the loss of vision and finally blindness unless corrected by a corneal transplant. More than 40.000 keratoplasties per year are performed in Europe and the United States each, with a continuous increase in recent years, and with success rates from more than 90 to less than 50 percent. Low success rates are associated with dry eyes, Herpes keratitis, corneal vascularization, recurring uveitis, acid burns, and traumatic anatomic structures of the anterior eye. The lack of donor corneas resulted in long waiting lists of patients in developed countries, and their non-availability in developing countries in millions of treatable blind people.



There is a long history of attempts to replace the human cornea by alloplastic material with either disappointing results, or complicated multiple surgeries associated with severe drawbacks for the patient. CORNEA combines several cutting-edge technologies in order to achieve a never before available implant design and precision of surgery, and open the chance to regain vision for otherwise blind people.

The artificial cornea to be developed in our project requires three chemically or physically different surfaces in order to meet the desired properties. The skirt should be of such a nature, that fibrin and tissue will stick on it, thus providing a good base for cell growth and healing. The optical part of the artificial cornea should display two different surfaces:

The 'inner' side (which is directed to the eye) of the artificial cornea should be coated with such a material, preventing from adsorption of proteins and cell growing, thus to guarantee that the optical part stays clear. The 'outer' side of the artificial cornea should be hydrophilic to provide a smooth surface and wettability by the tear film. The approach, to achieve these requirements was the coating with appropriate chemicals.

## CORNEA Consortium

The CORNEA project was performed by a consortium of seven small and medium size commercial enterprises (SME) and five public research organizations (RTD):

- CORONIS GmbH, München, Germany (SME; Project Coordinator)
- Eurocrystal S.A., Toulouse, France (SME)
- I.O. International Ltd., Croydon, UK (SME)
- Dr. Schmidt Intraocularlinsen GmbH, St. Augustin, Germany (SME)
- Rockmed B.V., Oirschot, The Netherlands (SME)
- Rhine-Tec Gesellschaft für virtuelle Instrumentierung mbH, Krefeld, Germany (SME)
- PESCHKE Medizintechnik GmbH, Nürnberg, Germany (SME)
- Fraunhofer Gesellschaft zur Förderung der Angewandten Forschung e.V., Institut für Angewandte Polymerforschung, Potsdam-Golm, Germany (RTD)
- Karol Marcinkowski University of Medical Sciences in Poznan, Poznan, Poland (RTD)
- Medical University of Silesia Katowice, Sosnowiec, Poland (RTD)
- Klinikum der Universität Regensburg, Regensburg, Germany (RTD)
- Martin-Luther-Universität Halle-Wittenberg, Halle, Germany (RTD)

## Work Performed and Results Achieved

Within the timeframe of 36 months (between 12 August 2005 until 11 August 2008) and a budget of about 2 Million € the CORNEA Consortium performed the following work.

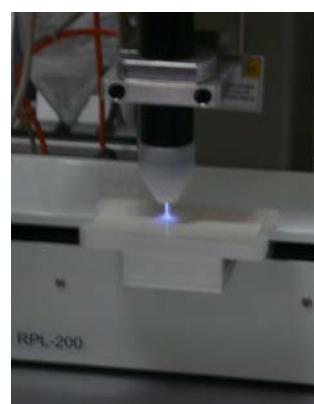
*Bulk polymer:* Keratoprostheses usually consist of a cylindrically shaped optical part and a surrounding skirt (called haptic) which ensures tight connection to the ocular tissue of the patient. The CORNEA Keratoprostheses should preferably be manufactured by mechanical shaping from one piece of polymer for long-term tight connection between the optic and haptic parts. The polymer should be hydrophobic (i.e. absorb less than 2 percent water) in order to avoid interaction with eye medications and dimensional changes due to changes in hydration. Moreover, the polymer should be flexible in order to allow the haptic to follow the movement of the surrounding corneal tissue and prevent local stress. Last not least, the polymer must be optically clear and should be from a group of polymers with a history of safe use in human eyes. Therefore, the consortium focused on the evaluation of various acrylic polymers with a glass transition temperature around 10 °C. This allows mechanical shaping at low temperature and flexibility at the temperature of the human eye. A number of different polymers was preselected and tested for coatability. The physico-chemical and biological properties of coated platelets were systematically investigated.

*Mechanical shaping:* The processes of cryo-lathing and cryo-milling of flexible, hydrophobic acrylic polymers was developed in order to manufacture keratoprostheses of various geometry for testing and later for adjustment to patients' individual needs.

*Coating process:* The consortium tried various processes of polymer surface activation as the first step in firmly coating the polymers.

Plasma activation proved to be the most effective one on the polymers under consideration. Subsequently the consortium developed three different coating processes:

- (a) multilayer coating with Fibronectin to ensure tissue growth on the keratoprostheses haptic
- (b) multilayer coating with Heparin Sodium on the 'inner' surface of the keratoprostheses optic to prevent membrane formation on the surface of the implant



(c) strongly hydrophilic coating by forming an interpenetrating polymer network on the 'outer' surface of the keratoprosthesis optic

The coating technology was transferred to one of the SME partners who established a production line in the clean room.

*Screening for coating performance:* The consortium developed an *in vitro* test with cell cultures to study the ability of ocular cell to adhere and grow on polymer surfaces with different coatings. Primary pigment epithelial cells from human corneas as well as epithelial and endothelial cells from pig eyes were employed to study cell adherence in a perfusion chamber. This screening method was used

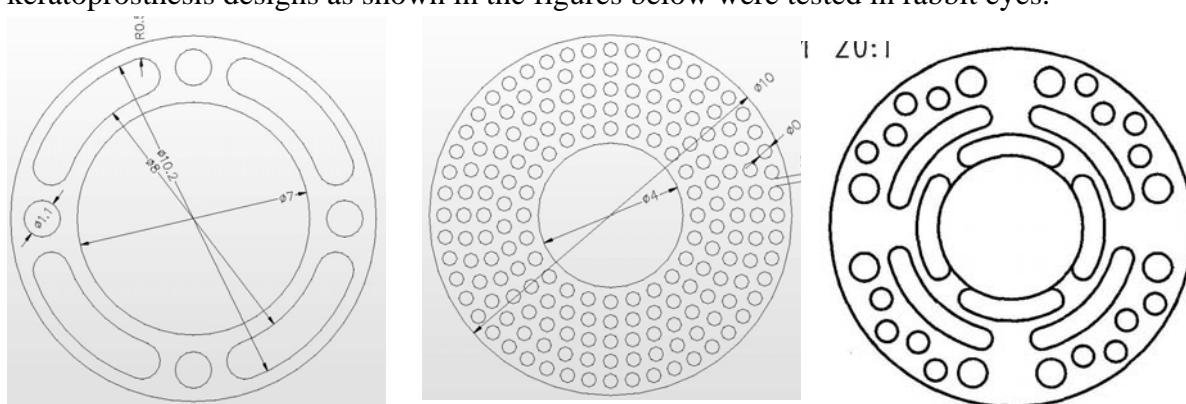
- to develop and optimize the coating process and
- to develop and test the effect of the sterilization method.



*Sterilization process:* Surgical implants need to be supplied sterile, i.e. free from viable microorganisms. Therefore, they need to undergo a sterilization process. During the CORNEA project it turned out that the standard sterilization processes used in the manufacture of ophthalmic implants such as intraocular lenses (steam sterilization or gas sterilization) will destroy the biochemical properties of the coated polymer surfaces: cells will no more adhere to the Fibrin coating after sterilization. Therefore, the Consortium developed a sterilization process where the kerat prostheses are cooled to  $-78,5^{\circ}\text{C}$  while being treated with gamma irradiation. This process was tested for both its influence on the bulk polymer as well as on the coatings, and validated with respect to microbiological effectiveness.

*Medical Advisory Board:* The CORNEA Consortium organized a symposium with experts in cornea surgery in December 2005 and established a Medical Advisory Board. In addition to the five Consortium partners with clinical experience the Medical Advisory Board assisted the CORNEA Consortium in the decision making process of keratoprosthesis design and surgical techniques.

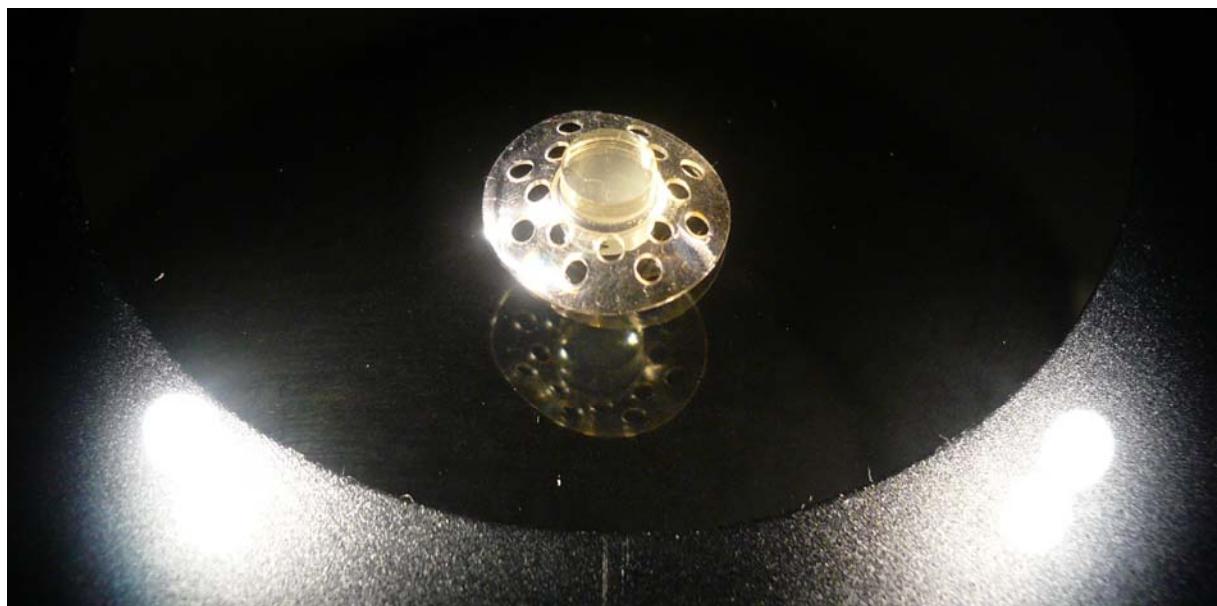
*Clinical performance testing in rabbit eyes:* The long-term performance of a keratoprosthesis cannot be predicted exclusively from *in vitro* testing. It is strongly influenced by the geometry and mechanical properties of the device. Within the CORNEA project three different keratoprosthesis designs as shown in the figures below were tested in rabbit eyes.



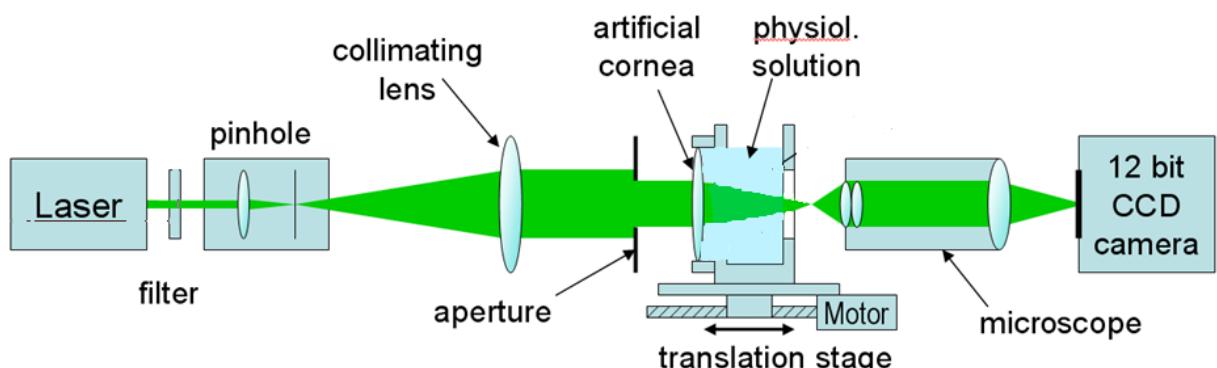
The first design (left figure) is characterized by a large optic diameter and is intended for intrastromal implantation (this means that the haptic be placed in a lamella cut inside the cornea). The designs in the middle and right hand side have a significantly smaller optic diameter; they are intended for epicorneal implantation (this means that the haptic be placed upon the cornea and be covered by tissue). The best performance in rabbit eyes was achieved with the design shown in the right figure. The haptic of the keratoprosthesis was well integrated in the ocular tissue of the rabbit, whereas, the optic remained optically clear. The animal was able to see through the keratoprosthesis as proven by test.



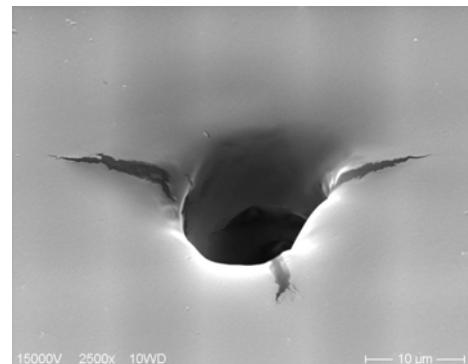
Based on the results of performance testing in animal eyes the geometric design of the keratoprosthesis finally to be implanted in human eyes was optimized as shown in the picture below.



*Optical performance:* The final CORNEA keratoprosthesis design was tested for optical performance in a set-up intended for the measurement of intraocular lenses but modified for the specific situation of kerat prostheses having the 'outer' optic against air. As expected the optical performance is good for light rays along the optical axis, however, has design related compromises for light rays with an angle to the optical axis.



*Stability:* The polymer of the keratoprosthesis was tested for hydrolytic stability, photostability, and stability against exposure to Nd:YAG laser shots and proven sufficiently stable; the picture on the right shows a scanning electron micrograph of the polymer surface after Nd:YAG laser exposure.



*Biological safety:* The following tests have been performed and confirmed the biocompatibility of the coated CORNEA keratoprosthesis:

- *in vitro* test for cytotoxicity of extracts
- acute eye irritation/corrosion test of extracts
- test for sensitization of extracts by the local lymph node assay – LLNA
- subcutaneous implantation test in rabbits

*Packaging:* A package has been developed consisting of two blisters with the inner blister shaped to safely contain the keratoprosthesis.



*Clinical evaluation:* Based on literature and preclinical test results a clinical evaluation in accordance with the European Medical Devices Directive 93/42/EEC was performed, concluding that the CORNEA keratoprosthesis has a similar risk profile to other comparable keratoprostheses on the market, and that the potential benefit to the physician and patients outweigh the potential risks by far. The overall residual design risks, manufacturing risks, and the risk/benefit ratio of the devices when used on patients according to the manufacturer's instructions for use are fully acceptable.

*Regulatory aspects:* The CORNEA keratoprosthetic is a Class III medical device according to MDD Annex IX, Rule 17. The CORNEA keratoprosthetic is intended for use in patients with corneal blindness, to be used exclusively when other therapies such as keratoplasty (transplantation of a donor cornea) have failed or are considered unlikely to be successful by the medical practitioner prescribing the device for an individual patient. The CORNEA keratoprosthetic will only be used in the treatment of 'ultima ratio' patients in close cooperation between the manufacturer and the prescribing ophthalmic surgeon. It will be provided as 'custom-made' device as defined in MDD Article 1.2 (d): 'any device specifically made in accordance with a duly qualified medical practitioner's written prescription which gives, under his responsibility, specific design characteristics and is intended for the sole use of a particular patient'.

The Technical Documentation prepared within the CORNEA project fully complies with the legal requirements of the European Medical Devices Directive. The newly developed device is ready for implantation in patients' eyes.

### Intentions for Use and Impact

The keratoprosthesis developed within the EU funded CORNEA project will be made available under the tradename 'MIRO CORNEA UR'. The implant will first be used on five patients' eyes, and after successful close follow-up of these initial patients on further 35 patients' eyes, before it will be made available to a larger number of specialized ophthalmic

surgical centers. The first 40 patients will be selected and monitored under a 'post-marketing clinical follow-up plan' and patients' informed consent obtained. This study has been submitted for approval to the Ethics Committee of Martin-Luther-Universität Halle-Wittenberg, Medical Faculty, and been approved under conditions on 18 June 2008.

The expected impact will be an artificial substitute for the human cornea for treating blind people or such with a damaged cornea.

Project Website

[www.cornea.coronis.net](http://www.cornea.coronis.net)

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